IRCN

First Joint Meeting of the **Argentine Society for Neurosciences** (SAN)

and the **Argentine Workshop in Neurosciences** (TAN)

Huerta Grande, September 4-6, 2009

IBRO/LARC

Universidad Nacional de Córdoba


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Logistic Organization

Silvina Ceriani

Welcome to the 1st Joint Neuroscience Meeting!

We are excited about the possibility of bringing together virtually all of those working in Neurosciences in Argentina, which in the past attended the meetings of the Argentine Society for Research in Neuroscience and/or the Argentine Workshop in Neurosciences. We also welcome the researchers from all over the world who have come to this meeting.

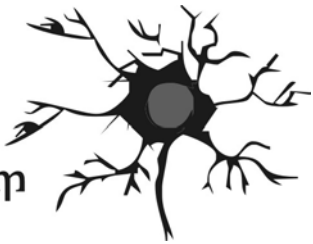
By the end this meeting we hope all of you will agree that this should be the first step in the construction of a new, more inclusive, space for enjoying fruitful discussions and exchanging ideas in an inviting environment.

¡Bienvenidos a la Primer Reunión Conjunta de Neurociencias!

Estamos muy contentos de poder unir a toda la comunidad neurocientífica Argentina y a investigadores de todo el mundo en este congreso.

Esperamos que este congreso sea el primer paso en la construcción de un espacio integral donde disfrutar de enriquecedoras discusiones y de fructíferos intercambios entre todos los participantes.

Program



Course outline: "Psychotropic Drugs"

September 2nd (Wednesday)

7:30 | 10:30 REGISTRATION

9:00 | 9:30 COFFEE BREAK

10:30 | 12.00 **Dr. Mitul Mehta**
Institute of Psychiatry, King's College, London, UK. "Psychopharmacology of serotonin and dopamine".

12:30 | 13:45 LUNCH

14:00 | 15:30 **Dr. Caitlin McOmish**
Sackler Institute for Developmental Psychobiology. Columbia. New York. USA. "Mechanisms of action of hallucinogenic drugs".

15:30 | 17:00 **Dr. Sidarta Ribeiro**
Instituto Internacional de Neurociencias de Natal Edmond & Lily Safra, Natal, Brazil,"Neurobiology of Marijuana and Ayahuasca".

COFFEE BREAK

17:30 | 19:00 **Dr. Mitul Mehta**
Institute of Psychiatry, King's College, London, UK. "Models and methods in pharmacological MRI: potential in drug development".

20:00 | 23:00 **DINNER**

September 3rd (Thursday)

9:00 | 10:30 **Dr. Marcelo Rubinstein**
INGEBI. Buenos Aires. Argentina. "Phenylethylamines and their effects on perception"

COFFEE BREAK

11.00 | 12.30 **Dr. David Lovinger**
National Institute for Alcohol Abuse and Alcoholism. National Institute of Health, Bethesda, Maryland, USA.
"Alcohol abuse and its psychotropics effects".

12:30 | 13:45 LUNCH

14:00 | 15:30 **Dr. John Williams**
Vollum Institute, Oregon Health & Science University, Portland, Oregon, USA.
"Neurobiology of opioid receptors".

15:30 | 16:45 **Dr. Marcelo Cetkovich**
Instituto de Neurología Cognitiva, Buenos Aires, Argentina.
"Mood stabilizers as neuroprotective drugs?"

COFFEE BREAK

17:15 | 18:30 **Dr. Silvia Wikinski**
Instituto de Investigaciones Farmacológicas (UBA- CONICET), Buenos Aires. Argentina.
"Animal models of depression, action of antidepressants".

18:30 | 19:45 **Dr. Juan Belforte**
Facultad de Medicina, UBA, Buenos Aires, Argentina
"Animal model of schizophrenia.
Role of the glutamatergic system".

20:00 | 21:30 DINNER

21:30 | 00:00 Roundtable on the use of recreational drugs and their effect on society.
Alejandra Folgarait, scientific journalist.
Sebastián Basalo, Journalist, Editor of THC magazine
Geraldine Peronace, Psychiatrist.
Roberto Baistrocchi, Psychiatrist, member of SEDRONAR.

Meeting outline: First Joint Meeting of the Argentine Society for Neuroscience (SAN) and the Argentine Workshop in Neurosciences (TAN)

September 4th (Friday)

7:30 | 8:45 REGISTRATION

9:00 | 13:00 Symposium I: ISN symposium on Dopamine and addiction
(Chairs: Drs. M. Rubinstein, INGEBI/ VA Alvarez, NIH, USA)

9.00 | 9.50 **Dr. John T. Williams**
Vollum Institute, Oregon Health & Science University, Portland, Oregon, USA.
"The kinetics of dopamine mediated synaptic transmission"

9.50 | 10.40 **Dr. Verónica A. Álvarez**
National Institute for Alcohol Abuse and Alcoholism (NIAAA), National Institute of Health (NIH), Bethesda, Maryland, USA.
"Functional and morphological plasticity of synapses induced by cocaine"

10.40 | 11.20 COFFE BREAK

11.20 | 12.10 **Dr. David Lovinger**
National Institute for Alcohol Abuse and Alcoholism (NIAAA), National Institute of Health (NIH), Bethesda, Maryland, USA.
"Dopamine-Dependent Striatal Synaptic Plasticity"

12.10 | 13.00 **Dr. Marcelo Rubinstein**
Instituto de Investigaciones en Ingeniería Genética y Biología Molecular (INGEBI-CONICET), Facultad de Ciencias Exactas y Naturales, UBA, Buenos Aires, Argentina
"Dissection of dopamine D2 receptor function by conditional mutagenesis into the mouse genome"

13:00 | 15:00 LUNCH

15:00 | 16.30 Young Investigators Colloquia I (30 min sessions)
Andrea Godino
Instituto de Investigación Médica Mercedes y Martín Ferreyra, Córdoba, Argentina.

"Neurochemical circuits involved in body sodium balance regulation"
Laura Kaczer
Laboratorio de Neurobiología de la Memoria, Departamento de Fisiología y Biología Molecular y Celular, IFIBYNE-CONICET, Facultad de Ciencias Exactas y Naturales, UBA, Argentina
"Contrasting role of octopamine in appetitive and aversive learning in the crab Chasmagnathus"

Soledad Galli
Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, UBA, Argentina
"What pixels do and do not tell about colocalization in fluorescence microscopy: applications in neuroscience"

16.30 | 19:00 Poster Session I
19:00 | 19.30 A tribute to Dr. Eduardo Soto, by Dr. Hugo Maccioni (UNC)

19.30 | 20.30 De Robertis Plenary talk
Dr. Alex Kacelnik
Universidad de Oxford, UK
"Concepts of rationality"

20.30 | 22.30 DINNER
22.30 |23.30 SAN business meeting
23:00 Fogón

September 5th (Saturday)

9:00 | 13:00 Symposium II: Trophic factors, mechanisms and roles in synaptogenesis (Chair: Dr. G Corfas, Childrens Hospital, USA)

9.00 | 9.50 **Dr. Gustavo Paratcha**
Instituto de Biología Celular y Neurociencias, Facultad de Medicina, UBA, Argentina.
"NCAM, an alternative signaling receptor for GDNF in hippocampal and cortical neurons"

9.50 | 10.40 **Dr. M. Fernanda Ledda**
Instituto de Biología Celular y Neurociencias, Facultad de Medicina, UBA, Argentina
"Formation of neuronal synapses by GDNF-induced cell adhesion"

10.40 | 11.20 COFFEE BREAK

11.20 | 12.10 **Dr. Vivian Budnik**
Department of Neurobiology, University of
Massachusetts Medical School, Worcester, MA, USA
"Transmission of Wnt signals during synapse development"

12.10 | 13.00 **Dr. Gabriel Corfas**
Dept. of Neurology, Harvard Medical School, Boston, MA, USA
"Synapse formation in the vestibular epithelium: the roles of neuregulin and BDNF"

13:00 | 15:00 LUNCH

15:00 | 17:00 Poster Session II

17:00 | 20:00 Symposium III: Creating brain rhythms
(Chair: Dra. MV Sánchez-Vives, ICREA-IDIBAPS, Barcelona, España).

17.00 | 17.50 **Dr. Igor Timofeev**
The Centre de Recherche Université Laval Robert-Giffard, Canadá
"Sleep, wake and plasticity in thalamocortical networks"

17.50 | 18.40 **Dra. María Victoria Sánchez-Vives-** ICREA-IDIBAPS,
Barcelona, España.
"Mechanisms of generation and control of slow (1Hz) and fast (15-80 Hz) rhythms"

18.40 | 19.00 COFFEE BREAK

19.00 | 19.50 **Dr. German Sumbre**
Ecole Normale Supérieure, París Francia.
"Entrained rhythmic activities as perceptual memory of time interval"

20:00 | 21:00 **TAN Plenary talk:**
Dr. Nicholas Spitzer
Universidad de California, San Diego, USA
"Activity-dependent neurotransmitter respecification: novel neuroplasticity"

21:00 | 23:00 DINNER

23:00 | 24:00 TAN business meeting

24:00 | **Neuroparty**

September 6th (Sunday)

10:00 | 11.30 Young Investigators Colloquia II (30 min sessions)

Diego Moncada
Laboratorio de Memoria, Instituto de Biología Celular y Neurociencia "Prof. E. De Robertis", Facultad de Medicina, UBA; Argentina.
"Tagging and Capture: A general mechanism of long term memory formation"

Diego Rayes
INIBIBB, UNS-Conicet, Argentina
"Muscle Nicotinic Receptors in Nematodes"

Fernando Sepúlveda
Laboratory of Neurophysiology & Laboratory of Neurobiometals, University of Concepcion, Chile
"Aβ causes membrane perforations in hippocampal neurons"

12:00 | 13:00 Ranwell Caputto Plenary talk

Dr. Ranulfo Romo
Universidad Autónoma de México - México
"Turning sensation into perception across cortex"

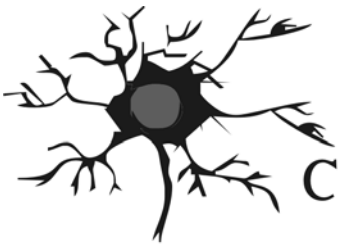
13:00 | 15:00 LUNCH

15:00 | 17.30 Poster Session III

COFFEE BREAK

17.30 | Neurofilms: THE DREAM/ workshops

Meeting adjourns....



Course and Meeting abstracts

"Psychopharmacology of dopamine and serotonin"

Mitul Mehta
Institute of Psychiatry, King's College, London, UK

Dopaminergic and serotonergic projections from the brainstem innervate widespread regions in the mammaliam brain and are implicated in mood, behaviour and cognition. As such both these systems are of relevance to understanding altered cognitions and treatment effects in neurological and psychiatric disorders. Classically dopamine has been associated with modulation of spatial working memory, evidenced by studies in rodents and monkeys. In humans, the relevance of the animal work is shown by systemic manipulation of dopamine transmission combined with neuropsychology and functional brain imaging. Numerous studies now demonstrate that baseline variability is predictive of drug effects using neuropsychological assessment and indices of endogenous variability such as variations in COMT genotype. Direct measurement of endogenous markers of the dopamine system, such as the dopamine D2 receptor have been important in understanding associations with cognitive performance measures. For example spatial planning is positively correlated with striatal dopamine D2 receptor availability as measured with [11C]-raclopride positron emission tomography. The dynamic engagement of dopamine systems can be measured using changes in [11C]-raclopride binding which is also sensitive to spatial planning, as well as reward and motor functions. To date, methodology to measure endogenous serotonin release in humans in vivo has not been successful, although using different ligands of the serotonergic system (e.g. 5-HT 1A) show inter-individual variability associated with performance of cognitive tasks of episodic and working memory, that are partly predicted by systemic manipulation of serotonin using acute tryptophan depletion or direct receptor agents. Research in experimental animals suggests dissociable effects on tasks of flexibility and response inhibition and early indications indicate that these effects are also relevant for humans. Important challenges for the future include the use of a broader range of receptor ligands and tracers and develop and validate methodology to assess endogenous levels of neurotransmitters beyond the dopamine system and extend this work into psychiatric patient populations.

"Neurobiology of Marijuana and Ayahuasca"

Sidarta Ribeiro
Instituto Internacional de Neurociencias de Natal, "Edmond & Lily Safra", Natal, Brazil.

Marijuana and ayauasca have been traditionally used for the induction of mental alterations. The cannabinoids present in marijuana cause a wide range of physiological and psychological effects, with important changes in perception and memory. Ayauasca, an Amazonian hallucinogenic brew that acts through the serotonergic system, is used in religious rituals to trigger potent visual imagery and emotional modulation. In this talk I will present biochemical, electrophysiological and systemic mechanisms that may underlie the mental changes induced by marijuana and ayauasca.

"Models and methods in pharmacological MRI: potential in drug development"

Mitul Mehta
Institute of Psychiatry, King's College, London, UK

Functional brain mapping using magnetic resonance imaging (MRI) has proven utility in delineating brain networks associated with specific brain functions, defining regional abnormalities in neurological and psychiatric disorders as well as in describing the effects of psychoactive medications on regional brain activity. However, to date, there are no examples of functional MRI routinely incorporated into clinical practice or advancing drug development for use in clinical practice. Nonetheless the ability of fMRI to provide surrogate endpoints in assessing the efficacy of novel centrally acting compounds has repeatedly been suggested to have defined utility in multiple stages of drug development, from validation of candidate biomarkers to guiding decision making early in clinical trial design and even in understanding the reasons for failure should a compound not prove viable for widespread clinical use. This talk will review fMRI combined with psychopharmacology, and introduce critical areas for research development necessary for reliable and central application in drug development.

"Mood stabilizers as neuroprotective drugs?"

Marcelo Cetkovich
Instituto de Neurología Cognitiva, Buenos Aires, Argentina.

Bipolar disorders, previously referred as manic-depressive illness, are one of most prevalents psychiatric conditions, being cause of great disability. Almost 6% of the population is affected by this condition if sublte forms –so called "bipolar spectrum"-are included. Early in 1900´s Emil Kraepelin split endogenous psychosis in Manic Depressive Illness and schizophrenia. He stated that main difference was the deteriorating course and cognitive impairment in schizophrenic patients, not present in Manic Depressives. Recent developments demonstrated that such a difference is not so, showing that affective patients are more impaired than previously admitted, shortening distance with schizophrenia. Executive function seems to be affected in both disorders, perhaps with differences in the severity and pathophysiology.

Bipolar disorders are characterized by a delay in diagnosis due to misdiagnosis with unipolar depression and schizophrenic psychosis. Once diagnosis is made, main therapeutic approach involves mood stabilizers. Lithium, sodium valproate, carbamazepine and lamotrigine are among the most effectives and widely used. The mechanism of action to develop stabilization remains elusive, despite the fact that besides lithium, they are anticonvulsants. Neurobiology of affective disorders shifted from a pure neurochemical understanding to so called "neurotrophic theory", since the discovery of stress effects on hypocampus neurogenesis and synaptogenesis. Mood regulating circuits are affected by this process. Lithium carbonate has been used for the last 60 years in the treatment of mood disorders. Its mechanism of action includes effects on neurotransmitter systems like NA and 5-HT. Recent findings showed that Li is able to inhibit Protein Kinases, among them, GSK3. This enzyme is a key factor in the sustaining con citoeskeleton and is involved in the metabolism of Tau protein. Tau protein metabolism is affected in neurodegenerative disorders like Alzheimer disease, frontotemporal dementia and Dementia with Loewy body inclutions. This raises the question if lithium carbonate and other mood stabilizers with the same mechanism of action have a place in the field of neuroprotection. Some neuroimaging data support this, and there are groups checking Li preventive effect on EA.

"Animal Models of Depression, Action of Antidepressants"

Silvia Wikinski
Instituto de Investigaciones Farmacològicas (UBA-CONICET), Buenos Aires, Argentina.

Depression is a highly prevalent disorder all over the World. The World Health Organization estimates that more than 120 million people are currently affected and that, by 2020 it will be the second cause of burden due to health problems. Although since 1950 many antidepressant drugs were developed, according with the latest evidences, significant proportions of patients do not respond to treatment or relapse in the short term. It remains necessary to reach new insights on the neurobiology of depression in order to be able to design new pharmacological treatments.

Depression is undoubtedly a human disease, but for the investigation of the potential utility of new compounds several animal models are employed. Additionally, supported on some similarities between the symptoms of depression and behavioral parameters in rodents, some other approaches are used to investigate the neurobiology of the disease.

In this lecture the most frequently employed models of depression will be presented and their advantages and limitations will be discussed. Focus will be put on the stress-based experimental models: chronic mild stress, chronic restraint stress and the learned helplessness paradigm.

Mechanism of action of antidepressant drugs is still controversial. Since the '80, when the monoaminergic theory of depression and of the action of antidepressants were proposed several other theories have been presented. Currently the neurotrophic and the neurogenic hypotheses are the most cited. I will present evidencies supporting each of these hypothesis, as well as their pitfalls. I will also present the results from our laboratory concerning the plastic changes induced by exposure to inescapable stress in the learned helplessness paradigm and by the chronic treatment with the glucocorticoid corticosterone. There will be also shown the effects of the treatment with the antidepressant fluoxetine, the mood stabilizer valproic acid and those obtained by the exposure to an enriched environment. Our results show that inescapable stress induces a long lasting diminution of synaptic and cytoskeletal markers in the hippocampus, that chronic treatment with corticosterone deeply affects intermediate neurofilaments and MAP2 in the same area, and that all these changes are accompanied by alterations in the in vitro glutamate release. While fluoxetine reverses behavioral and synaptic parameters, it fails to correct the cytoskeletal

alterations. Valproic acid and enriched environment, on the contrary, exert a corrective effect on these parameters too. Preliminary results which could explain the mechanism by which cytoskeletal proteins are affected upon stress, together with the modifications in the CRF signaling cascade in animals exposed to learned helplessness will be also presented.

"Animal models of schizophrenia: role of the glutamatergic system"

Juan E. Belforte
Facultad de Medicina, UBA, Buenos Aires, Argentina.

The seminal discovery that PCP, a psychotomimetic drug, noncompetitively blocks the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor channels led to the theory that NMDA receptor hypofunction may be a key to the etiology and pathophysiology of schizophrenia. This theory was expanded based on postmortem studies and genetic linkage analysis and constitutes one of the leading hypothesis in the field. Based on this theory, several pharmacological and genetic manipulations have been developed to generate animal models of the disorder. In an "ideal" animal model of a disease, the phenotypes obtained will recapitulate the human phenotypes, however, in the case of schizophrenia, this is hard if not impossible to achieve since rodents cannot for example self-report hallucinations, or have suicidal thoughts. However, schizophrenia, as well as other psychiatric disorders, is associated with quantitative phenotypes called intermediate traits or endophenotypes. Behavioral symptoms, neuroanatomical pathology, neurophysiological responses, and neurochemical abnormalities are examples of disease components or endophenotypes that can be modeled in animals. Although no animal manipulation will ever completely model all aspects of complex psychiatric disorders like schizophrenia, many different animal models, each serving a different purpose, will be useful for the characterization of different aspects of the disorder. Models based on acute or chronic administration of pharmacological agents and genetic manipulations will be presented and compared in this talk.

"The kinetics of dopamine mediated synaptic transmission"

John Williams
Vollum Institute, Oregon Health Sciences University, Portland, USA

Dopamine plays a role in multiple physiological processes ranging from movement and reward to the regulation of hormonal balance. Dopamine receptor agonists or antagonists are used for the treatment diseases such as schizophrenia, depression, attention deficit disorder and Parkinson's disease. Recent work also indicates that the altered regulation of dopamine release induced by many drugs of abuse plays a critical role in early processes linked to early aspects of addiction. Thus there is a considerable understanding of the physiological role of dopamine in the central nervous system. There is likewise an enormous literature on molecular and biochemical aspects of dopamine signaling. Studies range from, the expression of the multiple isoforms of dopamine receptors and second messenger cascades in cell lines to, biochemical and electrophysiological examination of the actions of dopamine and receptor agonists on neurons in various parts of the central nervous system. Thus the signaling cascades that are activated by dopamine receptors are well characterized.

In spite of the wealth of knowledge of the dopamine system, little has been done on the actions of synaptically released dopamine at the cellular level. This hole in knowledge is not for the lack of effort, but lies in the fact that robust physiological detectors linked to dopamine synapses have been difficult to find in the major projection areas. With the use of recordings from dopamine neurons in brain slices from mouse, the inhibitory synaptic potential (IPSP) that results from the dendritic release of dopamine will be described. The goal will be to determine how the dendritic release of dopamine is altered following the induction of excitatory synaptic plasticity resulting from the treatment of animals with cocaine. The robust connection between the dendritic release of dopamine and the activation of an IPSC remains the best and probably only site at which dopamine transmission has been directly examined.

"Functional and morphological plasticity of synapses induced by cocaine"

Verónica A. Álvarez
National Institute for Alcohol Abuse and Alcoholism (NIAAA), National Institute of Health (NIH), Bethesda, Maryland, USA

The study investigates the changes in synaptic strength and dendritic spine morphology that are induced by repetitive exposure to cocaine in the nucleus accumbens (NAcc). Using transgenic mice expressing GFP under D1- or D2-dopamine receptor promoter, we identify cell-specific changes in AMPA-mediated synaptic transmission and dendritic spines number and morphology in the two populations of medium spiny neurons of the NAcc. Behavioral measurements of locomotor activity after each repetitive cocaine exposure are used to determine the development of psychomotor sensitization in the D1-GFP and D2-GFP mouse line. The results show that behavioral sensitization, but not cocaine exposure, correlates with increases in synaptic strength and dendritic spine density in D1-expressing medium spiny neurons of the Nacc.

"Dopamine-Dependent Striatal Synaptic Plasticity"

David Lovinger
National Institute for Alcohol Abuse and Alcoholism (NIAAA), National Institute of Health (NIH), Bethesda, Maryland, USA

Long-lasting changes in synaptic transmission are thought to contribute to striatal-based learning and memory. Dopamine participates in the induction of both long-term potentiation (LTP) and long-term depression (LTD) in striatum. We are currently exploring the mechanisms underlying these forms of synaptic plasticity at both glutamatergic and GABAergic synapses onto striatal medium spiny neurons. We are also examining the role of these forms of plasticity in striatal-based skill and habit learning.

"Dissection of dopamine D2 receptor function by conditional mutagenesis into the mouse genome"

Marcelo Rubinstein
INGEBI-CONICET and FCEyN, University of Buenos Aires, Argentina.

Dopamine transmission participates in the extrapyramidal control of locomotor activity, spatio-temporal organization of goal-oriented behaviors, the reinforcing properties of natural rewards and the synthesis and release of pituitary hormones. Efforts to determine the specific contribution of the dopamine D2 receptor (D2R) in these functions have been limited by the fact that pharmacological agents interact with other dopamine receptors –mainly of the D2R-class and in all brain and peripheral areas simultaneously. To dissect the functional roles of D2Rs we have studied mutant mice carrying null Drd2 alleles using a wide battery of neurochemical and behavioral paradigms. Although this analysis revealed several differential phenotypes that helped us to assign specific functions of the DR2 in dopaminergic transmission, we also learned the limitations of the mouse gene knockout technology. Compensatory adaptations of the developing nervous system to the absence of D2Rs was evidenced by a hypolocomotor state that was significantly less severe than that induced by the acute pharmacological blockade of D2R-like in WT mice. Also, the central phenotypes observed in the D2R knockout mice may be difficult to interpret due to the concurrent peripheral deficiencies observed such as high serum prolactin levels, growth hormone deficits and late onset pituitary tumors. In addition, our studies failed to discriminate post- and presynaptic components of D2R stimulation. Improvements to bypass these drawbacks could be achieved through a conditional gene knockout strategy that permits the region- or cell-specific disruption of the D2R gene and/or the temporal control of gene inactivation. To this end, we used the Cre/loxP system to create a strain of mutant mice in which the critical exon 2 is flanked by two loxP sites. Molecular and behavioral sudies demonstrated that C57Bl/6J congenic (n=10) homozygous Drd2flox/flox mice are overtly indistinguishable from their Drd2+/+ wild-type littermates. Along this talk, I will present recent data obtained after crossing Drd2flox/flox mice with transgenic mice carrying expressing Cre from different promoters that are allowing us to dissect the specific role of the D2R in particular cell-types, brain regions and/or times.

"Concepts of Rationality"

Alejandro Kacelnik
University of Oxford, UK

Neuroscience aims at understanding, predicting and modifying action either by identifying underlying mechanisms or by making inferences from the hypothetical goals of the actor. Both approaches must eventually converge, but it seems unlikely that either one will replace the other any time soon. As a behavioural ecologist, I spend much of my time engaged in the second approach, using optimality concepts to predict the behaviour of animals facing ecologically realistic problems, and then testing and modifying these predictions by means of behavioural experiments. One over-arching concept in the behavioural ecologist's tool-kit is rationality: for functional inferences to be effective, it must be assumed that the behaviour of organisms keeps some logical and stable relation to its consequences. Rationality, however, is used in very different ways across disciplines. In psychology behaviour is deemed to be rational if the process by which it emerges involves reasoning (rather than it being emotionally or unconsciously driven). In economics, rational actors are those whose different decisions show consistency in maximising some function (utility), regardless of the process of decision or the properties of the utility function. Finally, in evolutionary biology and behavioural ecology rationality is defined as the maximisation of evolutionary advantage, namely the maximisation of the spread of the actor's genes in its population. I will survey and discuss these concepts, and illustrate them with research examples from the study of decision-making. Reference: Kacelnik A., (2006) Meanings of rationality. In: Rational Animals? Eds: M. Nudds and S. Hurley. pp. 87-106. Oxford University Press, Oxford

"NCAM, an alternative signaling receptor for GDNF in hippocampal and cortical neurons"

Gustavo Paratcha
Instituto de Biología Celular y Neurociencias Prof. E. De Robertis
Facultad de Medicina, UBA, Buenos aires, Argentina.

Glial cell line-Derived Neurotrophic Factor (GDNF) signals through the canonical signaling receptor Ret and a glycosyl-phosphatidylinositol-anchored co-receptor GFR-1. Signaling by GDNF has been shown to be more complex than originally assumed. The discrepant expression between GFR- and Ret has suggested the existence of alternative signaling-transducing GDNF receptors. In recent years, we show that the Neural Cell Adhesion Molecule (NCAM) can function as a novel signaling receptor for GDNF ligands. Association of NCAM with GFR-1, downregulates NCAM-mediated cell adhesion and promotes high-affinity binding of GDNF to NCAM, resulting in rapid activation of cytoplasmic protein tyrosine kinases Fyn and FAK in cells lacking Ret. In hippocampal and cortical neurons, GDNF stimulates axonal growth and presynaptic maturation via binding to NCAM and independently of Ret. This evidence reveals an alternative pathway for GDNF signaling that does not require the Ret receptor.

"Formation of neuronal synapses by GDNF-induced cell adhesion"

M. Fernanda Ledda
Instituto de Biología Celular y Neurociencias, Facultad de Medicina, UBA, Buenos Aires, Argentina.

The formation of neuronal synapses involves the precise assembly of the machinery responsible for neurotransmitter release at the presynaptic side and recruitment of neurotransmitter receptors to the postsynaptic density (PSD). Recent evidence indicates that cell adhesion molecules (CAMs) participate prominently in the key steps of synapse formation, inducing trans-synaptic adhesion and promoting an accurate alignment of pre- and postsynaptic terminals. The glial cell line-derived neurotrophic factor (GDNF) receptor GFR-1 is enriched at pre- and postsynaptic terminals in hippocampal neurons, suggesting that it has a role in synapse formation. We demonstrate that GDNF triggered trans-homophilic binding between GFR-1 molecules and cell adhesion between GFR-1-expressing cells. This represents the first example of a cell-cell interaction being mediated by ligand-induced cell adhesion molecule (LICAM). In the presence of GDNF, ectopic GFR-1 induced localize presynaptic differentiation in hippocampal neurons, as visualized by clustering of vesicular proteins and neurotransmitter transporters, and by activity-dependent vesicle recycling. Presynaptic differentiation was markedly reduced in neurons lacking GFR-1. Gdnf mutant mice showed reduced synaptic localization of presynaptic proteins and a significant decrease in the density of presynaptic puncta, indicating a role for GDNF signaling in hippocampal synaptogenesis in vivo. We propose that GFR-1 functions as a LICAM to establish precise synaptic contacts and induce presynaptic differentiation.

"Transmission of Wnt signals during synapse development"

Vivian Budnik
Department of Neurobiology, University of Massachusetts Medical School, Worcester, MA, USA

Wnts play pivotal roles during development and in the mature nervous system. However, the mechanisms by which Wnt signals are transmitted between cells have remained a poorly understood process, given that Wnt proteins are tightly bound to membranes and not readily diffusible in the extracellular milieu. Here we demonstrate a novel mechanism for synaptic Wnt signal transmission through presynaptic release of exosome-like vesicles containing the Wnt-binding protein Evenness Interrupted/Wntless/Sprinter (Evi/Wls/Srt). We show that at the Drosophila larval neuromuscular junction (NMJ) Evi is required for the secretion of the Wnt-1 homolog, Wingless (Wg). Evi is released from presynaptic terminals in the form of a vesicle, and this vesicular release is required for Wg signaling at the postsynaptic muscle cell during synapse development. We also show that Evi acts cell-autonomously in the postsynaptic Wnt-receiving cell to target dGRIP, a dFrizzled-2 (DFz2), Wg-receptor-interacting protein to postsynaptic sites. Upon Evi loss of function, dGRIP is not properly targeted to synaptic sites, which interferes with Wnt signal transduction in the postsynaptic cell. These findings uncover a previously unknown cellular mechanism by which a secreted Wnt is transported across synapses by Evi-containing vesicles, and reveal novel functions of Evi in both the Wnt-producing (the motorneuron) and the Wnt-receiving (the muscle) cell

"Supporting Cells Regulate Synapse Formation In The Inner Ear"

Joshua Murtie[1], Maria Gómez-Casati[1], Carlos Rio[1], Konstantina Stankovic[1],[2], M. Charles Liberman [2] , Gabriel Corfas[1]

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Despite that all vestibular hair cells and their associated sensory nerve terminals are surrounded by supporting cells (SCs), the roles of the SCs in the postnatal vestibular epithelia remained poorly understood. Recent evidence indicates that SCs have many characteristics of glia, including expression of erbB receptors. Furthermore, vestibular sensory neurons express NRG1, an erbB receptor ligand. Since we have and others found that NRG1-erbB signaling is a key regulator of neuron-glia interactions, we tested if erbB signaling in SCs of the vestibular sensory epithelium is important for cell-cell interactions in the vestibular epithelium using a transgenic mouse line in which erbB receptor signaling in these cells is blocked by expression of a dominant-negative erbB receptor (DN-erbB4).

At P21, DN-erbB4 mice displayed behaviors consistent with vestibular dysfunction including ataxia, spinning behavior, and inability to swim. Evoked potential recordings showed that vestibular function was severely affected, even though macular epithelia were normal in size and general structure. FM1-43 dye uptake and NFH staining were also normal in mutant mice, indicating that hair cell mechano-transduction and afferent innervation were normal. However, synaptic site numbers (defined as the colocalization of RIBEYE and GluR2/3 staining) were dramatically reduced, suggesting a synaptic defect. Interestingly, the synaptic alterations were accompanied by a dramatic reduction in BDNF expression in SCs. This is quite remarkable because it has previously been shown that BDNF is essential for normal inner ear development, but there was no evidence that it is also required for synaptogenesis. To clarify its role in the post-natal ear, we developed transgenic lines with inducible BDNF knockout or overexpression specifically in SCs. BDNF knockdown in SCs resulted in vestibular dysfunction and reduced synapse density in the utricle similar to that found in DN-erbB4 mice. Correspondingly, forced expression of BDNF by SCs of DN-erbB4 mice rescued the phenotype, including behavioral, physiological, and morphological measurements. Together, these results

indicate that supporting cells contribute to the formation/maturation of synapses in vestibular epithelia and that this contribution is mediated by reciprocal signals between sensory neurons and SCs involving NRG1-erbB and BDNF-TrkB signaling.

"Sleep, wake and plasticity in thalamocortical networks "

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Slow-wave sleep (SWS) is characterized by large amplitude and slow EEG waves. Cortical neurons are hyperpolarized and silent during EEG depth positive waves and are depolarized and fire spikes during EEG depth negative waves. During both waking state and REM sleep EEG activities reveal activated pattern and majority of cortical neurons is depolarized and fire spikes. Thalamocortical neurons are hyperpolarized during SWS and depolarized during REM sleep. Recording from anesthetized animals suggest that during depth-positive EEG wave thalamocortical neurons are silent and during EEG depth negativity they generate multiple IPSPs occasionally accompanied with rebound spike bursts. Recordings from reticular-thalamic neurons suggest that their activity resembles activity of cortical neurons. Therefore, all neurons within thalamocortical system oscillate between silent and active states during SWS and are likely active during other states of vigilance. It is well known that sleep contributes to memory formation. How synaptic plasticity induced by sleep affects memory formation remains unknown. Our current studies demonstrate that field potential responses induced by sensory pathway stimulation were more variable in amplitude during SWS than those occurring during REM sleep or waking state. Importantly, after a period of SWS the N1 responses during wake were enhanced in amplitude, suggesting that network responses were facilitated by sleep. Intracellular recordings confirmed that synaptic responses during SWS were more variable in both amplitude and latency than in the two other states. During SWS the responses varied from large amplitude to failures. Synaptic responses during waking state that followed a period of SWS were enhanced as compare to responses that occurred during prolonged waking period. Using minimal intensity stimulation in vitro, we found that stimulation with patterns obtained during SWS and lasting over 10 min induces either synaptic facilitation or

depression that lasts over 1 hour. We conclude that silent states of SWS dampen steady state synaptic states (depression or facilitation) induced by waking pattern of activity. This synaptic reorganization likely mediates memory formation. Supported by CIHR, NIH, FRSQ and NSERC

"Mechanisms of generation and control of slow (<1Hz) and fast (15-80 Hz) rhythms"

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The cerebral cortex is a neuronal network where excitatory and inhibitory neurons have recurrent connections. This network generates oscillatory rhythmic activity at different frequencies including slow (< 1Hz) and fast (15-80Hz) oscillations. This emerging patterns of activity are the result of the integration of intrinsic neuronal properties and interneuronal connectivity, and therefore its analysis reveals information about the underlying network and its functionality. These oscillations were initailly described in the cerebral cortex in situ (Steriade et al., 1993; Steriade et al., 1996). However, in the cerebral cortex in vitro contains enough cortical network to generate not only slow rhythms (Sanchez-Vives and McCormick, 2000), but also fast ones (Compte et al., 2008). This is relevant because it means that the local circuitry is enough to generate activity like the one that occurs during slow wave sleep that can be recorded in extense cortical areas (Massimini et al., 2004). Similarly, the local circuitry is enough to generate beta and gamma frequencies, generally associated to cognitive tasks (Gray and Singer, 1989; Fries et al., 2001). This locally generated activity can be incremented and synchronized at long distances in vivo (Gregoriou et al., 2009), even when its celular basis are probably the same as in the cortical slices.

During this presentation I will discuss different mechanisms participating in the generation of cortical rhythms, such as the interplay between excitation and inhibition (Compte et al., 2009), or the different emerging patterns in different cortical areas where the excitatory/inhibitory balance is different (Sanchez-Vives et al., 2008). The impact that different

factors have on the activity generated by a local neuronal network are often unpredictable and counterintuitive. For this reason the combined experimental and computational approach, is of great interest. The interaction between the experimental results and those from model of the cortical network (Compte et al., 2003) will be discussed.

Supported by MICINN (Spain).

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"Entrained rhythmic activities of neuronal ensembles as perceptual memory of time interval"

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The ability to process temporal information is fundamental to sensory perception, cognitive processing and motor behaviour of all living organisms, from amoebae to humans. Neural circuit mechanisms on the basis of neuronal and synaptic properties have been shown to process temporal information over the range of tens of microseconds to hundreds of milliseconds. How neural circuits process temporal information in the range of seconds to minutes is much less understood. Studies of working memory in monkeys and rats have shown that neurons in the prefrontal cortex, the parietal cortex and the thalamus exhibit ramping activities that linearly correlate with the lapse of time until the end of a specific time interval of several seconds that the animal is trained to memorize. Many organisms can also memorize the time interval of rhythmic sensory stimuli in the timescale of seconds and can coordinate motor behaviour accordingly, for example, by keeping the rhythm after exposure to the beat of music. Here we report a form of rhythmic activity among specific neuronal ensembles in the zebrafish optic tectum, which retains the memory of the time interval (in the order of seconds) of repetitive sensory stimuli for a duration of up to ~20 s. After repetitive visual conditioning stimulation (CS) of zebrafish larvae, we observed rhythmic post-CS activities among specific tectal neuronal ensembles, with a regular interval that closely matched the CS. Visuomotor behaviour of the zebrafish larvae also showed regular post-CS repetitions at the entrained time interval that correlated with rhythmic neuronal ensemble activities in the tectum. Thus, rhythmic activities among specific neuronal ensembles may act as an adjustable 'metronome' for time intervals in the order of seconds, and serve as a mechanism for the short-term perceptual memory of rhythmic sensory experience.

"Activity-dependent neurotransmitter respecification: novel neuroplasticity"

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Appropriate specification of neurotransmitters during embryonic development is essential for the function of circuits, and transcription factor cascades establish default transmitter phenotypes (Lee & Pfaff, 2001). Environmental influences then modulate transmitter expression through early calcium-dependent electrical activity, increasing or decreasing the number of neurons expressing a particular transmitter by as much as fifty percent (Borodinsky et al., 2004; Dulcis & Spitzer, 2008).

We have identified a molecular mechanism that links endogenous embryonic calcium spike activity with an intrinsic genetic pathway to specify neurotransmitter choice in the embryonic nervous system. Early activity modulates transcription of the GABAergic/glutamatergic selection gene tlx3 and requires a variant cAMP response element (CRE) in its promoter. The cJun transcription factor binds to this CRE site, modulates transcription, and regulates neurotransmitter phenotype through its transactivation domain. Calcium signals through cJun N-terminal phosphorylation, integrating activity-dependent and intrinsic neurotransmitter specification. This mechanism provides a basis for early activity to regulate genetic pathways at critical decision points, switching the phenotype of developing neurons.

Because target-dependent regulation also plays important roles in neuronal development we have used a neuron-muscle co-culture system to investigate the impact of muscle targets on transmitter specification. Neuron-muscle contact reduces expression of the non-cholinergic transmitters, GABA, glycine and glutamate, while having no effect on choline acetyltransferase (ChAT) expression. Muscle activity is necessary for this target-dependent reduction of non-cholinergic transmitter expression. In addition, co-culture with muscle cells suppresses early spontaneous calcium spike activity in neurons and the presence of muscle cells abolishes activity-dependent transmitter specification. These results demonstrate that target-dependent regulation can be crucial in establishing neurotransmitter phenotypes and altering early neuronal excitability. Once neurons have made contact with their targets, the influence of target-derived factors overrides control by early activity.

Acknowledgements: This work was supported by NS15918 and MH074702 from the NIH.

"Turning sensation into perception across cortex"

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Investigations in several sensory systems have shown how neural activity represents the physical parameters of sensory stimuli in both the periphery and central areas of the brain. This knowledge has paved the way for new questions that are more closely related to cognitive processing. For example, are the neural representations of sensory stimuli related to perception? In this respect, it has been shown that quickly adapting (QA) neurons of the primary somatosensory cortex (S1) are directly involved in frequency discrimination of vibrotactile stimuli. But exactly which components of these neurons' stimulus-evoked responses are associated with the discrimination is not known. Most of the QA neurons of S1 show phase-locked responses to the periodic mechanical sinusoids, in the form of single spikes or bursts of spikes. This suggests that discrimination could be based on observing the temporal intervals between responses to each stimulus period. However, about one-third of the QA neurons in S1 also have a firing rate, averaged over the duration of a stimulus that is a function of the periodic stimulus frequency, with higher firing rates in response to higher stimulus frequencies. Thus, an observer of the stimulus-evoked activity in the QA neuronal population of S1 could discriminate between periodic vibrotactile stimuli either by comparing the precise temporal intervals between spikes or by comparing the overall spike rates elicited by the two stimuli. In this talk, I will address the problem of the neural code(s) for perceptual discrimination by analysing the responses of single neurons in S1 and higher cortical areas of trained monkeys while they discriminated between two consecutive vibrotactile stimuli. The results suggest that a firing rate/spike count code covaried in S1 and higher cortical areas with the psychophysical performance where past an current sensory information are combined, such that a comparison of the two evolves into a perceptual decision.

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Young Investigators abstracts

Neurochemical circuits involved in body sodium balance regulation

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Changes in body water/sodium balance are tightly controlled by the central nervous system (CNS) to avoid an abnormal cardiovascular function and develop of pathological states. This process of sensory integration takes place in different nuclei, with diverse phenotype and at different levels of the CNS. The aim of the present work was to study the specific neurochemical groups, their roles, their connections and the associated endocrine responses during body sodium depletion or sodium overload conditions. For this purpose we combined the immunohistochemical detection of different neurotransmitters, a retrograde transported dye and a marker of neural activity. We have also analyzed the firing frequency changes employing "in vivo" single-unit extracellular recording. Our main results demonstrated that in body sodium depletion states the serotonergic cells of the dorsal raphe nucleus (DRN) are activated after body sodium status was reestablished, independently of the concentration of the NaCl consumed, suggesting that this system is involved in the inhibition of sodium appetite under conditions of satiety. In contrast, the paraventricular and supraoptic oxitocinergic neurons were activated, and the oxytocin plasma levels increased only after hypertonic NaCl intake, in both depleted and nondepleted animals, suggesting that this system is involved in the processing of hyperosmotic signals. Our hodological results provide insight into how the different neurochemical groups form a neural network that regulates body fluid balance showing the main integratory nuclei involved in the satiety phase of sodium appetite. Finally, the electrophysiological experiments may allows us to confirm in an "in vivo" model, that the DRN serotonergic neurons increases their firing frequency during an increase in systemic sodium concentration and osmolality, possibly to modulate sodium and water intake/excretion and avoid an extracellular volume expansion.

Contrasting role of octopamine in appetitive and aversive learning in the crab Chasmagnathus

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Biogenic amines are implicated in reinforcing associative learning. Octopamine (OA) is considered the invertebrate counterpart of noradrenaline and several studies in insects converge on the idea that OA mediates the reward in appetitive conditioning. However, it is possible to assume that OA could have a different role in an aversive conditioning. We pharmacologically studied the participation of OA in two learning processes in the crab Chasmagnathus granulatus, one appetitive and one aversive. Our results demonstrate that the role of OA is divergent in these two types of learning. It is shown that the aversive memory is impaired by an OA injection applied immediately or 30 minutes after the last training trial. By contrast, the appetitive memory is blocked by OA antagonists epinastine and mianserine, but enhanced by OA when injected together with the supply of a minimum amount of reinforcement. Finally, double-learning experiments in which crabs are given the aversive and the appetitive learning either successively or simultaneously, allow us to study the interaction between both types of learning and analyze the presumed action of OA. We found that the appetitive training offered immediately, but not one hour after an aversive training, has an amnesic effect on the aversive memory that mimics the effect and the kinetic of an OA injection. These findings lead to a novel scenario of OA action in learning and memory, showing that it would act differently in memory processes of opposite signs.

What pixels do and do not tell about colocalization in fluorescence microscopy: applications in neuroscience

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The subcellular localization of proteins and cellular structures is crucial for their function and regulation and can be assessed by fluorescence labeling and microscopy. The colocalization of two or more markers within the cell is defined as an overlap in the physical distribution of the molecular populations within two or three-dimensional space, which may be complete or partial. Analysis tools do not necessarily fit all circumstances as cells contain a plethora of structures of multiple morphologies, from linear elements of the cytoskeleton, punctuate and isotropic compartments such as vesicles, endosomes or vacuoles, to more complex forms such as Golgi and the network-like endoplasmic reticulum. Analysis should be able to discriminate real colocalization from the random localization of two free molecules in the same compartment. The certainty of the physical dimensions and location of small objects in the two-dimensional and even more in the three-dimensional space is subject to the limits of resolution in optical microscopy. Whether two fluorochromes are located on the same physical structure or on two distinct structures is sometimes hard to estimate. Indeed, it is difficult to endeavor whether a protein is localized to mitochondria or Golgi due to the small size of these organelles, particularly when the protein has a widespread distribution within the cell. We introduce a novel statistical approach that quantifies colocalization in any region of an image without the bias of visual interpretation in a variety of cellular systems with different colocalization extent. With this method we were able to infer different mechanisms that govern key processes in neuronal pathology as Parkinson's disease and in neuronal growth and survival as mediated by NGF receptors, by accurately determining the localization of key molecules in definite organelles.

Tagging and Capture: A general mechanism of long term memory formation.

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The understanding of the mechanisms underlying learning and memory processes has been one of the largest challenges of the neuroscience during the last century. Interestingly, despite daily life memories are formed among some of multiple intertwined learning events, little is known about the mechanism involved in their interactions.

At this time, using different hippocampus-dependent and one hippocampus-independent learning tasks, we show that in rats subjected to weak training protocols that induce solely short term memory (STM), long term memory (LTM) is promoted and formed only if training sessions took place in contingence with a novel, but not familiar experience occurring during a critical time window around training. This process requires newly synthesized proteins induced by novelty and not only evidences how different learnings are able to interact, but also reveals a general mechanism of LTM formation which begins with the setting of a "learning tag" established by either a weak or a strong training.

Here, we show the first comprehensive set of evidences indicating that a behavioral tagging process, analogue to the electrophysiological synaptic tagging and capture process and sharing tag properties like a transient lifetime, independence of protein synthesis and specificity of input, is acting in different learning tasks, dependent of different brain structures, suggesting it as a general mechanism of long term memory formation.

Muscle Nicotinic Receptors in Nematodes

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Nicotinic acetylcholine receptors (AChRs) are pentameric neurotransmitter-gated ion channels that mediate synaptic transmission in both vertebrates and invertebrates. Caenorhabditis elegans is a model of parasitic nematodes and has emerged as a model organism for studying the nervous system. C. elegans has one of the largest AChR subunit families known. Nevertheless, the composition and roles of AChRs in C. elegans muscle remain to be resolved. Nematode muscle AChRs are of interest as they are targets for anthelmintic drugs.

By using single-channel and whole cell recordings of in vitro differentiated C.elegans muscle cells, we analyzed the activation properties of nematode levamisole-sensitive AChR (L-AChR). Our results revealed that the widely used nematocide drugs, levamisole, pyrantel and morantel, are agonists 5 to 10-fold more potent than the neurotransmitter ACh. We demonstrated that UNC-63, UNC-38, UNC-29, LEV-1 and LEV-8 subunits assemble into a single L-AChR, being the first three essential for receptor function throughout development. Although LEV-1 is preferentially incorporated into L-AChRs, the lack of this subunit allows the expression of functional receptors with different kinetics. In addition, we found that LEV-8 also acts as an accessory subunit, and plays a key role in the desensitization of L-AChRs.

We studied a strain with impaired locomotion in which the UNC-63 subunit carries a mutation (C151Y) that mimics the one observed in a congenital myasthenic syndrome (CMS) patient. This mutation reduces expression, the channel open probability and the opening rate of L-AChRs, similar to the activation profile reported for the human CMSs. Moreover, drugs used for treatment of these disorders partially rescue the phenotype of the mutant worms. Therefore, we validate this strain as an invertebrate model for human CMS.

These studies contribute to the understanding of molecular mechanisms underlying functional diversity of nAChRs and offer an excellent strategy for screening novel therapeutic agents.

Aβ causes membrane perforations in hippocampal neurons.

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The working hypothesis of Alzheimer´s Disease (AD) is that excess Aβ either i) binds to membrane receptors affecting their functions, ii) interferes with signaling cascades or iii) directly disrupts neuronal membranes causing pore formation leading to alterations in ionic homeostasis. Although the latter is an attractive hypothesis because it could explain several effects of Aβ on brain neurons, it has not been demonstrated to occur in brain neuronal membranes. In the present study, we found that synthetic Aβ aggregates were able to localize in synaptic regions and increase intracellular Ca2+ by a pore forming mechanism. Patch clamp experiments in cell-attached mode using Aβ (500-1000 nM) inside the patch pipette showed that Aβ has a rapid, concentration-dependent and potent perforating property in neuronal membranes. Analysis of the charge transferred during the capacitative response indicates that the effect of Aβ was similar to those of gramicidin and amphotericin, two other peptides commonly used to form perforates in neurons (Aβ1-40 = 219±22, Aβ1-42 = 250±24, gramicidin = 235±23, amphotericin = 210±15 fC, n=15). Cell imaging experiments using 500 nM Aβ and ethidium bromide (EtBr, 5 µM) in the patch pipette showed the presence of EtBr inside the neurons after ~ 20 min, thus providing direct evidence that small molecules can pass through these Aβ perforations. Interestingly, application of a mini-peptide (Na7 or Na4a, 20 µM) designed to block changes in membrane conductance associated with the amyloid pore caused a strong blockade of all these Aβ effects, supporting the idea that Aβ induces perforations in brain neurons and that they can be pharmacologically blocked.

In conclusion, the present results indicate that Aβ perforations were critical to induce an increase in intracellular calcium in hippocampal neurons. Furthermore, these results strongly suggest that amyloid pores could be involved in synaptic dysfunction mediated by Aβ aggregates.

Funding. F.J.S funded by Ph.D. fellowship from CONICYT. This work was supported by Ring of Research PBCT ACT-04 (L.G.A. and C.O.) and CIE-05 (L.G.A.)

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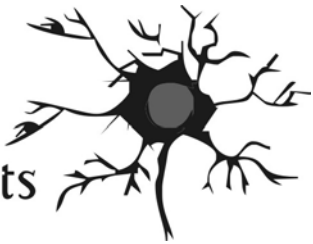

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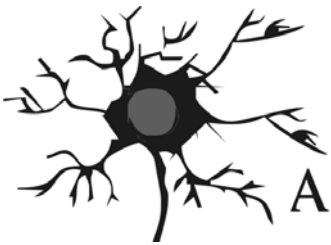

Abstracts

Poster Number (1) Session 1

ANXIOLITIC EFFECTS OF ETHANOL IN PREWEANLING RATS MEASURED BY MEANS OF THE LIGHT-DARK PARADIGM.

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One of the properties of acutely administered ethanol is the reduction of anxiety. In infant and adult rats it has been shown that ethanol has anxiolytic effects in a variety of paradigms. The light-dark test is a paradigm usually utilized to evaluate the effects of anxiolitic drugs (including ethanol). This test is based on the innate aversion of rodents to brightly illuminated areas.The goals of the present study were: a) to evaluate the sensitivity of this test to the anxiolitic effects of ethanol in preweanling rats, and b) to analize whether ethanol intake in infant rats varies as a function of whether the intake test was conducted in a brightly or dark condition. In Exp 1, 14-day-old rats were given 0 or 0.5 g/kg ethanol 5 minutes before testing in the light-dark test. In Exp 2 preweanling rats were tested in terms of ethanol (6) or water intake in a brightly or in a dark environment during two consecutive days. In Exp 1 ethanol increased the amount of time that pups expent in the brighly area. This result indicates that this technique is useful to evaluate anxiolitic effects in infant rats. Additionally this result is consistent with previous studies showing anxiolitic effects of ethanol in preweanling rats. In Exp 2 rats tested in the light condition consumed more ethanol (relative to water) than animals tested in the dark condition, indicating that the anxiolitic effect of ethanol may contribute to the acceptance of the drug in preweanling rats.

EXPLORING VISUAL FEEDBACK PARAMETERS THAT DETERMINE THE PERCEPTION OF A DISTORTED SPACE

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Vision is an important information source when moving in a new environment. When a motor task is initiated, an original motor plan is compared with available feedback, to calculate an error. This process enables us to modify movements in order to achieve a certain goal. We are performing an experiment in which the feedback is manipulated experimentally in order to mismatch actual movements (e.g. linear transformations). This experiment aims to assess which visual feedback distortions are crucial for motor error correction and distortion perception. When the distortion is perceived, motor corrections are observed. On the other hand, subjects can perceive the error either as its own variability or as an experimental manipulation depending on its characteristics (e.g. magnitude of the distortion). We manipulate visual feedback in a virtual reality drawing setup, based on a mirror and a Wacom digitizing tablet. This device has a high spatial resolution (0.01mm) and sample rate (200Hz). In the experiment the subjects trace a figure without being able to see their drawing hand and then report if they perceived a feedback distortion. Error correction is obtained from drawing trajectories in time. We expect to find critical geometrical parameters (eigenvectors and eigenvalues of the linear transformations) of visual feedback distortions that determine motor error correction and perception of distortion.

Poster Number (3) Session I

BEHAVIORAL TAGGING IS A GENERAL MECHANISM OF LONG-TERM MEMORY FORMATION

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It is currently proposed that memories are stored by stable changes in synaptic weight modifying the activity of specific neuronal circuits. Then, synapses activated by learning will require the supply of new plasticity-related proteins (PRPs) for the formation of long term memory (LTM). In consequence, there should be a mechanism limiting the action of PRPs to recently activated synapses. To address this biological problem, the synaptic tagging and capture hypothesis postulated that a transient local synaptic tag is set at those recently activated synapses where PRPs will be specifically captured. Using two different behavioral events, it was possible to separate tagging from PRP synthesis. We demonstrated by using one hippocampus-dependent learning task that, in rats subjected to weak training protocols that induce only short term memory, LTM is promoted and formed when training sessions took place in contingence with a novel experience occurring during a critical time windows around training. The process named "behavioral tagging" requires protein synthesis induced by novelty. Here, we decided to study whether this process can be observed using other hippocampus-dependent (spatial object recognition) and an hippocampus-independent (conditioned taste aversion) tasks. We found that behavioral tagging operates in different hippocampus- and cerebral cortex-dependent learning tasks with different behavioral features, suggesting that it represents a general mechanism in LTM formation. These findings show the first comprehensive set of evidences indicating the existence of a behavioral tagging process, sharing synaptic tag properties like transient lifetime, independence of protein synthesis and specificity of input.

Cognition, Behavior and Memory

Poster Number (4) Session 1

LOL, OR JUST :). DISTANCE EFFECT DURING CATEGORIZATION AND COMPARISON OF FACIAL EMOTIONAL EXPRESSIONS IN PEOPLE WITH AUTISM SPECTRUM DISORDERS

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Behavioural studies suggest that people with Autism Spectrum Disorders (ASD) are impaired in facial emotional expression processing. Here, we tested the ability to accurately evaluate the intensity of another individual's emotional expression by investigating the putative existence of a distance effect in groups of typical and ASD adult subjects. The experimental task involved categorization and analogical comparison of various intensities of facial emotional expressions. Distance between intensities of facial emotional expressions and stimulus visibility were manipulated and effect of these parameters on objective and subjective measures of performance were investigated. Both groups showed a similar distance effect in the high stimulus visibility condition. However, this effect was observable in subjective measures of performance only in the typical group, suggesting abnormal introspective estimate of performance in ASD. For the typical group, a distance effect was still observable in the low visibility condition, but with a stronger effect on subjective confidence. This suggests that an analog comparison was still made but that the internal representations involved in this comparison was barely accessible to the conscious monitoring system. By contrast, the ASD group did not show any distance effect in the low visibility condition. Low visibility thus seem to affect ASD subject's ability to categorize and evaluate intensity of facial emotional expressions, which supports the hypothesis of an abnormal uneffortful and implicit understanding of other's intensity of emotion in everyday social interactions. cabalangofeld@yahoo.com.ar

Poster Number (5) Session I

A POSSIBLE ROLE OF MEDIAL PREFRONTAL CORTEX 5-HT2AR IN THE RESOLUTION OF MEMORY TRACE INTERFERENCE DURING RETRIEVAL

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The medial pre frontal cortex (mPFC) has been involved in several higher order functions including behavioral flexibility, attention, inhibitory control, decision making, goal-directed behaviors, interference and response selection. The interference theory refers to the idea that forgetting occurs because the recall of certain items interferes with that of other items. Thus, the retrieval of two memory traces that share certain neuronal circuits will activate the PFC to prevent interference. The result would be the subsequent forgetting or suppression of one of the traces in favor of the other one. 5-HT modulates several responses like mood, impulsivity, aggression and cognition. It works through the activation of 14 receptors. In particular, the mPFC expresses high levels of 5-HT2a receptor (5-HT2aR), which have been the focus of intense study as a key player in the modulation of cortical activity. It is not clear which is the role of the serotoninergic system and the 5-HT2aR in particular during response selection and interference processes. We studied the possible role of the 5-HT system and the 5-HT2aR in interference processes using different versions of the novel object recognition task (NOR). In all the experiments rats received local injections of the selective 5-HT2aR antagonist, MDL 11,939, 15 minutes before the test phase. Animals injected with MDL 11, 939 showed deficits in temporal order NOR with no changes in attention or in a single memory trace NOR. We also did an object in context recognition test, in which blockage of 5-HT2aR prevented the mPFC to make a suitable response selection, suggesting that mPFC is important when there is competition of memory traces to recall the more relevant one.

Cognition, Behavior and Memory
Poster Number (6) Session 1

PAST AND FUTURE SPATIAL REPRESENTATION OF HIPPOCAMPAL NEURONS DURING SLEEP

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The ability to anticipate future rewards or threats is crucial for survival. The activity of hippocampal neurons encodes and predicts spatio-temporal features of regular environments. This allows the hippocampus to be involved in the formation of episodic memories, including the sequential ordering of events. Consolidation of newly acquired memories involves neuronal reverberation during sleep. However, it is unclear whether neuronal ensemble simulations of future events occur during sleep. To address this issue, the present study assessed the ability of hippocampal neurons to predict, during sleep, the reward location in an ordered changing spatial task. Through the implant of multielectrode arrays, we recorded the activity of CA1 neuronal ensembles in a pre-trained rat. After sleeping in the Sleep-box for half an hour, mildly food-deprived rat were put in the center of a cross maze and allowed to search for a reward pellet. After each sleep cycle the reward target was repositioned to the next arm, according to a clockwise sequential order. Template matching algorithm based on Pearson correlation was used to detect pattern similarity between matrices of neuronal ensemble activity. Our preliminary results suggest higher Pearson correlation between sleep and the subsequent arm than sleep and the previous arms. This indicates that hippocampus is involved with future event prediction. Further investigation of the data is ongoing.

Poster Number (7) Session I

ERK ACTIVATION INDUCED BY FEAR CONDITIONING IN ETHANOL WITHDRAWN RATS: MODULATION BY MK-801

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The extracellular signal-regulated kinase (ERK) pathway has been shown to be involved in drug addiction and memory formation. This pathway is regulated by NMDA receptor activation. We have shown that withdrawal from chronic ETOH administration results in a clear enhancement of contextual fear conditioning. In order to explore the neural substrates and the potential mechanism involved in the increased contextual fear response we examined: 1) the ERK1/2 activation in the central (CeA) and basolateral (BLA) nuclei of the amygdala and in the dorsal hippocampus (dHip) and 2) the effect of NMDA receptor antagonist MK-801 on fear conditioning and ERK activation in ETOH withdrawn rats. Male Wistar rats made dependent via an ETOH-containing liquid diet (6 v/v) for 14 days. Rats were injected with MK-801 (0.1 mg/kg ip) 30 min prior to contextual fear conditioning on day 3 of ETOH withdrawal. Half of the rats were sacrificed for Western blot assay at different time points after fear conditioning and the other half was behaviourally evaluated in the conditioned context 24 h later. High basal levels of pERK1/2 were found in CeA and dHip from ETOH withdrawn rats. ERK activation was significantly increased both in control (60 min) and ETOH withdrawn rats (30 and 60 min) in BLA after fear conditioning. MK-801, at a dose that had no effect in control rats, prevented the increase in ERK phosphorylation in BLA and attenuated the freezing response in ETOH withdrawn rats. These results suggest that the increased fear in ETOH withdrawn rats may be explained by changes in ERK1/2 phosphorylation that depend on NMDA receptor activation in BLA, a structure critically involved in the processing of emotional information.

Cognition, Behavior and Memory
Poster Number (8) Session 1

STRESS INDUCES BOTH ENHANCED ANXIETY AND INCREASED P35 EXPRESSION IN BASOLATERAL AMYGDALA: INFLUENCE OF MIDAZOLAM.

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Stress exposure has been widely related with the development of psychopathologies. Particularly an acute restraint session provokes an enhanced anxiety-like behaviour. We have previously shown that this excessive anxiety is related with an increase of p35 levels selectively in the Basolateral Amygdala (BLA). In the present work, we attempt to elucidate if prior midazolam (MDZ) administration, which normalizes stress-induced anxiogenic behaviour, prevents the increase on p35 expression induced by restraint. Adults Wistar rats (290-320 grs) received a dose of 0.5 mg/kg of MDZ i.p. or vehicle (VEH) and later on subjected to a 30 min restraint session. One day later, animals were behaviourally tested on the elevated plus maze (EPM). Another group of animals received a dose of 0.5 mg/kg of MDZ i.p. or vehicle (VEH) followed by the stressful experience. Thirty minutes after stress rats were sacrificed for the immunohistochemichal analysis of amygdalar nuclei. We found that prior MDZ administration prevents both the increase on p35 levels in BLA and the potentiation of the anxiety-like behavior induced by stress.

Poster Number (9) Session I

CONTROLLED RELEASE ALLOWS LONG-TERM TREATMENT WITH GABAPENTIN WITHOUT AFFECTING MEMORY RETRIEVAL

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After more than a decade, the long-term clinical treatment with the anticonvulsant-antinociceptive drug gabapentin (GBP) is still related to adverse cognitive side effects. The administration of a single dose of GBP immediately after training improves retention performance of mice in an inhibitory avoidance task, probably due to enhanced consolidation caused by disinhibition of central cholinergic pathways. On the contrary, when GBP is given twice a day during 7 days, retention performance is impaired. This effect would also involve cholinergic modulation, but inhibitory, and would be due to impairment of memory retrieval. In the present work we used a monolithic implant made of GBP-loaded poly(epsilon-caprolactone) matrices, which allowed the controlled release of the drug at doses similar to those given with the repeated twice-a-day injections, but without the fluctuations of plasma levels of the drug and allowing constant levels at least during 7 days. When implants were inserted in a subcutaneous pocket in the side of the mice, immediately after training in the inhibitory avoidance task, retention performance is improved, and when the insertion was delayed 3 h after training, performance was not affected. Hence, the facilitatory effect would be due to improvement of memory consolidation. These results could lead to a clinically relevant conclusion: maintaining stable plasma levels, GBP could be administered at a total dose similar to that given with the repeated injections, but without the impairment of memory retrieval, suggesting that some of the adverse cognitive effects observed in the clinical practice could be avoided by stabilizing plasma levels of the drug.

ACQUISITION OF A NEW TASK MIGHT IMPAIR MEMORY CONSOLIDATION OF AN INHIBITORY AVOIDANCE TASK IN MICE

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When a subject is exposed to successive different learning experiences, the novelty of the second experience can interfere the consolidation of memory of the first one. Novelty usually induces a quick habituation, reflected by the rapid decrease of responding to the new environment or situation. In this sense, the exposition of mice to the nose-poke habituation task (NPH, second learning task) after training on the inhibitory avoidance task (IA, first learning task), impaired retention performance on the IA, indicating an interference caused by the second learning situation.What is the reason for this interference To gain more insight on this question, in the present work we used the muscarinic antagonist scopolamine (SCOP), a drug already known to cause anterograde, but not retrograde amnesia at low doses. The dose of 0.5 mg/kg of SCOP given immediately after training on the IA task, did not affect retention performance, suggesting that consolidation of the IA is not affected. The same dose given 20 min before training on the NPH task, impaired performance, suggesting that it blocks acquisition of the NPH. When mice were trained in the IA task, received SCOP immediately after it, and 20 min later was exposed to the NPH task, retention performance on the IA was not impaired. These results could be suggesting that the blockade of the acquisition of the second task might be the critical step causing the anterograde amnesia induced by the novel learning situation.

Poster Number (11) Session I

EFFECTS OF AN AVERSIVE MEMORY ON THE REWARDING EFFECTS OF ETHANOL IN ETHANOL DEPENDENT RATS

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Stress has been shown to facilitate the rewarding effects of drugs of abuse including ethanol (ETOH). We have previously shown that retrieval of fear memory facilitates subsequent ETOH consumption in ETOH withdrawn rats. Given that the rewarding properties of ETOH might be involved in such increased ETOH intake, the effect of retrieval of fear memory on the rewarding properties of ethanol was assessed using the conditioned place preference (CPP) paradigm. Male Wistar rats were allowed to consume an ethanol-containing liquid diet (6 v/v) for 14 days. After 72 h of withdrawal, the pre-conditioning session for CPP was performed (10 min). The next day, one group of rats was exposed to 3 footshocks (0.4mA, 3s, 30 s intershock interval). The CPP conditioning began 24 h after fear training and rats received 4 saline and 4 ETOH pairings (1 g/kg, ip) on alternating days into the assigned CPP compartment for 8 min. One day after of the last ETOH injection, the contextual fear response was evaluated 2 h prior to the CPP test (10 min). Consistent with previous work, ETOH withdrawn rats showed an enhanced contextual fear response. ETOH produced neither CPP nor place aversion in both control and ETOH withdrawn non-fear trained rats. However, significant CPP for ETOH was induced following retrieval of contextual fear memory in ETOH withdrawn rats. These data suggest that an aversive memory can affect the motivational properties of ETOH in withdrawn rats.

ARE MUSCARINIC MECHANISMS INVOLVED IN LONG-TERM MEMORY STORAGE OR IN BEHAVIORAL EXPRESSION OF STORED MEMORIES

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In the crab Chasmagnathus, a strong training builds up a long-term memory which is mRNA - and protein synthesis-dependent. However, a weak training generates a memory with the same characteristics which is stored but not behaviorally expressed. The general hypothesis is that memory storage and long-term memory expression are mediated by different mechanisms. Muscarinic mechanisms are implicated in learning and memory processes in either vertebrates and invertebrates. In Chasmagnathus it was described that Scopolamine (SCP), a muscarinic antagonist, has an amnesic effect when it is administered either pre or post training, concluding that the memory storage is selectively regulated by a muscarinic mechanism. The aim of this project is to determine whether muscarinic mechanisms are involved in long-term memory storage or long-term memory expression. The hypothesis is that SCP administrated pre training would affect memory storage. On the other hand, SCP administrated post training would affect long-term memory expression. The possibility to facilitate the long-term expression of a non expressed memory during reconsolidation, allow us to distinguish between amnesia vs. lack of expression.

Poster Number (13) Session 1

COUPLING OF NEURAL ACTIVITY BETWEEN THE DENTATE GYRUS AND THE CA3 FIELD DURING MEMORY ENCODING AND RETRIEVAL

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Despite the intense research on the hippocampal involvement in memory formation, there are several open questions regarding the specific role of hippocampal subregions in the encoding and retrieval of different types of memories. The dentate gyrus (DG) is a subregion of the mammalian hippocampus characterized by its sparse axonal projections to CA3 field cells, the so-called mossy fibers (MF). It has been suggested that the DG may be responsible for pattern separation or orthogonalization of sensory information during the encoding of memories, but not during its retrieval [Treves & Rolls (1992) Hippocampus 2:189]. According to this model, the MF pathway would impose activity patterns in CA3 during encoding, while processing in CA3 during retrieval would be dominated by its direct inputs from the entorhinal cortex. To test this hypothesis, we set out to characterize the electrophysiological coupling between DG and CA3 during the encoding and retrieval of spatial memories. In order to assess simultaneously the spiking activity and local field potentials in the DG and CA3 regions, we performed chronic implants of staggered microelectrode arrays in the hippocampus of Long Evans rats. Behavior and neural activity were recorded during successsive explorations of an open field with and without novel objects. We expect the DG-CA3 coupling to be higher at the start of the first exploration session, declining thereafter in good correlation with the decrease in exploration. A spatial delayed match-to-sample task known to depend on the DG is also being implemented to assess the dynamics of the DG-CA3 coupling during short-term memory aquisition and retrieval.

ELECTROPHYSIOLOGICAL MARKERS FOR FREE WORD ASSOCIATIONS

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Since the times of Jung, word association experiments have been proposed as a tool to analyze and diagnose brain states. The underlying hypothesis of this method is that identifying structure in word associations may reveal the way we store and retrieve semantic memories, i.e. understanding the shape of semantic space. Previous work in our lab has established a metric to assess distances between words –based on regularities in text corpus - which can be used in experiments of word association. Other metrics developed to characterize semantic space rely on semantic relations, dictionaries and thesaurus. Many experimental works have investigated the goodness of these metrics to account for different psychophysical data, , but there has been very little physiology involved. We carried out free word association experiments, in which the subject is presented randomly in each trial one word from a list of the 100 more frequent nouns in Spanish. Subjects responded the first word that came into his/her mind. In order to have an insight into the electrophysiology involved in these tasks, during the whole experiment high-density EEG recordings were carried out.Our main aim was to understand which markers in the EEG covary with semantic distance. Our results show that 1) a sequence of components which unfold over 400 ms tightlylocked to simulus presentation, 2) a relatively early (300 ms) negative correlation between a phasic posterior response and distance, suggesting that the stronger the response evoked by the word, associations are shorter 3) a late, sustained and diffused region of positive correlations indicating a large-scale coherent state which might be a correlate of the distance of a semantic-association.

Poster Number (15) Session 1

GABAERGIC MODULATION OF MEMORY IN THE CRAB CHASMAGNATHUS

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It is well-known that memory processes such as consolidation and reconsolidation can be modulated by the GABAergic system. Hence, compounds that enhance the action of GABA impair these processes; while compounds that reduce the action of GABA enhance them. Extinction is a complex phenomenon but generally is regarded as a new learning that suppresses the original memory. The role of GABA on the extinction process is still on debate, but an increasing number of reports suggest the GABAergic system as the major player on the extinction memory. Thus, it's seems, that GABA plays different roles in consolidation and extinction. In the first process, it seems to be no more than an order-molecule; however, in the second one, it probably acts as the main principal component of the process. In our project, we propose that in Chasmagnathus granulatus the GABAergic system may be differentially regulated in both learning processes. To test this hypothesis, the first approach was to study the distribution and composition of the GABA receptors along the nervous system of the crab. Two techniques, western blots analysis and inmunohystochemistry were used to determine, for the first time, the localization and the composition of the GABAA-like receptors in the crab. The results obtained here suggest that it would be possible to combine the aforementioned techniques with pharmacological–behavioural procedures to test if the different learning processes could be differentially regulated by the GABAergic system.

Cognition, Behavior and Memory
Poster Number (16) Session I

TIME WINDOW REQUIRED TO ELICIT A FACILITATORY EFFECT OF PREVIOUS LEARNING OVER THE PERFORMANCE IN A DIFFERENT TASK

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The exposure in two consecutive days, for 3 minutes, to an Open Field (OF) exerted a facilitatory effect on the performance of Wistar rats in a Step Down Inhibitory Avoidance task (IA) (Snitcofsky et al., this session). It is well known that N-Mehyl-D-Aspartate receptors (NMDAR) are involved in synaptic plasticity and related functions, such as learning and memory. To evaluate the role of the NMDAR on this facilitation, we have investigated the effect of an i.p. injection of MK801 (0.07 mg/kg), a non-selective NMDAR blocker given 20 to 30 minutes before the OF test (second exposure), in adult male Wistar rats, on the performance in an IA task. Neither the MK801 injected nor the control group (injected with saline) showed the OF facilitatory effect in the IA performance. Although control animals reached the learning criteria in this task, while treated animals did not, there were not statistically significant differences. On the other hand, the same dose of MK801 injected 20 min before the IA training session, did not affect the OF facilitatory effect over this task. However, at variance with the data reported in the literature, this same dose of the antagonist given 20 min before IA training to rats without previous OF exposure, did not show any significant effect. Preliminary electrophysiologycal assays (Field potentials) in hippocampal brain slices corroborated that MK801 (20 µM) blocked LTP induction at the Schaffer collateral-CA1 cells synapse. In brief, we could not conclude whether the NMDAR is directly involved in this phenomenon, but there would be a relatively short time window lasting 30 to 40 min, when the facilitation is labile enough to be affected by "aversive manipulation" of the animals (injections). However, 20 minutes before training in the IA, the facilitation seems to be established, and neither MK801 nor the manipulation and injection modified this effect.

Poster Number (17) Session 1

DIFFERENTIAL EFFECT OF ISOLATION IN ADULTHOOD ON FRUSTRATION, ANXIETY AND PHYSICAL PAIN RESPONSES IN RATS.

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Previous research has demostrated that devaluation or omission of an expected reward has aversive properties, and suggest that the elicitated emotional state presents similar characteristics to anxiety responses and physical pain. Social isolation generates alterations in anxiety and pain reactions. Two experiments are presented. Their aims were to investigate the possible impact of isolation in adulthood on anxiety responses measured by the Elevated Plus Maze (EPM), sensibility to physical pain measured by the Hot Plate test (HP), and reactions to different situations of reward devaluation or omission in rats: the consummatory successive negative contrast (cSNC), the consummatory extinction (Ec), and the partial reinforcement effect on the incentive devaluation (PREID). In Experiment 1, sixty days old rats were randomly assigned to two housing conditions: grouped and isolated. The former were more active and showed less anxiety in comparison with the isolated ones in the EPM. Significant differences were not found in the cSNC, Ec and HP. In Experiment 2, isolated subjects presented less sensibility to physical pain in the HP, and no differences were found between conditions in the EPM and the PREID. As a whole, the results show that anxiety responses and sensibility to pain are affected by isolation, but reward devaluation and omission are not. The differences between physical and psychological pain and the implications of using isolation protocols at the frustration research are discussed.

FROM LOCAL TO GLOBAL: IDENTIFYING STRATEGIC SHIFTS OF ATTENTION AND GOALS IN A RAPIDLY CHANGING SETUP

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A challenge of current neuroscience is to understand the unfolding of largely superposed processes in daily life activity. How does a sequence of sensory-motors process in constant interaction organizes in coherent action allowing us to drive, run or do sports. Transforming a highly complex ethological situation such as, for example, a tennis match into a controlled environment which captures its critical features poses an interesting experimental challenge. To achieve this goal we motivate the utilization of experimental setups based on the structure of simply video games, in our case, a variant of the "Arkanoid". The principal experimental virtue of these designs is that, in spite of the small amount of relevant objects (which allows controlled and categorical measures in a relatively low dimensional space) it results in a dynamic sequence of goals and rewards and sequence of actions which resonates with our cognition – which might explain why these games are so addictive. We used an eye-tracker to parse motor action in discrete sequences. Do subjects follow moving objects or fixate to objectives And how does this change at different stages of the game We found that subjects explored the scene in accordance with different states of the game state. For instance, a very robust finding - of which players are completely unaware - is that when the ball goes up, ocular trajectories are dominated by fixations. On the contrary, when the ball goes, down trajectories are dominated by pursuits. This suggests a sequence of shifting from global (exploring fixations) to focused attention (precise tracking of the ball) depending on the urgency of immediate actions. We present follow up experiments to asses this hypothesis.

Poster Number (19) Session I

EFFECT OF LESIONS OF THE MEDIAL PALLIUM ON THE USE OF VISUAL CUES IN SPATIAL LEARNING IN AMPHIBIANS

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We are analyzing the neural mechanisms that rule the spatial learning, looking for common patterns potentially present in a common ancestor to several classes of vertebrates. It is known that the mammalian hippocampus is an important structure involved in spatial learning; but yet, its function in other vertebrates such as amphibians is unknown. Amphibians have an area supposed to be homologous to the mammalian hippocampus, the medial pallium. The main goal of the present work was to study the implication of this structure in a simple spatial orientation task. Eighteen partially dehydrated toads (Bufo arenarum) were divided in 3 groups: Medial pallium lesioned, Intact and Sham controls. Animals were daily trained in a plus maze for 10 sessions (3 trials per session) for the acquisition of a basic spatial orientation strategy: use of a visual cue to reach a container full of water (this reward was always associated with the visual cue in the maze). Animals of both control groups acquired the spatial orientation, but the lesioned animals never reach the goal. This result suggests that medial pallium is involved in basic spatial orientation strategies in amphibians and, therefore, it is possible that hippocampus and medial pallium be partially functional equivalents.

Cognition, Behavior and Memory
Poster Number (20) Session I

THE NMDA ANTAGONIST MK-801 BLOCKS STRESS-INDUCED REINSTATEMENT IN THE CONDITIONED PLACE PREFERENCE MODEL

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In previous results we have showed that using the conditioned place preference procedure, a single 30-min immobilization stress session induces the reinstatement of cocaine seeking behavior in animals previously conditioned with this drug. Moreover, we have also demonstrated that 72 hours after the reinstatement test, these animals reinstate again after a priming dose of cocaine. Based on recent research that suggests that the NMDA antagonist, MK 801, blocks cocaine-induced reinstatement, we aimed to prove that this blockade is also present after stress-induced reinstatement, providing at the same time further evidence for the shared neurobiological mechanisms between stress and cocaine. Male Wistar rats were injected with cocaine 10-mg/kg ip and confined to one of two compartments in four alternated daily sessions drug/vehicle; being the preference for each context later evaluated. The extinction phase consisted in successive associations with vehicle in both compartments. Reinstatement was evaluated measuring the time spent in each compartment after 30 min of immobilization stress and, 72 h later, in response to a cocaine priming injection (5 mg/kg). We demonstrated that a systemic injection of MK 801 (0.01 or 0.02 mg/kg) administered 15 minutes before the stress session, blocked stress-induced reinstatement and that this blockade persisted for at least 72 hours when was evaluated in response to a cocaine priming injection. These results support the hypothesis of a potential role of the NMDA receptor in the cocaine seeking behaviour induced by stress or cocaine. Further experiments are designed to identify the contribution of the reward and memory processes in the long-lasting MK-801 disruptive effects in addiction

Poster Number (21) Session I

MOLECULAR MECHANISMS IN THE SWITCH BETWEEN RECONSOLIDATION AND EXTINCTION OF FEAR MEMORY

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When contextual associative memory is reactivated by context re-exposure, two apparently competing processes, reconsolidation or extinction, may be induced. A brief re-exposure to the training context induces memory reconsolidation, while a prolonged re-exposure induces the inhibition of the conditioned response, a process known as memory extinction. Two main hypotheses, not mutually exclusive, intend to explain memory extinction. The first one implies a pathway that inhibits the original memory circuit. The other implies a weakening of the original trace. Using contextual fear conditioning in mice, we studied the role of transcription regulation in reconsolidation and extinction of memory. We observed that hippocampal NF-kB activation is necessary for reconsolidation, but not for extinction. Besides, hippocampal calcineurin phosphatase (CaN) activity is required for the formation of extinction memory but not for reconsolidation of the original memory trace. Considering that NF-kB is activated by IkB phosphorilation and PKA kinases, we asked whether CaN is dephosphorilating and thus inhibiting NF-kB during extinction. Inhibition of CaN in hippocampus increased hippocampal NF-kB activity and impeded memory extinction. Besides, CaN is known to activate another transcription factor, NFAT. We observed that hippocampal inhibition of NFATc4 impeded extinction, whereas no effects where observed in reconsolidation. Thus, our results suggest that CaN inhibition of NF-kB and activation of NFAT are involved in the regulation of gene expression that determines the switch between memory reconsolidation and extinction. These results, also supports the hypothesis that the extinction of memory implies a weakening of the original trace.

Cognition, Behavior and Memory
Poster Number (22) Session I

BEHAVIORAL ALTERATIONS IN MICE LACKING SPARC

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SPARC (secreted protein, acidic and rich in cysteine) is a matricellular protein that is highly expressed during development, tissue remodeling, and repair. In the brain, SPARC is expressed by radial glia during embryogenesis and postnatal development. In adulthood, SPARC expression is restricted to the SVZ, the Bergmann glial cells in the cerebellum, and the molecular layer of the hippocampus. Moreover, SPARC expression is upregulated in the denervated hippocampus, suggesting a role of this molecule in synaptic plasticity. However, the role of SPARC in modulating brain function has not been studied. We performed behavioral analysis of SPARC knockout (KO) and heterocygotic mice to test whether SPARC affects higher brain functions. We found that SPARC KO mice show normal locomotor activity but reduced exploration in the open field and the novel object exploration tests. SPARC KO mice showed reduced reactivity to spatial novelty, but normal reactivity to a novel object. We observed no differences among genotypes in habituation, showing normal non-associative memory. SPARC KO mice showed increased anxiety-related behavior in the open field and light-dark tests. Finally, SPARC KO mice showed reduced depression-related behavior in the tail suspension and forced swimming tests. This is the first behavioral characterization of mice with altered expression of SPARC. These results suggest a role of SPARC in modulating behavioral programming and/or adult behavior.

Poster Number (23) Session I

SPATIAL NOVELTY INTERFERES WITH LONG-TERM MEMORY PERSISTENCE DURING A LATE CRITICAL TIME WINDOW

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Persistence is a characteristic attribute of long-term memories (LTMs). We recently showed that persistence of LTM requires a late protein synthesis-dependent phase in the hippocampus. Nevertheless, little is known about the effect of the acquisition of new information on LTM persistence. Here, we demonstrate that exposure to a novel environment (an open field, OF) 11h after an strong inhibitory avoidance training (IA) interferes with the persistence of this memory trace 7 days, but not 2 days after training. This effect is observed during a critical time window since exposure to a novel OF 5h and 8h post training does not affect IA memory. However, the interference is absent when the OF is familiar. In addition, when OF memory formation is blocked by intra-hippocampus infusion of KN62 –a CamKII inhibitor-, the effect of the exploration of the novel OF on LTM persistence of IA training is completely prevented. Based on these results, we suggest that IA LTM persistence can be interfered by exposure to a novel, but not a familiar environment 11hs after training. A possible explanation could be that these two memories compete for proteins products thus decreasing the availability of proteins necessary for LTM persistence of IA memory.

ON MAKING THE WRONG CHOICE: WHY THE UNCONSCIOUS COULD PREVENT YOU FROM WINNING THE PERON CUP.

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In 1952 the Autódromo Juan y Oscar Alfredo Gálvez was inaugurated with a Formula One-like event named after Gral. Juan Domingo Peron, president at the time. The competition was won by Juan Manuel Fangio. During a competition, racers have to make split second decisions with very partial and high dimensional information. We are faced with a similar, perhaps less extreme, situation in everyday life when driving, playing a sport, playing video games, etc. A relatively popular theory in the area of decision making proposes two separate and complementary mechanisms for this process: 1) conscious decisions: deterministic, rational, verbalizable, slow and 2) Unconscious decisions: probabilistic, emotional, non-verbalizable, fast. Furthermore, it is hypothesized that conscious decisions work better when the problem at hand is of low dimensionality, and vice-versa.Taking the analogy of the racer, we programmed a simple racing video game / experiment that was played during last years Neurotaller to explore these hypothesis. The players were presented with a rectangular 2D track - with bifurcations - were they had to complete one lap as fast as possible. At each bifurcation they have to make the decision to either go left or right. The two alternatives have variable length. We show that the decisions are affected by the overall shape of the track – i.e. subjects tend to choose the side of the path that keeps them closer to the center of the track.This most likely due to the illusion that convex contours are perceived as shorter than concave ones. From this we suggest that unconscious decisions are better only in those cases of high dimensionality where one possesses an accurate statistically-inferred model for the problem.

Poster Number (25) Session 1

THINKING ABOUT CHESS: AN ETHOLOGICAL APPROACH TO DECISION-MAKING

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Decision-making has been widely studied in the laboratory. To assure sound statistics the number of choices in these experiments is small. However, in most real-life situations –when buying a pair of shoes, or choosing a vacation destiny- deciders choose within a broad number of options accessing only partial information. Studying decision-making in such ethological context is challenging since it is difficult to evaluate –from a normative or subjective perspective– the elements and the goodness of a choice. Here we capitalized on one of the largest and unexplored databases of complex (many outcomes, many dimensions involved in each outcome) human decision making: chess. Before making a move, a chess player weights many alternatives in function of its convenience, risk, complexity... leading to a choice. In time-controlled games, the total time is finite and subjects play according to an implicitly chosen time investment policy. A principal advantage of this experimental setup is that the outcome of the decision can be accurately evaluated by contemporary chess software. We have so far downloaded about 500.000 games which roughly correspond to 40.000.000 decisions. This number increases at about 20.000 games per day. We observed 1) a clear pattern of time-investment heavily weighted in the mid-game which indicates strategic fluctuations in the decision criterion and 2) a very weak correlation between invested time and outcome of the choice confirming that hunches are at least almost as effective as calculated choices. We present a large number of elements of decision-making which can be explored with this rich database.

Cognition, Behavior and Memory
Poster Number (26) Session I

SEROTONIN AND FEEDING BEHAVIOUR IN A NECTIVOROUS ANT

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Biogenic amines play an important role in the control and modulation of many actions and processes in both vertebrates and invertebrates. Particularly, serotonin (5-HT) is involved in behavioural and physiological feeding related processes. In insects, the regulation of feeding is governed by complex mechanisms which are controlled by external factors and also by their internal state. The ant Camponotus mus is able to modulate the nectar intake rate by changing the activity of its sucking pump, depending only on the colony requirements (J. Comp. Physiol. A 194:491, 2008; J. Insect Physiol. 55:518, 2009). Carbohydrate-starved ants reach higher intake-rates by increasing pumping frequency. Considering this modulation, the aim of this study was to determine the effect of serotonin on pumping activity and on feeding behaviour in C. mus. For this, two different groups of ants from the same colony were fed either with sucrose solution (control group) or with sucrose solution containing serotonin (5-HT group). Thereafter, the feeding behaviour and the electrical activity of the sucking pump were recorded. Serotonin promoted a decrease in sucrose-solution feeding 3:30 hours after the oral administration in a dose-dependent manner. Although the feeding time was the same for both groups, the volume of solution ingested by 5-HT treated ants was lower than the ingested by control ants, which implies a lower intake rate. This reduction was mainly due to a decrease in the volume of solution ingested per pump contraction and, when the administration of the drug was maintained for a few days, also to a decrease in the pumping frequency. Our results show a depressant effect of 5-HT on nectar feeding regulation in this insects.

Poster Number (27) Session I

MILD COGNITIVE IMPAIRMENT AND NORMAL AGING. QUANTITATIVE DIFFERENCES IN THE COGNITIVE AND BEHAVIORAL PROFILES

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Biological aging brings psychophysical and behavioral changes expected, which defines ormal aging and what difference those conditions away from the norm, are considered pathological aging. The latter includes the mild cognitive impairment (MCI) as a syndrome characterized by an acquired alteration of one or more prolonged cognitive functions supported by neuropsychological assessment. Some authors define it as a transitional state between normal aging and dementia. Both conditions are accompanied by subjective complaints in general faults evident mnesic disorder. The purpose of this study was to compare the cognitive and behavioral profiles of normal subjects and subjects with MCI admitted to the Hospital Nacional of Clinicas, Córdoba, Argentina. The results showed differences in the mean scores obtained in neuropsychological tests measuring decrease in the functions of verbal and visual evoked short and medium term, verbal recognition, phonemic fluency, and ability visoespacial much memory complaint corroborated subjects with MCI compared with normal cases. Equally evident is the marked differences in behavioral profiles of both groups, as assessed by scales measuring behavioral psychiatric symptoms.

Cognition, Behavior and Memory
Poster Number (28) Session II

LONG-TERM MEMORY IN FIELD CONDITIONS IN THE CRAB CHASMAGNATHUS GRANULATUS

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The memory triggered by the presentation of a Visual Dangerous Stimulus (VDS) in the crab Chasmagnathus granulatus was deeply characterized in our laboratory from diverse standpoints. This new line of research aims to study a learning process in field conditions. Here, we test whether the long-term memory described in simplified life conditions may also be found in conditions of high complexity. The experiment was carried out in the mudflats of Gral. Lavalle, Bs. As. Three distant areas were recorded. Animals were trained with 15 trials of the VDS with 3 min of inter-trial interval. A Pre-Training (PT) and a Testing session (TS) were registered before and after Training respectively. During Day 1 the Short Term Group (STG) received no treatment while the Long Term Group (LTG) was trained with the 15-3 schedule. Both groups were tested with the complete training protocol at Day 2. A single VDS group (s-VG) was given a unique VDS presentation. Percentage of outdoors animals during each session at Day 2 was calculated for each group. The surface activity resulted similar during PT but a clear difference between LTG and STG was disclosed after the 2nd phase of Training and TS. The time interval between the entering of a crab into its burrow and the following re-emergence (re-emerging latency, REL) revealed no significant difference between groups during PT but higher RELs values were obtained for STG vs. LTG and s-VG at TS. These results showed that the memory of the iterative VDS presentation can endure for 24 hs in conditions of high complexity. In turn, the behavioral difference between LTG and STG demonstrates that the crabs studied in the recording area were the same both days, while no tagging method was required.

Poster Number (29) Session II

STUDYING THE ROLE OF TRANSCRIPTION FACTOR ACETYLATION DURING MEMORY CONSOLIDATION

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Besides the histone acetyltransferases (HATs) and histone deacetylases (HDACs) action on chromatin, these enzymes could acetylate transcription factors (TFs) and regulate its activity. We are interested in investigating if acetylation of the TF nuclear factor kappa beta (NF-B) is a mechanism underlying memory consolidation. Upon activation, NF-B protein inhibitor (IB) is degraded, resulting in NF-B translocation to nucleus and gene expression activation. IB disassembly permits NF-B phosphorylation, leading to CREB binding protein (CBP, a prominent HAT) - NF-B association and enhancing NF-B-dependent transcription. CBP could acetylate this TF, affecting its DNA binding, IB assembly or transactivation. In order to end its transcriptional activity, HDAC-3 associates to NF-B in the nucleus and deacetylates it, allowing IB binding and nuclear exportation. In a recent study, we showed that the HDAC inhibitor sodium butyrate (NaB) facilitated memory by allowing a weak training session to induce long-term memory, in two phases of drug sensibility during consolidation. The time windows for drug effect fit well with two time windows for NF-B inhibitor effect previously reported. Together, these studies suggest that NaB treatment may increase NF-B activation as a mechanism for memory facilitation. We will evaluate this hypothesis, using the novel object recognition (NOR) task in mice. Recent data showed that NaB injection immediately post training induced NOR memory enhancement. Our first aim was to evaluate if NF-B has a role in NOR memory. We administrated a NF-B inhibitor (decoy strategy) in different brain structures. We found memory impairment when NF-B inhibitor was injected intracerebroventricularly or intrahippocampally, but not into the insular cortex, a nucleus already implicated in this task. Results suggest that NF-B in hipocampus would have a role in NOR memory consolidation. We are planning to test whether acetylation of non-histone substrates, as TFs, could be involved in memory formation.

BEHAVIORAL AND MOLECULAR CHARACTERIZATION OF A TRIPLE TRANSGENIC MOUSE MODEL OF ALZHEIMER'S DISEASE.

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Progressive memory loss and cognitive dysfunction are the hallmark clinical features of Alzheimer's disease (AD). Moreover, senile plaques containing mainly amyloid-β (Aβ) peptides, neurofibrillary tangles composed of hyperphosphorylated tau (β), and neuronal loss are the major features of AD. However, Aβ are elevated without plaque formation or nerve cell loss, yet learning and memory deficits are evident in early stages of AD. Identifying the molecular triggers for the onset of AD-related cognitive decline presently requires the use of suitable animal models, such as the triple transgenic mouse model of AD (3xTg-AD), which develops both amyloid and tangle pathology. Here we characterize the onset of learning and memory deficits in these transgenic mice, in addition to determining different molecular markers that correlate. Impaired performance was seen at different ages (4 – 6 months) in the transgenic mice in the Novel Object Recognition task (NOR). Furthermore, molecular markers (phosphoERK, calcineurin and Nuclear Factor kappa B) were determined at 3 and 6 months in hippocampus and cortex, in order to establish potential early markers that likely correlate with the memory impairment observed. Taken together, our results will contribute to elucidate molecular pathways that early dysregulate and are partially responsible for the mild cognitive impairments observed in early stages of AD.

Poster Number(31) Session II

DORSAL STRIATUM LESION DISRUPTS CONDITIONED SOMATOMOTOR BUT NOT NEUROANDOCRINE RESPONSE TO TOME FEAR CONDITIONING.

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Conditioned behavioral and autonomic emotional responses areseparately disrupted by lesion of different amygdala targets. Previousstudies from our laboratory showed that dorsal striatum (DS) isinvolved in tone fear conditioning (TFC) (Ferreira et al., 2003;2008). In this context it is important to investigate whether lesionof the DS - a structure that receives direct and indirect projectionsfrom the amygdala - selectively interferes with the somatomotorresponse of freezing, sparing the hormonal fear response. The aim ofthis study was to evaluate the hormonal response (by assessing therelease of corticosterone) and somatomotor response (freezing) inanimals with DS bilateral lesions submitted to the TFC. In experiment1, we sought to standardize the hormonal response in conditioned (C)and pseudo-conditioned (PC) animals. Freezing response was differentbetween (C) and (PC) groups. However, corticosterone levels did notdiffer between the groups. In Experiment 2, another set of animals wassubmitted to DS lesion and TFC training and test. Behavioralperformance in TFC was impaired in lesioned animals compared with shamanimals, but corticosterone plasma levels were not different betweengroups. These results suggest that corticosterone levels do notreflect associative features of conditioned fear response and confirmthat DS mediates the somatomotor freezing response. The presentobservations are also in line with other studies showing thatdifferent amygdala targets are involved in mediating fear conditionedresponses.

Cognition, Behavior and Memory
Poster Number (32) Session II

PREVIOUS EXPERIENCE WITH DEFENSIVE BEHAVIOURS IN THREATENING ENVIRONMENTS MIGHT MODULATE ACTIVE BEHAVIOURS IN THE FORCED SWIMMING TEST.

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Many animal models of depression are based in the Learned Helplessness theory, which states that the ability to control or predict aversive events can modulate their impact on future mood and behaviour. The open arm in the Elevated Plus Maze (EPM) is aversive for rats, so we examined if a chronic-inescapable exposure to it would induce depressive-like behaviours in a unique session of the Forced Swimming test (FST). Three groups of adult male Wistar rats were used: 15 minutes, 4 consecutive days of exposure to an inescapable open arm (OA group), inescapable closed arm (CA group) or no exposure to the arms (Control). CA was included to ensure middle stress levels. Behavioral measures were immobility, swimming, climbing and diving. Results showed significant differences between groups only in diving. Post hoc analysis revealed that scores for diving were: CA OA = Control. Contrary to our hypothesis, OA didn't differed from the others in the measures commonly affected by antidepressants (swimming, climbing and floating), suggesting the procedure as unable to induce depressive-like behaviours. Surprisingly, CA differed from OA and Control in diving, considered an active behaviour (opposite to passive behaviours, i.e., floating). Previous experience with a threatening environment that allows defensive behaviours (such as protecting the body against the walls of the closed arm or hiding at the end of it) may account for this difference. Hiding is a typical defensive behaviour in rats. It must be noted that neither OA nor Control previously experienced the possibility to cope effectively with threatening environments. OA had no escape from the open arm or FST. Control didn't have escape possibilities in the FST, and never faced a threatening environment (such as any arm in the EPM), so no defensive

behaviour was used before the FST. These considerations are supported by the fact that Control and OA did not differ from each other in diving, but both differ from CA. It is suggested that memory of defensive behaviours might modulate this difference.

CONSUMMATORY INDUCTION THROUGH POSTINGESTIVE CONSEQUENCES BUT NOT S-S ASSOCIATION BETWEEN SUBSEQUENT FOODS

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The sequential presentation of two foodstuffs may increase the consumption of the first when the following meal is of higher hedonic value i.e., an induction effect. It is commonly assumed that this induction is based on a stimulus-stimulus S-S learned association between subsequent incentives. We describe two experiments where we found an induction effect in sheep and tested its putative mechanism. In experiment 1, sheep consumed a food with high fiber content oat hay OH followed by either an empty feeder control 1, more OH control 2, a food rich in protein group P, or a food rich in carbohydrates group C. Groups P and C ate more OH than both controls, thus showing an induction effect. In experiment 2, we used two flavors associated with OH in a within-subject design where one flavor was always followed by a food rich in protein and the other always followed by an empty feeder. In a choice test, sheep showed a strong preference for the flavor followed by protein. Afterwards, we induced gastric sickness in all animals administering LiCl after they had access to either the protein food for half the subjects or a non-experimental already familiar food for the other half of subjects. If sheeps preference depended on an S-S association, we expected to revert the original preference in the group intoxicated after protein consumption but not in the other group. Despite developing an aversion to the corresponding food, flavor preferences remained unaltered in both groups. This suggests that the induction effect and flavor preference were determined by postingestive consequences of the protein-rich food but not by an S-S association between flavor and the subsequent foodstuff.

NEUROANATOMIC DISTRIBUTION OF ANGIOTENSIN II-LIKE NEUROPEPTIDE WITHIN THE CENTRAL NERVOUS SYSTEM OF THE CRAB CHASMAGNATHUS. PHYSIOLOGICAL CHANGES TRIGGERED BY WATER DEPRIVATION.

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Angiotensins neuropeptides appear to emerge early in evolution. Their classical osmoregulatory functions in vertebrates have been shown in some invertebrates. Our results in the euryhaline and semiterrestrial crab Chasmagnathus granulatus, led us to demonstrate that water deprivation triggers an increased brain angiotensin II-like immunoreactivity (ANGII-ir), which improves memory processes through ANGII receptors. We suggested that the release of brain angiotensins in response to water shortages would be an ancient mechanism for coordinating different functions that together would enable organisms to cope with this environmental change. Here, our working hypothesis is that angiotensinergic neuropils will have their own dynamics when animals are confronted to water deprivation. We first described the neuroanatomic distribution of ANGII-like neuropeptide. Our results indicate that ANGII-ir is strongly expressed in specific neuronal processes of all major areas, comprising the three optic neuropils, medulla terminalis and hemiellipsoid body, and the proto-, deuto- and tritocerebrum of supraesophageal ganglia, especially in the medial protocerebrum containing the central body. Secondly, we evaluated the physiological changes in ANGII-like level in different brain neuropils for water-deprived crabs. We found a decrease in ANGII-ir after 2 hours of water deprivation in the olfactory neuropil but an increase in the central body that returned to the basal level after 6 hours. In addition, after 6 hours of deprivation we found a profound decrease in ANGII-ir in several brain areas. These results suggest that several functions are regulated by this neuropeptide while animals are coping with water-shortages.

A PAVLOVIAN-CONDITIONING IN THE CRAB

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The traditionally, associative learning paradigm in the crab (Chasmagnathus granulatus) is based on its escape response elicited by the presentation of a visual danger stimulus (VDS), an opaque rectangle passing over the animal. Upon the iterative presentation of VDS, the crabs escape-response declines and a strong freezing-response is built up. This paradigm is based on the association between the environmental features of the training site (the context) and the features of the screen moving over the animal (the signal). Thus, such memory was termed as the context-signal memory (CSM). In this work, we developed a new pavlovian-conditioning for an associative learning designed to/for increase the contingency between the context and the VDS. This new paradigm, consist on the same number of VDS's presentation but paired with a light from above; during the intertrial interval the light is presented from below. The above illuminated context constitutes the CS. Previous results demonstrated that the light from below determine the CS offset (Pérez-Cuesta et al, 2007; Hepp and Pedreira, submitted). We found that this new paradigm, as well as the classical one, is context specific and also depends on protein synthesis. We also demonstrate that a brief reexposure to the light (27 seg) is sufficient to induce the reconsolidation process. * and α contributed equally to this work.

DISRUPTING MEMORY PERSISTENCE

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Persistence is a main attribute of long-term memories. Memory persistence could be positive in some cases but could also become maladaptive in other cases such as in different anxiety disorders. It has been recently described by our laboratory that a late translation phase around 12 h post-acquisition is essential for memories to persist. BDNF activation of ERKs in the hippocampus is a key point in this process. Antidepressants are widely used drugs which have shown to alter BDNF mRNA and serotonin concentration in the hippocampus and modify emotion processing after one-dose acute administration. For that reason they appear to be good candidates for manipulation of memory persistence. Here we show that acute infusion of rats with either fluoxetine or venlafaxine hinder persistence but not formation of a memory trace when administered i.p. 11 h or intra-hippocampal 12 h post inhibitory avoidance (IA) training but on the contrary enhance memory when given immediately after training. We also show that the effect of venlafaxin on persistence can be blocked by the intra-hippocampal administration of the 5-HT2A/2C antagonist ritanserin. Therefore these results suggest that fluoxetine and venlafaxine hamper memory persistence with at least venlafaxin doing it by increasing 5-HT2A/2C receptors activation in the hippocampus.

THE PHASE OF LABILIZATION/RECONSOLIDATION UPDATES NEW AVERSIVE INFORMATION TO A PREVIOUSLY CONSOLIDATED FEAR MEMORY.

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Consolidated memories may result into a labile one after retrieval, requiring a re-stabilization process, defined as reconsolidation, which is dependent on protein synthesis. The functional significance of this process remains unknown; one hypothesis proposes that this phase is essential to incorporate new environmental experiences to the original memory, a process defined as memory updating. Adult male Wistar rats were subjected to a contextual fear conditioning paradigm using only 1 shock (weak training session). One day after training, rats were subjected to a stressful situation (restraint for 30 min.) and another group remained in their homecage without manipulation. Half of the rats were re-exposed to the original context of conditioning (test 1) for 3 minutes one day after the stress. There was an increase of freezing only in those animals re-exposed to the associated context, which was maintained for 10 days during a new re-exposure to the training context (test 2). Pharmacological manipulations (benzodiazepines and NMDA antagonists) that attenuate the stress consequences or prevent the fear memory reconsolidation, as well as very short period of re-exposure to the associated context, prevented stress-induced increase in freezing. We conclude that the reactivation session allows the updating of new environmental information corresponding to a traumatic event (inescapable stress) into an already consolidated fear memory.

MATE MAROTE: INTERACTING WITH CHILDRENS MINDS

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During a person´s life, but specially during infancy and childhood, the brain is a plastic organ changed by the environment and the way the person interacts with it. And education is a very important part of it. In this sense, cortical changes can be related to cognitive changes, bringing the oportunity to relate mind, brain and education. A new discipline studying this subject exists not so far ago: neuroeducation, combining cognitive neuroscience and behavioral methods to investigate the development of mental representations and, possibly, to use neuroscience pre-existing knowledge to improve different teaching approaches. During the last two years we have been developing "Mate Marote", a cognitive trainer educational software to exercise different aspects of cognition in order to understand its overall and specific impact –for each cognitive demand: control, self-monitoring, and exploration -, and its transfer to other cognitive processing and academic performance. The ultimate goal of this project is to generate a free, enjoyable and actually easily accessible software in order to optimize learning and cognitive skills in school-age children with broad performance range and different socioeconomic backgrounds. We present the first preliminary results: 1) An increase in working memory capacitites, and 2) Identification of action plans in complex games, which allow to identify and train planning strategies. We discuss future challenges of the project and how to asses whether results transfer to other learning environments, and particularly to school performance.

Cognition, Behavior and Memory
Poster Number (39) Session II

MOLECULAR MECHANISMS INVOLVED IN THE EFFECT OF IL-1BETA ON MEMORY CONSOLIDATION AND THEIR MODULATION BY ALPHA-MSH.

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Molecular mechanisms involved in the effect of IL-1beta on memory consolidation and their modulation by alpha-MSH P Gonzalez1, I Machado1, A Vilcaez3, L Carniglia2, M Lasaga2, T Scimonelli1. 1IFEC CONICET Dpto. Farmacología. FCQ. UNC. 2Inst. de Investigaciones en Reproducción. F. Medicina. UBA. 3CIQUIBIC CONICET Dpto. Química Biológica. FCQ. UNC. We previously reported that administration of IL-1b (5ng) in dorsal hippocampus impairs the consolidation of a contextual fear memory. Treatment with a-MSH (.05ug) blocked this effect. However, the mechanisms involved in the cytokine's effect have not been established yet. It has been demonstrated that activation of p38 and Jun-kinase are involved in the inhibitory effect of LPS and IL-1b on LTP in vitro. Also, this effect was attenuated by a NF-kB inhibitor. The present experiments show that intrahippocampal injection of IL-1b after training in a contextual fear paradigm induced a decrease in glutamate release of synaptosomes from dorsal hippocampus. a-MSH administration did not reverse this effect. The inhibitory effect of IL-1b on memory consolidation was not reversed by the NF-kB inhibitor SN50 (20ug). However, western blot analysis demonstrated that IL-1b induces a significant increase in nuclear NF-kB in dorsal hippocampus. Probably, as described before, astrocytes are the source of the increase in NF-kB, and so, this effect was not involved in memory consolidation. Preliminary results show that the inhibition of p38 by SB203580 (100uM) reduced the effect of IL-1b on memory consolidation.The results are consistent with the idea that IL-1b-induced impairment in memory consolidation is mediated by a decrease in glutamate released and p38 activation in dorsal hippocampus.

Poster Number (40) Session II

PERSISTENT MEMORIES INDUCE IMMEDIATE EARLY GENES EXPRESSION IN THE CORTEX

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A fundamental question in memory research is how brains can form enduring memories. Basically, there are two main models of memory consolidation: The most accepted one, establishes that memories are initially and temporarily stored in the hippocampus and later transferred to the cortex for persistent storage during a process named system consolidation. An alternative view, proposes that the cortex may also have a crucial role in the initial steps of memory formation and the hippocampus may not be disengaged from memory processing as early as it has been originally proposed. Little is known about the molecular, cellular and systems mechanisms underlying permanent memory storage. However, recent studies have begun to shed light on how remote memories are organized in the cortex. The aim of this work is to study the role of neocortical areas in inhibitory avoidance (IA) memory consolidation and persistence. By using immunocytochemistry technique, we evaluated the expression of immediate early genes (IEGs) - zif268, c-fos – after two types of training that generate memories with different duration. Our preliminary findings suggest that late after training, differential gene expression is induced in the cortex and that the level of expression is correlated with the duration of the memory. Having this in mind, we further intend to investigate the role of the expression of these IEGs in the storage of persistent memories.

REVISITING THE UNLIMITED CAPACITY AND PRE-ATTENTIVE VIEW OF ICONIC MEMORY: COGNITIVE AND NEUROPHYSIOLOGIC ESTUDIES

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Crowded stimuli are initially stored in a high-capacity sensory buffer which decays exponentially in hundred of milliseconds. Only a fraction of this buffer – referred as iconic memory - access higher cognitive states such as working memory or consciousness. Previous studies have omited the question of how this sensory buffer interacts with the ongoing dynamic state of the brain. The aim of this work is to analyze the interaction of ongoing cognitive or attentional processes with the sensory representations in iconic memory, and to revisit its pre-attentional conceptualization. We hypothesize that these factors modulate and influence the initial sensory representation of the stimuli, thus limiting the capacity of this memory and consequently the later access of the items to working memory or consciousness. We used a partial report paradigm where subjects had to report the identity of a letter presented in a cued position of a circle array around a fixation point, where the delay between stimulus and cue was systematically varied. We provide evidence of the limited capacity of iconic memory using different numbers of items in the array. We suggest that this limited capacity arise from a limited distribution of attentional resources (with a finite capacity) and we provide examples of different dynamics across spatial positions. A simple mathematical model assuming a limited buffer capacity explains this memory saturation effect. Finally, we present an EEG study to analyze the interaction between attention and iconic memory.

Poster Number (42) Session II

PARSING A PERCEPTUAL DECISION IN A SEQUENCE OF MOMENTS OF THOUGHT

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Theoretical, computational and experimental studies have converged to a model of decision making in which sensory evidence is stochastically integrated to a threshold, implementing a shift from an analog to a discrete form of computation. Understanding how this process can be chained and sequenced - as virtually all real-life tasks involve a sequence of decisions - remains an open question in neuroscience. We reasoned that incorporating a virtual continuum of possible behavioral outcomes in a simple decision task- a fundamental ingredient of real-life decision making – should result in a progressive sequential approximation to the correct response. We used real-time tracking of motor action in a decision task, as a measure of cognitive states reflecting an internal decision process. We found that response trajectories were spontaneously segmented in a discrete sequence of explorations separated by brief stops (about 200 ms) – which remained unconscious to the participants. The characteristics of these stops were indicative of a decision process - a "moment of thought": their duration correlated with the difficulty of the decision and with the efficiency of the subsequent exploration. Our findings suggest that simple navigation in an abstract space involves a discrete sequence of explorations and stops and, moreover, that these stops reveal a fingerprint of moments of thoughts. We design an EEG study to further evaluate these results and to find neurophysiological correlates of these stops.

LOCALIZED NMDA RECEPTOR ABLATION AS TOOL FOR MEMORY DISSECTION IN CHASMAGNATHUS GRANULATUS

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The main objective of this project is to identify the central nervous system (CNS) areas associated with the mnemonic processes in an invertebrate model, the crab Chasmagnathus granulatus. A well-known technique employed to determine these areas implies the administration of neurotoxic drugs by localized microinjection. To reach this proposal we divided the technique into three parts: First, we created a stereotaxic map of the crab nervous system. The results show that it would be possible to generate a coordinates system of reference for the eyestalks and the supraesophageal ganglion (SEG), considering external anatomical features. Second, we choose a neurotoxic agent: the ibotenic acid, a glutamatergic agonist, which acts on the NMDA type receptors. However, to determine the target areas it is necessary to know the distribution of these receptors through the nervous system. Thus, immunohistochemistry techniques were applied using anti-NMDAR1antibody to characterize their distribution. An NMDA like receptor (NR1L) signal was observed with a broad distribution all over the structures. With Western Blot techniques we evaluated the antibody specificity and the molecular weight of this receptor subunit in Chasmagnathus. The next step was the localized administration of ibotenic acid by microinjections in the (SEG) and the evaluation of its effect by immunohistochemistry. The brains treated with the drug show a deceased signal for NR1L when compared with vehicle injected brains. This decrement was evaluated at a sub-cellular level. Finally, we will perform localized-lesions and we will evaluate the correlation between the zones injured and the behavioral changes observed.

Poster Number (44) Session II

INSTRUMENTAL RESPONSES OF THE COMMON TOAD (BUFO ARENARUM) ACCORDING TO DIFFERENT EXTERNAL SALINE SOLUTIONS

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Amphibians' uptake water through the skin and have the ability to assess the osmotic and ionic properties of their external environments. The use of external solutions of different osmolarity as reinforcers provides an opportunity to analyse the behavior of animals without changing the systems perceptual committed. The aim of this study was to analyse the behavior of the common toad Bufo arenarum in an instrumental learning procedure using different concentrations of saline solutions as reinforcements. Three groups of toad, partially dehydrated, were trained in a runway situation: Appetitive (reinforced with deionized water in a container in the goal box, where animals gain weight), Aversive (reinforced with 800 mM NaCl solution, where they lose weight), and Neutral (reinforced with 300 mM NaCl solution, where they does not win nor lose weight). Running latency and pre and post-session weights were recorded. During the reinforcement period at the container, the amount of displacement and rubbing were recorded. Results showed a significant decrease of running latencies for the Appetitive group. The Aversive and Neutral groups presented high latencies with no differences between them. Once groups arrived in the goal compartment, Appetitive group showed the highest time on the container, as well as displacement and rubbings. The Neutral group significantly increased their time on the container and the amount of displacements through the sessions. The Aversive group presented a minimal time on the container. Globally, our results show that this training situation could be used for a comparative study of appetitive and aversive learning phenomena. In addition, we also are exploring the involvement of the medial pallium (homologous region to mammalian hippocampal formation) and the striatum (homologous area to mammalian amygdala) using the histochemical technique of AgNOR.

Cognition, Behavior and Memory
Poster Number(45) Session II

SEXUAL HORMONES AND FRUSTRATION

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Frustration is defined as an emotional state caused by the decrease in or omission of the quantity or quality of an appetitive reinforcer in the presence of an expectative of reward or reinforcers of greater magnitude. One procedure used to induce frustration is consummatory extinction, in which the animals at first receive access to a sucrose solution, and later receive no reinforcer and instead, have access only to an empty sipper tube. Testosterone (T) causes a reduction in the anxiety of male rodents, whether released in an endogenous way or administered by an exogenous method. Furthermore, the depletion of the gonadal axis has opposite effects to those found with the administration of T. To date, no studies have been found that investigate the effect of this sexual hormone in the processes of frustration, making this study the first antecedent on the effect of sexual hormones on the omission of an appetitive reinforcer. The results suggest that an increase of T (through repeated administration) as well as a decrease of the same (through castration) would modulate the frustration response of animals when faced with the loss of an expected reinforcer.
Keywords: Testosterone, frustration, extinction, castration, rats.

BRAIN MECHANISMS OF INFORMATION INTEGRATION IN A VISUAL SCENE

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Turing machines, the backbone of current computers, rely on a very simple premise: an exhaustive serial computation mechanism, even of elementary operations, can result in a very powerful computing device. The human brain relies in part in such mechanism and the analysis of a visual scene constitutes one of the clearest examples. When exploring a scene, we systematically produce a discrete sequence of fixations, gathering information in each instance of the sequence. To the current date, we do not have an understanding of the physiological events underlying such sequence. Here we setup to explore markers of such sequence in the human brain in combined EEG and Eye Tracking experiments in which subjects subjects searched for two targets hidden in 20 distributed patches. Each patch contained one single target or distractor, masked by a crowding flanker which assured that search was fully sequential. We studied the EEG responses following and prior to each fixation in relation to local properties such as content of the current fixation location, or global properties such as position in the sequence of fixations (with the order and times internally generated by the participant). We observed robust and reliable evoked potentials during free-viewing. A segment of the unfolding of these events was reminiscent of experiments of simple fixations: early occipital potentials evoked in all fixations and delayed frontal and parietal potentials which occurred mostly in fixations to a target. We also observed a late and frontal potential locked and prior to the response, and after the first fixation, which are not observed in simple fixation experiments and might constitute a correlate of sequence-boundary markers.

Cognition, Behavior and Memory
Poster Number (47) Session II

A DELAYED WAVE OF C-FOS EXPRESSION IN THE DORSAL HIPPOCAMPUS IS INVOLVED SPECIFICALLY IN PERSISTENCE OF LONG-TERM MEMORY STORAGE

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The most remarkable feature of the brain is its capacity to collect and store information to produce appropriate changes in behavior. Memory is a temporally graded process during which transcription and translation steps are required in the first hours after acquisition. Although persistence is a key characteristic of memory storage, little is known about its mechanisms. Here, we show that long-lasting but not short-lived inhibitory avoidance (IA) long-term memory (LTM), is associated with a delayed expression of c-Fos in the hippocampus. Importantly, this late wave of c-Fos is necessary for maintenance of IA LTM storage. Moreover, inhibition of transcription in the dorsal hippocampus 24 h after training hinders persistence, but not formation of LTM. These findings indicate that a delayed phase of transcription is essential for maintenance of a hippocampus-dependent memory trace. Our results support the hypothesis that recurrent rounds of consolidation-like events take place late after learning in the dorsal hippocampus in order to maintain memories.

Poster Number(48) Session II

DOPAMINE WOULD BE NECESSARY FOR AVERSIVE LEARNING IN A CRAB

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Dopamine (DA) is a biogenic amine involved in a variety of physiological processes. Regarding cognition, it has been proposed that DA could act in the signaling of an aversive stimulus, while other amine, octopamine, could mediate a positive reinforcement. However, a recent paper from LNM has challenged this idea, proposing that the function of the amines is not reduced to only one kind of learning. It has been proved that octopamine is not only necessary for appetitive learning, but also interferes with an aversive one. Here, we show preliminary results using CSM, an aversive paradigm extensively used in the laboratory. When Chlorpromazine, a D2- like antagonist, is administered before training no memory is disclosed at test session. This result supports the idea that DA is necessary for an aversive learning. In order to further characterize DA role in learning, we developed a new aversive paradigm trying to reproduce natural conditions. In this, we use a device with a hole in the center resembling the animal's burrow. Our first results indicate that, at training session, the presentation of the visual danger stimulus elicits a defensive response of the animals, getting into the holes, which is very similar to the behavior observed at the field. Next day, at test session, trained animals make more entrances into the burrows than controls. This result may indicate that the hole is actually being recognized as a "safe place" which trained animal prefer when being reinstalled at the learning context. Our next step is to fully characterize dopaminergic involvement in this new aversive paradigm.

Cognition, Behavior and Memory
Poster Number (49) Session II

NICOTINIC CHOLINERGIC MECHANISMS ON MEMORY RECONSOLIDATION OF AN INHIBITORY AVOIDANCE RESPONSE IN MICE.

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When a well-consolidated memory is recalled it becomes transiently sensitive to disruption to the same treatments that affect consolidation. This new window of susceptibility is referred as memory reconsolidation. Here we investigate the effect of nicotinic receptor (nAchR) ligands infused bilaterally in the dorsal hippocampus after memory reactivation of the inhibitory avoidance response in mice. The nAchR antagonists were mecamylamine (MEC, α3β4, 1-30 ug/side), dihydro-β-eritroidine (DHβE, α4β2 , 3–30 ug/side) and methyllycaconitine (MLA, α7,1-30 ug/side). Mice that were over-reinforced (1.2 mA, 50 Hz, 1 s) on the learning trial, exhibited a high retention performance 48 h after training. The immediate intrahippocampal infusion of MEC, DHβE or MLA after the retention test, that is, after memory reactivation, significantly impaired retention performance in a dose- and time-dependent manner. When memory was retrieved 48 h training and the drugs were given immediately after it, spontaneous recovery was not observed in a new retrieval session 21 days after original learning. Although we cannot definitively discard a retrieval deficit, the results obtained are in accordance with the storage deficit interpretation. Retention performance was unchanged in drugs - treated mice not undergoing memory reactivation session. These results, taken together, indicate that different nicotinic antagonists impaired reconsolidation of an inhibitory avoidance task in mice, suggesting a critical participation of the cholinergic nicotinic pathway in this memory processes.

Poster Number (50) Session II

ASSESSMENT AND FOLLOW-UP OF THE INFANT COGNITIVE AND NEURODEVELOPMENT OF BABIES WHO BORN IN HIGH AND MIDDLE RISK.

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Assessment of the infant neurodevelopment contributes information for the early diagnosis of developmental problems and the treatment of young children. The aim of this study was to measure cognitive and neuromotor functioning, as indirect measures to assess Central Nervous System (CNS) functioning in order to detect CNS precocious dysfunction. The scales selected, 1) CAT-CLAMS: Clinical Adaptative Test/Clinical Linguistic Auditory Milestone Scale. Capute et al. (1996), and 2) Method for Neurological Evaluation within the First Year of Life of Amiel Tison et al. (1981)- were administered to 17 infants born to HIV-infected women, 2 preterm babies with congenital syphilis, 10 preterm babies and a group of 28 seronegative to HIV healthy babies, born in term from healthy mothers (control group), with a median follow-up of 12 months. Our preliminary results show no significant statistical difference between neuromotor (Chi square test) and cognitive development of the HIV exposed and control samples (Chi square test/ T test de Student). At this moment, we should not compare the "premature" (prematurely born) group, because it's small size. In spite of that, we will present the most interesting case studies of the preterm sample. At this moment, preliminarily, we don't find significant neurodevelopmental delays in the HIV exposed babies of our sample. REFERENCES -Amiel-Tison, C. & Grenier, A. (1981). Valoración neurológica del recién nacido y del lactante. Barcelona: Toray-Masson. -Capute AJ, Accardo PJ (1996a). The Infant Neurodevelopment Assessment: A Clinical Interpre tative Manual for CAT-CLAMSProbl Pediatr. August 1996: 238-257. -Capute AJ, Accardo PJ (1996b). The Infant Neurodevelopmental Assessment: A Clinical Inter pretative Manual for CAT-CLAMS in the First Two Years of Life, Part 2. Curr Probl Pe diatr September 1996: 279-306.

A FRONTO-PARIETAL NETWORK MEDIATES THE PREDICTIVE ACTIVATION OF THE MIRROR SYSTEM IN RESPONSE TO AN ABSTRACT CUE

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It is believed that the ability to understand the actions and the intentions of other people is made possible by the brains mirror neuron system through its direct connection between action and observation. But how exactly do we predict the actions of others We performed a functional magnetic resonance imaging (fMRI) study to explore which brain regions are activated predictably by abstract stimuli that anticipate an action. Participants view dynamic videos of a human hand moving either the index or the pinky. Each movement was preceded by an abstract colored cue. A third colored cue was presented in anticipation of a still hand. Subjects practiced the association between the abstract cue and the video before going into the scanner. Once in the scanner, they were shown the same sequence of stimuli arranged in two different blocks: during the observation blocks, they were instructed to passively observe the stimuli and were given an attentional task to make sure they were watching the screen. In the action blocks, they were told to mimic the movement observed with their right hand, starting as quickly as possible after movement onset. Three events were modeled using SPM: one timed to the onset of the abstract cue, one timed to the onset of a variable delay (ITI=3-12 seconds) and one timed to the onset of the video. The results show that a fronto-parietal network, composed of the anterior portion of the premotor cortex and posterior portion of the posterior parietal cortex (superior parietal lobule), is activated predictably in response to abstract cues associated with a movement. These results suggest that prediction of other people's actions could mediate the activation of the mirror system during action perception.

Poster Number(52) Session II

BEHAVIORAL SYMPTOMS: AN EARLY MARKER OF NEURODEGENERATIVE DISEASES

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Mild behavioral symptoms (SCL) was defined as the presence of disoriented notorious changes in the behavior of a person before age 60 and persisted at least 6 months. It has been observed that neurodegenerative diseases, other than Alzheimers disease, are accompanied by affective changes (depression, anxiety, etc..) And disorders (agitation, isolation, etc.). In many cases, behavioral symptoms often prevail over the cognitive. Furthermore, although not sufficient by themselves to diagnose dementia, they are useful for predicting and forecasting the same. The present study evaluates a cognitive behavioral and 30 subjects from 55 to 80 years of both sexes who attended on a voluntary basis to the Hospital Nacional de Clinicas, Cordoba Province.The objective of this project was to detect behavioral symptoms and to reflect the importance of them in the early diagnosis of neurodegenerative diseases. Of the sample studied, 50 of subjects showed significant scores on the variables depression, anxiety, irritability / emotional lability, and 15 showed slight alteration in more than one cognitive function.

ABSENCE OF RENEWAL EFFECT IN THE NEGATIVE CONTRAST PARADIGM

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Rats downshifted from 32 sucrose to 4 sucrose consume less of the 4 solution than rats in a control condition that experience 4 sucrose throughout. This negative consummatory contrast effect is also known to occur when the downshift occurs in a novel conext. We tested the following hypothesis: Animals that are subject to both a sucrose downshift and a novel context, and that then recover their consummatory behavior, are expected to show negative contrast again when they are returned to the original context. In Experiments 1 and 2, the return to the original context failed to renew the negative contrast. Experiment 3 showed that rats were able to discriminate between original and novel contexts, as extinction did cause a renewal effect on the consummatory behavior. These results suggest that, unlike extinction, negative contrast is not subject to renewal effects when the original context is reintroduced. Similarly, Norris, Daniel, & Papini (2008) found spontaneous recovery of consummatory behavior, but not of negative contrast. Norris, J. N., Daniel, A. M., & Papini, M. R. (2008). Spontaneous recovery of consummatory behavior, but not of consummatory successive negative contrast. Learning and Motivation, 39, 296-312.

Poster Number (54) Session II

MIDAZOLAM ADMINISTRATION AFTER STRESS EXPOSURE PREVENTS THE DEVELOPMENT OF A NEGATIVE EMOTIONAL STATE

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The exposure to threatening stimuli induces exaggerated emotional response related to fear and anxiety in response to a new environmental stimulus, a mechanism defined as Emotional Sensitization. The Amygdala plays a key role in the processing of aversive information. In fact, the emergence of a negative emotional state has been functionally associated with a reduced GABAergic transmission in this brain area. We study the effect of MDZ administered after stress in the occurrence of the emotional sensitization assessed by both an associative and a non-associative learning paradigm. Contextual Fear Conditioning (CFC) and Elevated Plus Maze (EPM) were used as associative and non-associative paradigms respectively. Male Wistar rats (280-300g) were used to perform the experiments. Immediately after a restraint session (30 min), animals were injected with MDZ 1.5mg/Kg,i.p. The formation of fear memory test was evaluated by the freezing response of stressed and control animals, in a paired or in an unpaired context. We observed high freezing levels in stressed animals who were conditioned in the presence of context and footshock contingency. No significant difference among the others groups was detected. On the other hand, the EPM was performed 24h after the restraint session. The stressed animals injected with VEH (Saline solution) exhibited the typical enhancement of anxiety. In contrast, similar open arm exploration was observed among stressed animals given with MDZ or control animals with VEH or MDZ. To identify the neuroanatomical substrate involved in this sensitization to the anxiety response, we locally infused MDZ (2ug/ul) or VEH into BLA or into CeA bilaterally, immediately after the stress session. In both areas we observed an anxiety decrease of stressed animals injected with MDZ as compared to the rest of groups.

Cognition, Behavior and Memory
Poster Number (55) Session II

DO MEMORIES COMPETE FOR PROTEINS

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The formation of long-term memories requires protein synthesis. We have demonstrated that learning of a task which only induces short-term memory can be stabilized into a long-term memory (LTM) if another novel experience brings in the necessary proteins. The phenomenon, named "behavioral tagging", is observed when a weak inhibitory avoidance (IA) training induces a learning-tag which captures plasticity related proteins (PRPs) derived from the exploration of a novel open field (OF) to promote IA-LTM. Therefore, we decided to study the effects of this protein capture on the OF-LTM and found that induction of IA-LTM occurs in detriment of OF-LTM. This suggests that both IA and OF tags compete for protein sources and the availability of these plasticity factors determines which of the memory traces will become stable over time. In the present work we show that under certain circumstances memories can compete for their consolidation and it depends on PRPs supplies to the tagged sites. When PRPs amount is limited, competition is favored; but when PRPs synthesis is greater, there is an improvement in the promotion of the IA-LTM. Because of its role in synaptic remodeling, we also investigated the requirement of Arc/arg 3.1 as a PRP in the formation of LTM of both tasks as well as in the promotion of IA-LTM when its weak training is combined with novel OF exploration. We found Arc is necessary for the formation of both memories and it constitutes one of the PRPs captured by the tags previously set at IA-training. In sum, we show that depending on the amount of PRPs synthesis, different memory traces are able to "share" or compete for their resources, being Arc one of the proteins in dispute.

CONSISTENCY EFFECT DISSOCIATION IN READING AND WRITING IN SEMANTIC DEMENTIA PATIENTS

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The effects of lexical frequency and consistency have been reported in English semantic dementia patients both in reading aloud and writing (Patterson, Lambon Ralph, Jefferies, Woollams, Jones, Hodges & Rogers, 2006). In Spanish the lexical frequency effect is observed in both tasks, but the consistency effect only in the writing tasks. The aim of this work is to show the consistency and lexical frequency effects in a writing task in Spanish semantic dementia patients and compared them with their performance in reading aloud. Ten semantic dementia patients were tested with two tasks of the "64 Semantic Battery" (Green Heredia, Sage, Lambon Ralph & Berthier): reading aloud and dictation. These tasks consist of a total of 64 words. The dictation task is composed by 8 frequent-consistent words, 15 non-frequent-consistent, 15 no frequent-consistent, and 23 no-frequent-no consistent in the dictation task. Two analysis of variance were conducted considering the proportion of patients who could read and write properly. In the writing task, a lexical frequency effect in consistent words was not found. The analysis showed significant differences in non-consistent word between low and high lexical frequency words. Moreover a consistency effect in low lexical frequency words was found but not in high lexical frequency words. In Spanish, semantic dementia patients show in non-consistency words, a lexical frequency effect in writing. Consistency effect only occurs in low frequency words. These results can be interpreted as a result off the semantic deficits.

BEHAVIORAL PHARMACOLOGY OF OCTOPAMINE IN A NEOTROPICAL STINGLESS BEE, MELIPONA SCUTELLARIS

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Biogenic amines help to regulate the behavior of vertebrates and invertebrates. In honey bees, Apis mellifera, octopamine (OA, invertebrate counterpart of noradrenaline) has been identified as a modulator of appetitive learning and gustatory responsiveness. So far, it has remained an open question whether OA similarly modulates these abilities in stingless bees (Meliponini). Due to their close phylogenetic relationship with bees of the genus Apis and their wide diversity in foraging behavior, meliponine bees have received increasing scientific interest during the last decades. In the present study, we tested the sucrose-response thresholds (SRT) of the stingless bee Melipona scutellaris before and after oral administration of different concentrations of OA. After OA treatments at concentration of up to 0.02M of this biogenic amine, the sucrose responsiveness of the bees significantly increased, but decreased at higher OA-concentrations. The forager odor learning performance, evaluated by means of differential conditioning, also improved after the administration of OA 0.02M. This observed improvement, however, was not statistically significant. Our results indicate that, similarly to honey bees, biogenic amines modulate the sucrose responsiveness of M. scutellaris foragers and, perhaps, also their associative learning abilities, which has relevant consequences for other types of behavior in this bee species. The incorporation of stingless bees within this behavioral framework, thus, opens a promising field for comparative research on chemosensory processes at behavioral, cellular, and molecular levels. Supports: CNPq; FAPESP - 06/50809-7, APNCyT (PICT2006-1155).

Poster Number (58) Session III

VISUALLY MEDIATED DECISIONS OF THE ESCAPE DIRECTION IN THE CRAB CHASMAGNATHUS

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A critical feature of evasive behaviors is the ability to localize the threatening stimulus in space and perform consequently. Such sensory-motor transformations must be fast and well tuned in escape behaviors, in which both the speed and accuracy of the evasive response determine whether an animal successfully avoids predation. Crabs are elusive prey with a short-latency (~100 ms) escape behavior. To a sudden approaching object, all crabs react by running in the direction opposite to the looming object. Thus, the direction of escape is highly determined by the direction of the object approach. However, when an object is coming straight from above, the information about the proper side to run becomes less certain. Even so, the animal must decide whether to run to the left or to the right (crabs run sideway). We began to investigate this decision making processes, which to a large extent is thought to take place in a group of identified giant neurons of the crab's brain. The study is performed by using a running simulator device located inside an arrangement of 5 computer screens (1 above and 1 on each side of the simulator). This allows us to precisely record the course of escape responses elicited by the image of an approaching object (an expanding black square) generated in the upper screen. We found that when the luminance of the four screens surrounding the crab at the horizontal level where equal, 50 of the animals ran to the left and the other 50 ran to the right. Upon repeated stimulus presentations, each individual tended to maintain the same escape direction, indicating the existence of individual directional preferences. On the other hand, when we varied the luminance between the horizontal screens, we found that 95 crabs decided to escape towards the screen with the higher luminance. These behavioral results establish solid bases for begin investigating the neuronal mechanisms involved in such decision making processes.

PREPROENKEPHALIN KNOCKOUT MICE DID NOT SHOW SENSITIZATION TO THE BEHAVIORAL EFFECTS OF COCAINE.

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Repeated as well as an acute exposure to psychostimulants like cocaine is characterized by enhanced neurochemical and behavioral responses to a subsequent administration of the same drug (sensitization). This phenomenon is associated not only with the dopaminergic mesocorticolimbic system, but also with other neurotransmitters systems, such as methionine-enkephalin (met-ENK). We previously demonstrated that acute and chronic administration of amphetamine or cocaine induce both an increase in met-ENK levels in key mesocorticolimbic brain areas, such as nucleus accumbens and prefrontal cortex, which suggest the involvement of the enkephalinergic system in the sensitization to psychostimulants. Thus, we studied the development of behavioural sensitization to cocaine in wild type (Penk +/+) and knockout (Penk -/-) preproenkephalin mice. Penk +/+ and Penk -/- male C57B/6J mice were treated with a daily saline or cocaine (15mg/Kg/day, ip) injection during 9 days, and were exposed to a challenge cocaine dose (7.5mg/kg, ip) on day 15 and 21. The locomotor activity was recorded 30 min after each injection. The acute locomotor response to cocaine was similar in wild type (Penk +/+) and knockout (Penk -/-). However, the behavioral sensitization to cocaine was not evidenced in the knockout mice as compared with their wild type controls. This finding is the first one showing the involvement of the enkephalinergic system in the cocaine-induced behavioral sensitization.

Poster Number (60) Sessión III

CHANGES IN HIPPoCAMPAL ARC PROTEIN EXPRESSION AND SYNAPTIC PLASTICITY BY THE PRESENTATION OF CONTEXTUAL CUES LINKED TO DRUG EXPERIENCE

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Hippocampal synaptic plasticity has been related to learning memory and adaptive processes developed during chronic administration of drug abuse. In this study, we investigated if the environmental context associated with drug experience was able to evoke the same behavioural alteration observed after chronic diazepam administration. We also studied the hippocampal synaptic plasticity and anatomical expression of Arc protein during withdrawal and retrieval as a marker of neuronal activity. We demonstrated that re-exposition to the initial context was associated with the expression of the anxiety sign, characteristic of benzodiazepine withdrawal, evoked on days 15 and 25. An increased hippocampal synaptic plasticity, on dentate gyrus, was observed in animals dependent on diazepam and during retrieval until day 15. However this correlation disappeared 25 days after the first exposure to the context. Moreover an over expression of Arc protein in dorsal dentate gyrus and CA1 during the first day, in the dependent animals and also during their re-exposition on day 15 was observed. In conclusion the behaviour evoked by the environmental context associated with the experience of the drug on day 25, but not linked to an increased hippocampal synaptic plasticity or over expression of Arc protein, may indicate that this behaviour on day 25 is not dependent on the hippocampus but may be dependent on other cortical areas of the brain.

Cognition, Behavior and Memory
Poster Number (61) Session III

HALOPERIDOL PREVENTS MEMORY DEFICIT INDUCED BY SLEEP DEPRIVATION IN RATS

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In our previous studies we showed that REM sleep deprivation (RSD) produces impairment in rats performance evaluated by the Multiple Trial Inhibitory Avoidance task (MTIA). In addition RSD produces an up-regulation of dopaminergic D2 receptors. We thus hypothesize that this altered dopaminergic system could be one of the basis of learning and memory deficits induced by RSD. The aim of the present study was to evaluate if haloperidol administration after 96h of sleep deprivation can prevent the deleterious effects on learning and memory in rats. Male wistar rats were submitted to 96h of RSD and trained on the MTIA. Haloperidol (3mg/kg) or saline (0.9) was administrated intraperitoneally 30 min before the training session. Thirty-eight animals were allocated into four groups: sleep-deprived that received haloperidol (n=8); sleep-deprived saline (n=10); control haloperidol (n=10); control saline (n=10). Training of MTIA consisted on each time the animal crossed to dark compartment of the apparatus it received a 0.7 mA/1sec footshock. Immediately after each footshock the animal was placed again in safe compartment until it remained for 2 min. Number of crosses to dark compartment was the measure of acquisition. Retention test were carried out 24h later. On retention test no footshock was delivered, only the latency to cross to the dark compartment was recorded. If the animal did not cross within 300 sec it was removed from the apparatus and a 300 sec latency was attributed. A one-way ANOVA revealed no impairment in sleep deprived animals on training session. On the other hand, during test session the performance of sleep deprived animals that received saline was impaired compared to other groups (Two-way ANOVA; p0.05). The sleep-deprived haloperidol group did not differ from the control groups showing that the drug was able to prevent the memory impairment induced by 96h of REM sleep deprivation. We conclude that the D2 dopaminergic receptors could be responsible for the memory impairment cause by REM sleep deprivation.

Poster Number (62) Session III

GRAPH ANALYSIS OF PSYCHOTIC DREAM REPORTS: QUANTITATIVE DIFFERENCES BETWEEN SCHIZOPHRENIA AND MANIA

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Psychoanalytic theory postulates that dreaming resembles the psychotic state, and that the analysis of dream reports is important to understand the mechanism of thought. Psychotic patients can be classified as either schizophrenic or maniac, based on qualitative thought differences. The aim of this study is to quantify thought differences among schizophrenic and maniac psychotic subjects using graph representations of their dream reports.We recorded and transcribed interviews of 24 subjects (8 schizophrenics, 8 maniacs and 8 controls), applied the SCID DSM IV, PANSS and BPRS scales to identify symptoms, and collected dream reports. These reports were parsed into semantics units (SU) and represented by a graph in which each node corresponded to a SU and each edge represented the link between SU . A non-parametric statistical test was used to assess significant differences (Kruskal-Wallis). We found that maniac reports contain more words (p=0,0016), SU (p=0,0038), nodes (p=0,0053) and edges (p=0,0046), and also speak more about their waking state (SU, p=0,0042; nodes, p=0,0067; and edges, p=0,003) than schizophrenic reports. Normalizing by the total number of words of the discourse, maniac subjects still speak more about the waking state (SU, p=0,0385; nodes, p=0,0498; and edges, p=0,0196). In contrast, normalized graphs representative of schizophrenic dream reports presented more nodes (p=0,0115) and a larger diameter (p=0,0134), in comparison with graphs from maniacs. Our data show quantitative differences between the graph representations in dream reports of schizophrenics and maniacs. The results reflect schizophrenic symptoms like “alogia”, and maniac symptoms like “logorrhea” and “flight of thoughts”.

IMPLICIT PREFERENCES AND GAZE IN THE COURSE OF A DECISION

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Breasts, hip and buttock size and shape are known to be important factors in sexual selection. Together with other body traits, these individual factors are combined to form a subjective idea of physical attractiveness. Individuals are often unaware of the relative weights of these factors in determining sexual preference and choice. The challenge of this work was to design an empirical and objective manner, in absence of explicit reports, of a person's relative weights of breast and buttocks in female attractiveness judgments. We addressed this question by studying the behavior of the gaze in the course of a decision. Previous studies have shown gaze bias only just before the decision is a proper indicator of preference. Based on this finding, we designed an experiment where subjects had to choose between two pairs of photographs. Each pair was presented in one side of the screen and contained a photograph of a breast in the upper visual field and a buttock in the lower visual field. Participants had to determine which of the two pairs resulted –as a whole- more attractive. We explored which element of the set they were gazing at different times of the decision process. The photographs were downloaded from different sites in the web and standardized to a common shape, contrast and luminosity. To have a quantitative measure of the attractiveness of these photographs, we asked 19 subjects to rate them in a continuous scale. We found a strong correlation between the average and individual rates, indicating that the measured score was reliable. Here we show preliminary results of the analysis of gaze behavior during the attractiveness judgment.

Poster Number (64) Session III

INCREASED SUSCEPTIBILITY TO DELETERIOUS EFFECTS OF STRESS EXPOSURE DURING NEURODEVELOPMENT.

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Chronic stress exposure can cause several damages, ranging from impairments in learning and memory to enhanced neuronal cell death. Previously, we have shown that 2 months old C57Bl/6 mice are resistant to deleterious effects of chronic stress exposure. Herein, we are presenting a comparative study of the behavioural and neurochemical response to early life stress, and stress in adulthood, in this strain of mice. For this purpose, pregnant mice were individually restrained 2 hours daily, since gestational day 14 until delivery. The prenatally stressed offspring (PS) were tested at 2 months of age together with control matched mice (C) and one-week restrained adult mice (AS). We found that female PS showed poor learning and memory performance as compared to C, in the habituation to an open field test, and passive avoidance and Y-maze tests. However, AS showed similar behaviour to C. In order to investigate possible oxidative alterations in the hippocampus of these animals, we analyzed the nitric oxide synthases (NOSs) activities, and basal and NMDA-stimulated production of reactive oxygen species (ROS). Results indicate a non-significant increase in total NOS activity in PS in relation to C, but there arise no differences between AS and C. In addition to this, no changes in basal and stimulated ROS production are found, neither in PS nor in AS animals, as compared to C. To sum up, we conclude that during neurodevelopment, C57Bl/6 female mice have increased vulnerability to the deleterious effects of stress on learning and memory as compared to novel mice. However, oxidative mechanisms are unlikely to be regarded as the main cause. Antioxidant defences, such us catalase and superoxide dismutase, are currently under study.

OPERANT SELF-ADMINISTRATION OF ALCOHOL AND SUCROSE IN ADOLESCENT RATS

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Alcohol exposure during adolescence is associated with later alcohol affinity. It is therefore important to analyze ethanol consumption patterns during adolescence. In the rat, this has been assessed by two-bottle choice or forced intake tests. There have been far fewer attempts, however, to analyze ethanol reinforcement in adolescent rats through operant tasks. This may be due to a lack of operant behavioral techniques that can be fully implemented within the short timeframe of adolescence. This study examined operant self-administration of alcohol or sucrose in male and female adolescent Sprague-Dawley rats. On postnatal day (PD) 30, the rats (n=58) were surgically implanted with cannulae made out of polyethylene tubing. These devices permitted intraoral infusion of the reinforcers. During PDs 32-34, the rats were placed in operant chambers equipped with a single hole for nose-poking. The experimental (paired) rats received an intraoral infusion of ethanol (3-5, increasing 1 each day; 5 ul) or sucrose (5, 30 ul) after each nose-poke. Daily trials lasted for 30 min; yoked controls were employed for each experimental condition. The data analysis indicated significantly more daily target responses in experimental animals that in yoked controls (Xs=41.71 and 6.09, respectively). Operant responses per session were similar across males and females but significantly higher in sucrose-reinforced animals than in paired rats given ethanol (Xs=55.93 and 28.79, respectively). Average ethanol intake per session was 0.20 g/kg. The experiment indicates that, without the need for a long training or an initiation phase, ethanol supports operant self-administration in adolescent rats, although at a much lower rate than does sucrose.

Poster Number(66) Session III

RECONSOLIDATION AND EXTINCTION OF MEMORY IN THE CRAB: MUTUAL EXCLUSION OR CO-EXISTENCE

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Memory reconsolidation and extinction are two mnesic processes that may share a functional relationship, since they are both involved in processing new information related to a previous learning. While extinction transiently replaces the expression of the old memory with a newly formed memory, it has been suggested that reconsolidation opens the old memory for updating. Moreover, either process can be triggered by an unreinforced conditionned stimulus (CS). However, it has been shown in a variety of paradigms that reconsolidation and extinction do not occur together as a consequence of CS presentation. Rather, only one of the processes is triggered, and which one is triggered depends on certain CS parameters such as duration. This has led to different interpretations proposing a negative interaction between reconsolidation and extinction during CS exposure. In our previous work with crabs, we had shown that when a single CS is presented only reconsolidation is triggered after a short (1 h) CS exposure, and only extinction is triggered after a long (1 h) one. In the present work, however, we have found that when different CSs are serially presented, namely a short reconsolidation-inducing CS followed soon by a long extinction-inducing CS, both reconsolidation and extinction are triggered. Moreover, we show here for the first time that the two processes develop simultaneously. These results demonstrate that there is no intrinsic constraint for the two processes to occur together, thus ruling out the possibility of a negative interaction of one process on the other. Instead, the results support our hypothesis of a mnesic mechanism driving memory to reconsolidation or extinction, which becomes operative after CS offset.

SEROTONIN AND APPETITIVE MEMORY

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Serotonin is a biogenic amine that can act as a neurotransmitter, neuromodulator or a neurohormone; and it is involved in a variety of physiological processes. Its localization in brain areas involved in cognition has made this amine a target for the study of learning and memory. Many reports have been published attributing to serotonin a direct or indirect role in diverse phases of vertebrate memory, and also, but with less frequency, in diverse phases of invertebrate memory. An aversive learning paradigm with the crab Chasmagnathus has been used extensively in our laboratory; it is based on the crab's escape response elicited by the presentation of a visual danger stimulus, which represents the negative reinforcement. Since this long-term memory results from an association between context and a signal, it is termed context-signal memory (CSM). Our previous results have shown that exogenous administration of serotonin negatively modulates both memory consolidation and reconsolidation of the CSM. Moreover, fluoxetine, an inhibitor of serotonin reuptake, also has an amnesic effect in both memory processes. Recently, a new appetitive learning paradigm was developed, supplying food as a positive reinforcement that becomes associated with the context where it was received. At test session, trained animals perform more exploratory activity than controls when reinstalled in the learning context. The aim of the present work is to characterize the effect of serotonin in this memory paradigm. Preliminary results show that fluoxetine administration has an amnesic effect in this appetitive learning. These results suggest that serotonin may have a detrimental effect on memory irrespective of the learning paradigm used.

Poster Number (68) Session III

CLONAZEPAM IMPROVES MEMORY WHEN ADMINISTERED CONTINGENT UPON RECONSOLIDATION IN HUMANS

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The reconsolidation hypothesis states that a consolidated memory could again become susceptible to facilitation or impairment for a discrete period of time, after a reminder presentation. When this happens, the memory enters a vulnerability phase (labilization), followed by a process of stabilization (reconsolidation). The reminder is the event that begins with the presentation of the learned cue and triggers the labilization-reconsolidation process of the memory. As it has been previously demonstrated in other species, the reconsolidation process was also recently described in a human declarative memory. Recently, our group showed that specific reminder parametrical conditions, ensure memory undergoing reconsolidation. Based on these results, we decided to explore the Gabaergic system contribution to the recosolidation process. In order to evaluate this, bezodiazepines were administered after a verbal task memory was labilized. Experiments were carried out in FLENI and the expermiental design consists in a 3 days task in which volunteers learn, on the first day, an association between five cue-syllables and their respective response-syllables. Then, during the second day, the paired associated verbal memory is labilized by exposing the subjects to the reminder and inmediately after that, Clonazepam (0.25mg) or placebo is orally administered. Finally, on the third day, the volunteers are tested for the acquired memory. Preliminary results indicate that when a gabaergic agonist was administered within the reconsolidation window of a declarative memory, memory retrieval was markedly facilitated. This effect, was not observed when the reminder parametrical conditions were changed or when placebo was administrated.

DEVELOPMENT OF A 3D TRACKING DEVICE BASED ON TWO NINTENDO WII CONTROLLERS

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Tracking human motion in real time provides an important insight into brain function and cognition. Commercial equipments designed for this purpose exist but they are typically expensive (more than U$3000). We developed an efficient and inexpensive device based on two Nintendo wii-controllers (wiimotes), each one with a cost of U$50. The wiimotes contains a 1024x768 infrared camera with built-in hardware blob tracking of up to 4 points. It communicates with the console or the pc via Bluetooth. Using two wiimotes we developed a motion tracking setup capable of tracking in 3D up to four infrared LEDs at 165Hz with a spatial resolution of 1mm. The wiimotes are connected to a computer and the algorithms responsible of the 3D reconstruction from the images taken with each controller were done in Matlab. We designed a layout of the tracking system optimised to study finger trajectories in a variety of experimental paradigms (e.g. reaching and grasping human movements). We are currently applying this system to record the trajectories of a finger in a task in which the subject points towards targets appearing on a computer screen.

Poster Number (70) Session III

NODAL DISTANCE EFFECTS IN STIMULUS EQUIVALENCE: AN ERP STUDY

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Equivalence classes paradigm has been applied to the study of abstract categories (Sidman, 1982; Zentall, 2002). An equivalence class is learned when, after training conditional discriminations between stimuli (AB, BC, CD), untrained properties of reflexivity, simmetry and transitivity emerge. It has been proposed that equivalence classes constitute an associative network, where each association between stimuli correspond to a link between two nodes. (Fields, Adams, Verhave and Newman, 1990). It has been observed that, after training AB, BC, CD associations, accuracy is higher and response times are lower for tests of derived relations separated by one node (AC, BD) than for relations separated by 2 nodes (AD, BD). This is known as "nodal distance effect". The current experiment studied nodal distance on behavioral measures and event-related potentials. 86 subjects learned two five-member equivalence classes (A,B,C,D,E) by matching to sample. Half the subjects were trained in an ordered sequence (AB-BC-CD-DE) and half in a non-ordered sequence (CD-DE-AB-BC). Derived relations of 1 (AC, CA), 2 (DA, DA) and 3 (EA, AE) nodes were tested. Percentage of correct responses was lower on tests of 3 node relations (p 0.001). The procedure was repeated on 17 subjects, testing for derived relations of 0, 1, and 3 nodes while measuring EEG activity. A positive, P300-like ERP was found between 400-600ms. The P300 was higher for the greatest nodal distance (p = 0.041), but only on subjects trained in an ordered sequence. Results suggest that relations with higher nodal distance pose greater cognitive demands, because they require activation of a larger number of elements in the associative network of the equivalence class.

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SYTANX AND MATH

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Hauser and Chomsky hypothesized that language and other distinctively human activities such as number manipulation relied on a recursive ability, capable of generating an infinite range of expressions from a finite set of elements. In turn, recursion results in a hierarchical syntactic organization of language and, tentatively, also of other manifestations of human thoughts. In the present work we study the role of syntax in arithmetic thinking. We explored whether symbol manipulation in arithmetic is processed spontaneously in a hierarchical tree structured way, investigating eye-movement sequences during equation solving. Participants were are asked to solve simple algebraic strings, involving three arithmetic operations. Operations in the string were grouped by parenthesis, generating two different syntactic structures: left ((3+2)-4)+1or right 1+(2-(3+4)) side branched trees. Since strings are arranged in a spatial dimension, we can make inferences about cognitive processing occurring during algebraic manipulation by measuring when and where readers move their eyes. Preliminary results have shown that when reading, the subject's gaze is first directed to the lowest branch of the tree (placed in the left o or in the right side of the screen depending on what string has appeared) and then it progresses sequentially to higher levels. This shows that, contrary to text reading, equations are not scanned symbol by symbol, in a spatially sequential manner but rather according to their syntactic structure. Thus, participants extract implicitly and spontaneously the syntactic structure of arithmetic operations which is then used to establish a precise sequence of operations.

Poster Number (72) Session III

HAND MOVEMENTS IN A NATURAL TASK AS A WINDOW TO COGNITION

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A strategy traditionally used to study human perception is to present simple and artificial stimuli such as lines or points, using brief presentations of a few milliseconds. But what is simple for the brain not necessarily is mathematically simple. The human brain evolved in an environment full of complex stimuli, and it acquired the ability to analyze and understand these stimuli in a quick and automatic way. For this reason, in recent years there is a tendency towards using natural tasks and dynamic stimuli, with continuous presentations, aiming to capture the inherent complexity of human activities. When studying natural tasks, the use of video games seems an ideal choice. It presents a dynamic and controlled scene, in which the subject must make decisions continuously: what is important and what is not to gain more information, when and how to move. In this work we present the results of a version of the popular game Arkanoid. In this simple task, with only three objects in a dynamic display (ball, base and a brick), the observed movement of the eyes and hands is very informative of the underlying cognitive activity. In particular, base movement strategies are is studied, analyzing when movements start and where they stop. We found than the players start moving the base when they acquire enough information about ball trajectory and impact location. Base is moved in a successive approximations' manner, stopping in locations that maximize the probability of catching the ball given the currently acquired information. We designed a model robotic player that can reproduce the essence of base movements. Here we present results that show their relation with different states of the rapidly changing environment.

BDNF ACTIVATES MTOR TO REGULATE GLUR1 EXPRESSION REQUIRED FOR MEMORY FORMATION

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The mammalian target of Rapamycin (mTOR) kinase plays a key role in translational control of a subset of mRNAs. In neurons, mTOR is present at the synaptic region, where it modulates the activity-dependent expression of locally-translated proteins independently of mRNA synthesis. Indeed, mTOR is necessary for different forms of synaptic plasticity and long-term memory (LTM) formation. However, little is known about the time course of mTOR activation and the extracellular signals governing this process or the identity of the proteins whose translation is regulated by this kinase, during mnemonic processing. Here we show that consolidation of inhibitory avoidance (IA) LTM entails mTOR activation in the dorsal hippocampus at the moment of and 3 h after training and is associated with rapamycin-sensitive increase in AMPA receptor GluR1 subunit expression, which was also blocked by intra-hippocampal delivery of GluR1 antisense oligonucleotides (ASO). In addition, we found that pre- or post-training administration of function-blocking anti-BDNF antibodies into dorsal CA1 hampered IA LTM retention, abolished the learning-induced biphasic activation of mTOR and blocked GluR1 expression. Interestingly, BDNF controls the biphasic requirement of mTOR during LTM consolidation through different mechanisms: an early one involving BDNF already available at the moment of training, and a late one, that needs de novo synthesis of BDNF. In conclusion, our findings demonstrate that: 1) mTOR-mediated mRNA translation is required for memory consolidation during at least two restricted time windows; 2) this kinase acts downstream BDNF in the hippocampus and; 3) it controls the increase of synaptic GluR1 necessary for memory consolidation.

Poster Number (74) Session III

TWO OPEN FIELD EXPOSURE FACILITATES PERFORMANCE IN AN INHIBITORY AVOIDANCE TASK

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We have studied the performance of adult Wistar rats in Inhibitory Avoidance (IA) with or without postweaning handling.IA consists in recording training and test latencies to step down onto a grid from a platform,avoiding a mild footshock. Rats were trained with different intensities (0.4-1.5 mA).Learning criteria was reached with 0.5mA or higher for males, and with 0,75mA for females,with postweaning handling.We then evaluated the influence of an Open Field (OF) on performance of male rats in IA,with or without handling.Rats were exposed to an OF for 3 min in two consecutive days;1 hour after the second session they were trained in IA (with either 0.75mA or 1mA);the test session was performed 24h later.Rats that were not previously trained in the OF were also evaluated.All groups reached the learning criteria.Those with handling,that were trained and tested in the OF,showed a significantly better performance in the IA (1 mA),compared with those that were not exposed to the OF;and they performed better than those with handling without OF exposure.Moncada

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Poster Number (75) Session III

IN SEARCH OF THE MECHANISMS THAT DIFFERENTIALLY DETERMINE LONG-TERM MEMORY STORAGE AND EXPRESSION

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Not every acquired experience builds a memory that can be expressed in the long term. Until now, deficits in memory expression were interpreted as deficits in memory storage, or in retrieval. However, evidence in the crab Chasmagnathus, and very recently in humans, have shown that encoded memory traces can be retrieved even in the absence of behavioral expression. This fact implies that the mechanisms involved in expression and storage of long-term memory are different. Our main goal is studying the mechanisms that determine during consolidation whether a memory trace will be behaviorally expressed on the long term. In this framework, we propose that to reopen the possibility for neuromodulators to improve memory expression is a functional value of reconsolidation. A first approach to this problem is to isolate the treatments that induce deficits in memory expression from those that induce "true amnesia". The basic behavioral protocol consists in the interference of memory consolidation followed by a subsequent post-reminder facilitator treatment. Under this circumstance, if memory expression is reinstalled after facilitation of reconsolidation, the mechanism interfered should be related to memory expression and not to memory storage. Angiotensin II is a neuromodulator that affects long-term memory expression. As other systems should be involved, initially we will study glutamatergic and muscarinic neurotransmission during acquisition and during consolidation, as well as NF-kB transcription factor. In order to understand at cellular level the processes involved in long-term memory expression, neurons and neuropils related to memory process will be studied both by in vivo neuroimaging and by markers of neuronal activity

P600 EFFECTS IN AN ARTIFICIAL GRAMMAR LEARNING TASK: MODULATION BY FREQUENCY OF TRAINED SYNTACTIC STRUCTURE

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Several studies have found a positive ERP component (P600) around 600 ms after the presentation of a syntactic violation in natural languages, and artificial grammars with semantic content (Osterhout & Holcomb 1992; Friederici, Steinhauer, Pfeifer, 2002;),. It has been proposed that P600 reflects an expectancy violation in the analysis of sequenced structures (Patel, 1998), disregarding the semantic content of the stimulus. Furthermore, if P600 indexes expectancy violation, the component should be modulated by the frequency of appearence of the structure, as more frequent structures would be associated with a greater expectancy. Our objectives were 1) to determine the neural correlates of artificial grammar learning, based on transitional probabilites between pseudowords, without semantic content 2) to analyze P600 modulation by frequency of appearence of syntactic structures. 19 right-handed subjects (20-32 years old) were trained by exposure to grammatical sentences, presented audiovisually. The grammar had two posible syntactic structures, the frequent structure was presented in 2/3 of the training examples. During test, subjects had to clasify new sentences as correct or incorrect, with half of them presenting syntactic violations. A bilateral positive P600-like component was found for incorrect sentences($p = 0.002$). Furthermore, a significant frequency effect was found in left hemisphere channels ($p = 0.001$). Results support the hypothesis that P600 indexes expectancy violations in the analysis of structured stimulus sequences. As this component is also elicited by linguistic stimuli, we propose that domain general statistical mechanisms are recruited for syntactic processing in natural languages.

SUPERIOR ENCODING OF INFORMATION WITH MORAL CONTENT

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The aim of this study was to test the hypothesis that information with moral content is more easily remembered than information without moral valence, and that this difference may imply an affective process.For this, we designed an experimental protocol inspired in classic studies on affective memory. In a first 'observation' phase, subjects passively observed stimuli consisting of association between abstract pictures and words pertaining to different semantic categories. Semantic categories included cold/hot, animate/inanimate, happiness/sadness, and morally good/morally bad. In the following 'test' phase, abstract pictures were presented alone and subjects had to remember to which category of words they were associated during the 'observation' phase. The results revealed that performance was significantly higher for pictures associated to words pertaining to the moral and emotional categories than for pictures associated to other categories. This suggests the specificity of the cognitive process implied and highlights the importance of the presence of moral valence in the information we perceive. Furthermore, in line with Haidt's hypothesis, we show that categorization of moral information does not rely on explicit knowledge. Moral categorization might therefore be more intuitive than semantic categorization and close to conditioning : the mere vision of an abstract stimulus associated to moral information is sufficient to ensure its superior encoding in memory.

Poster Number (78) Session III

MEMORY IMPROVEMENT BY STRESS DURING RECONSOLIDATION IN HUMANS.

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The capacity to predict the future based on its own past experience is crucial to animals and has an understandable adaptive significance. But it is also crucial to change their behavior in the light of the present experiences. The reconsolidation is a process in which the retrieval of previously consolidated memory returns to a labile state. Historically, an operative definition of memory reconsolidation is that it is a process in which the reactivated-labilizated memory can be disrupted by amnesic agents. However, this vulnerability per se does not demonstrate the possible functional roles of reconsolidation. We test the hypothesis that to reopen the possibility for neuromodulators -triggered by real-life events- to change long-term expression would be one functional value of reconsolidation. Experiments included three sessions: a Training Session (Day 1), a Reactivation Session (Day 6) and a Testing Session (Day 7) and four experimental groups which differ in the treatments during the Reactivation Session. Here we found, using a paired associate learning developed in our laboratory specially to study the reconsolidation, that human memory can be improved during reconsolidation by a natural stressor. The memory improvement is disclosed at Testing Session on the condition that the specific reminder that triggers reconsolidation was concurrent with the stressor. This effect during reconsolidation could occur because of the reinforcement of retrieval conversion links that are critical for long-term memory expression. Here, as in our previous experiments in crabs, we show experimental evidence that a natural stressor can change long-term memory expression during reconsolidation in a human declarative memory.

Cognition, Behavior and Memory
Poster Number (79) Session III

IS THE FOLSTEIN'S MINI MENTAL TEST AN APHASIA TEST

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Introduction: the Folstein's mini mental test (MMSE) is recognized as a valid measure for detecting dementia. However, it consists of 29/30 verbal items. The Brief Aphasia Evaluation (BAE) includes 10/72 aphasia items and 5/12 orientation items which are similar to most of the MMSE subtests except for its non-verbal one. Alternatively, the most unquestionable property of aphasia tests is the discrimination of patients injured in the verbal dominant hemisphere. Objectives: To study if this subgroup of 15 BAE items (MMSE-like): a) correlate with the rest of the BAE items (BAE-rest), and b) differentiate patients with left encephalic lesions (LP) from both patients with right encephalic lesions (RP) and healthy subjects (HS). Methods: A sample of 109 right-handed volunteers (37 LP, 34 RP, and 38 HS) was studied. The three groups were matched according to sex, age and education. Both groups of patients were also similar in multiple control variables. Results: The correlation between the "MMSE-like" and the "BAE-rest" was 0.89. They showed a sensitivity and specificity of 0.81 or above and of 0.84 or above, respectively; to identify the LP from the other two groups. Conclusion: There is a risk of misdiagnosing aphasia for dementia with the MMSE.

Poster Number (80) Session III

CONCURRENT AND CONCEPT VALIDITY-STUDY OF THE BRIEF APHASIA EVALUATION (BAE) IN PATIENTS WITH LATERALIZED ENCEPHALIC LESIONS

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Introduction: There is a lack of aphasia tests for Spanish speakers validated by the brain injury side. Objectives: To study the concurrent validity of this Brief Aphasia Evaluation (BAE) to differentiate patients with left encephalic lesions (LP) vs. patients with right encephalic lesions (RP) as well as LP vs. healthy subjects (HS). To study, through subtest-factor analysis, the BAE conceptual validity to generate a verbal homogeneous construct which explain most of the variance among subjects. Methods: Data were obtained from a sample of 109 right-handed volunteers: 37 LP, 34 RP, and 38 HS. The three groups were matched according to sex, age and education. Results: Both groups of patients were similar in: type and site of lesion, time since onset of disease, risk factors, presence of hemianopsia and hemiparesis, and frequency of inpatients. The Cronbach´s alpha coefficient indicated an internal consistency of 0.99 for the total score and of 0.88 or above for any of the subtests. All the subtests (with loadings of 0.65 or above) grouped in one unrestricted factor which explained 78 of the variance. The BAE showed a sensitivity and specificity of 0.84 or above to identify the LP (median as cut-off point). Conclusion: This test of free distribution demonstrated a satisfactory validity.

Cognition, Behavior and Memory
Poster Number (81) Session III

THE NEURAL SUBSTRACT OF GESTURE RECOGNITION WITHIN AND WITHOUT A NATURAL VISUAL CONTEXT

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Previous studies have linked action recognition with a particular pool of neurons located in the mirror neuron system. However, it is still unclear if transitive (tool use) and intransitive (communicational) gestures share the same neural substrates during action recognition processes. We used event-related fMRI to assess the cortical areas active during recognition of transitive actions compared to intransitive gestures. Perception of all types of gestures engaged the parietofrontal circuit: bilaterally premotor, parietal and superior temporal cortex, left inferior parietal lobe and right prefrontal cortex. The most striking finding was the greater activation of the left inferior frontal gyrus during recognition of intransitive actions. Results show that a similar neural substrate, with a distinct engagement underlies the cognitive processing of transitive and intransitive gestures recognition. Additionally we compared intransitive gestures within and without their natural context. All previous works have studied those gestures against a blank background; but in real life they are immersed in a contextual situation that helps understand their meaning. Using event-related fMRI we investigated the neuronal bases of symbolic gesture recognition within an appropriate visual context. Activation for both gesture tasks were found bilaterally in occipitotemporal regions, parietal association areas, premotor cortex, inferior frontal gyrus and in the right posterior superior temporal regions. The comparison between gestures within and without the context demonstrated an increment of the activity in the right inferior frontal gyrus. This area seems to be associated with the intentionality of the gesture.

INFERENTIAL LEARNING OF NEW VERBAL MEANINGS IN ADULTS: AN ERP STUDY

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In adults, language acquisition cannot be attained by mere exposure to the linguistic context, as is the case during infancy. Although the basis of this behavioral difference is unknown, it is possible that both groups rely on distinct learning mechanisms. For instance, implicit learning is highly relevant during language acquisition in infants (e.g. Gómez & Gerken 1999), while the acquisition of a second language (L2) in adults relies mainly on explicit mechanisms. Implicit learning is characterized as a passive process, where knowledge of information is acquired through simple exposure to it. Explicit learning, is characterized as a process where the structure of information is actively searched for. In the present work we studied whether adults could acquire new verbal meanings by a process of inferential learning, a process shown to be highly relevant in infants during language acquisition (Marklund & Lacerda 2006). 19 adults were trained by rapidly presenting 70 different examples of 5 geometric figures performing 6 possible movements. Each example was simultaneously described by an audiovisual sentence in an artificial language. During testing, new figure/movement combinations were presented in combination with sentences, half of which did not describe the movement shown in the image. Subjects had to respond rapidly whether the sentences corresponded to the image or not. 15 of 19 adults responded above chance (G-test). Analysis of eeg recordings during testing, showed a N-400 like component with maximal significant differences between correct and incorrect sentences in centro-parietal channels. Results show that adults can acquire new lexical meanings by a process of inferential learning, as shown in infants.

AN EARLY ERP SIGNAL RELATED TO PRIME-TARGET SYNTACTIC MISMATCH IN A LEXICAL DECISION TASK

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Two main questions in models of word processing are what information is accessed during word recognition, and which is the temporal dynamics of activation of this information. Event related potentials (ERP) from electroencephalographic (EEG) recordings during performance of language tasks seemed traditionally to support serial models of language processing (eg. Kutas et al 1988; Hagoort et al 1993). These models propose a sequential activation of phonological, semantic and syntactic information associated with words. More recent studies have found ERP signals associated with syntactic mismatches or violations within an early time window (200 ms), traditionally associated with phonological processing (Barber & Carreiras 2005). In this study we analyzed possible early ERP signals associated with a prime-target mismatch at the syntactic level in a lexical decision task. 26 right-handed native speakers of Spanish, were presented with 100 relevant prime-target pairs and 100 prime-target fillers (ISI 250 ms). All prime and relevant target words were Spanish verbs in 3rd ppl form, while 100 target non-words were fillers. 50 relevant prime-target pairs shared all verbal syntactic information (Same group), while 50 differed only in verbal mode between prime and target (Different group). Results showed a significant decrease in reaction time to targets of the Same group compared to the Different group (p0.02), showing activation of verbal mode during the task. EGG recordings showed significant differences in frontal channels in the amplitude of an early positivity peaking ca. 100 ms after target appearance. The pattern of results seem to support an early activation of verbal mode information during recognition of spanish verbs.

Poster Number (84) Session 1

DPP SIGNALING CONTRIBUTES TO SET BASIC PROPERTIES OF THE DROSOPHILA CIRCADIAN NETWORK

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Living organisms use circadian rhythms to maintain internal temporal order and anticipate daily environmental changes. Clocks employ self-sustained biochemical oscillators and manifest at molecular, physiological and behavioral levels. In Drosophila, a group of neurons expressing the Pigment Dispersing Factor (PDF) represent the so- called "central oscillator" of the fly brain. As a result of a missexpression screen using the GAL4/UAS system we identified a fly strain that causes period lengthening of the daily activity rhythms. The transposon landed within schnurri (shn), a nuclear component of the decapentaplegic (dpp) signal transduction pathway. shn overexpression in the PDF+ circuit is necessary and sufficient to generate a 25.5h period of locomotor behavior while downregulation of shn levels cause a deconsolidation of the behavioral rhythms. A detailed analysis of PER subcelular localization throughout the day indicated a delayed PER nuclear entry in the mutant compared to that of wild type flies, pointing to a specific effect of shn deregulation on the core clock mechanism. Interestingly, constitutive overexpression of activated receptors that initiate the dpp signalling cascade also gave rise to long period phenotypes. In contrast, downregulation of the endogenous receptors also impacted circadian rhythmicity. Recent reports point to the dpp pathway as a retrograde signal that set synaptic properties and, in combination with other cellular clues, establish the peptidergic fate of a specific circuit in the fly brain. In this context it is tempting to speculate that period lengthening could derive from a deregulated DPP signalling during development and/or maintenance of the PDF circuit.

Cronobiology
Poster Number (85) Session 1

TIME SWEET TIME: CIRCADIAN CHARACTERIZATION OF GALECTIN-1 NULL MICE

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Interactions between the immune and circadian systems are essential in the study of disease progression and treatment. The circadian control of immune factors, as well as the effect of immunological variables on circadian rhythms, might be a key element in both physiological and pathological responses to the environment. Among the relevant immune factors, galectins are a family of evolutionarily conserved glycan-binding proteins with both extracellular and intracellular effects, playing important roles in immune and inflammatory responses, tumour development and other biological process. Many of these actions have been proposed or confirmed by the use of mice with a null mutation in the galectin-1 (Lgals1) gene. To further analyze the role of endogenous galectin-1 in vivo, we aimed to characterize the circadian activity behavior of galectin-1 null mice. We analyzed wheel-running activity periods in constant darkness and phase responses to light pulses at CT15 in wild-type and KO mice. We found differences between both groups in both free-running period, which was longer in mutant than in WT mice (23.84 vs 23.55 hs, p0.05), and phase delays in response to LP (2.92 vs 1.90 hs, p0.05). We tested the effect of galectin-1 on cultures of per-luc bioluminescent mice suprachiasmatic nuclei (SCN) slices, but we found no effects on period or dampening of per-luc rhythms. We hypothesize that galectin-1 could be involved in the early development of the SCN, as in other brain areas, instead of having a specific role on the maintenance of the circadian rhythms. Finally, we looked for the expression of galectin-1 at the level of the SCN. This is the first study implicating galectin-1 in the mammalian circadian system.

Poster Number (86) Session 1

THE ELECTRICAL SILENCING OF PACEMAKER NEURONS CAUSE REVERSIBLE DISRUPTION OF CIRCADIAN LOCOMOTOR ACTIVITY IN DROSOPHILA MELANOGASTER

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Circadian rhythms regulate differents aspect of physiology and behavior, based on self-sustaining transcriptional feedback loops of clock genes. Over 150 neurons are implicated in circadian regulation of locomotor behavior in the fly brain but the small ventral lateral neurons (sLNvs) are at the top of the hierarchy. The preservation of molecular oscilation specifically in the sLNvs is necessary to command rhythmic behavior. The sLNvs express the neuropeptide PIGMENT DISPERSING FACTOR (PDF). Rhythmic release of PDF is thought to be important for the transmission of time information; daily structural changes of axonal terminals of this circuit might be relevant too. Electrical activity of PDF neurons is also required for rhythmicity. Silencing PDF neurons by expressing a K+ channel (KIR) during the lifetime leads to behavioral arrythmicity and blocks molecular oscillations in the sLNvs. To study this process avoiding developmental defects that might interfere with the analysis, we developed a new tool for temporal control of gene expression in PDF neurons. Silencing the PDF circuit only during the adult stage led to behavioral arrythmicity as previously described. Surprisingly, once kir expression was shut down, flies recovered rhythmicity in a phase reminiscent to that of the initial training. PERIOD oscillations in the sLNvs showed that the molecular clock remained intact through the silenced phase, supporting that arrhythmicity is a consequence of the incapability of these neurons to transmit information rather than an effect on the clock. Thus, electrical silencing could be directly affecting structural plasticity of PDF terminals, consequently changing the synaptic partners, and finally impacting circadian behavior.

Cronobiology
Poster Number (87) Session II

PASSING THE CIRCADIAN TORCH: SCN ASTROCYTES AND IMMUNE-CIRCADIAN INTERACTIONS.

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The immune and circadian systems are interconnected in a bidirectional fashion. Circadian variation in several cytokines levels, circulating blood cells and sensitivity to diverse drugs has been extensively described. Moreover, the administration of peripheral immune stimuli (such as LPS) is capable of altering the circadian rhythm of locomotor activity in mice. Finally, we have previously shown that SCN astrocytes are part of the interface in which the interaction between these two systems might occur. In this work we investigated this interaction in vitro. In particular, we assessed the effect of the proinflammatory cytokine TNF-alpha in cultured mouse SCN astrocytes and found that treatment with this cytokine significantly attenuated the expression of the clock gene Per. Next we examined if SCN astrocytes were capable of releasing a signal that could affect clock gene expression in other cells. We found that conditioned media from SCN astrocytes cultures stimulated with LPS or TNF-alpha induced per-luc expression in NIH-3T3 transfected fibroblasts. Furthermore, TNF-alpha and IL-1B also induce Per expression in fibroblasts cultures. Taken together, these results suggest that immune stimuli affecting SCN astrocytes are capable of altering their clock gene expression and also induces a response that can modify circadian genes in other cells.

Poster Number (88) Session II

NEUROGRANIN EXPRESSION OSCILLATES ON A DAILY BASIS IN THE HIPPOCAMPUS AND IS MODIFIED BY A VITAMIN A-DEFICIENT DIET.

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Neurogranine (RC3) is a postsynaptic PKC substrate involved in synaptic plasticity and implicated in the maintenance phase of LTP. RC3 and retinoid nuclear receptors, RARα and RXRβ, have been detected in the rat hippocampus. Here, we investigate whether RC3 displays a daily expression pattern in the rat hippocampus, and evaluate to which extent vitamin A deficiency could modify RC3 rhythmicity. Holtzman rats weaned at 21 d of age were immediately assigned to either the experimental diet, devoid of vitamin A (vitamin A-deficient group) or the same diet containing 4000 IU of vitamin A/Kg diet (control group) during 3 months. Hippocampus samples were taken every 4 h from control and vitamin A-deficient rats. Scanning of RC3 gene regulatory region for putative RAREs and clock-responsive E-boxes was carried out using MatInspector software from Genomatix. Total RNA was isolated using Trizol reagent. RARα and RXRβ mRNA levels were quantified by Real-time PCR. Daily RC3, Bmal1, Per1 and Cry1 transcript levels, were determined by RT-PCR. Protein levels were analyzed by immunoblotting. We found three E-boxes and two RAREs within 1550 bp upstream of the translation start codon in the RC3 gene. We observed RC3 expression displays a daily rhythmicity in the rat hippocampus. RXRβ mRNA levels were significantly reduced in the vitamin A-deficient rats. Daily rhythm of RC3 expression was phase shifted in the vitamin A-deficient group following changes in BMAL1 levels, probably by a lower availability of RXRβ. Above observations raise the possibility that nutritional factors might be essential to maintain the daily expression pattern of clock-controlled, learning-related, genes in the hippocampus.

Cronobiology
Poster Number (89) Session II

DAILY EXPRESSION OF REV-ERBβ AND RORα NUCLEAR RECEPTORS IS MODIFIED IN THE HIPPOCAMPUS OF VITAMIN A-DEFICIENT RATS

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The REV-ERB/ROR orphan NR subfamily regulates the expression of core clock genes and contributes to the robustness of the clock mechanism. Retinoic acid receptors are involved in the resetting of peripheral clocks and RARα and RXRβ nuclear receptors have been detected in the rat hippocampus. The objectives of this study were to investigate whether Rev-Erbβ and Rorα displayed a circadian expression pattern in the rat hippocampus, and evaluate to which extent vitamin A deficiency could modify their daily oscillation by modifying RAR and/or RXR expression. Holtzman rats weaned at 21 d of age were immediately assigned to either the experimental diet, devoid of vitamin A (vitamin A-deficient group) or the same diet containing 4000 IU of vitamin A/Kg diet (control group) during 3 months. Hippocampus samples were taken every 4 h from control and vitamin A-deficient rats. Total RNA was extracted using the Trizol reagent and following manufacturer's instructions. Transcript levels of Rev-Erbβ and Rorα were determined by RT-PCR. RARα and RXRβ mRNA levels were quantified by Real-time PCR. Protein levels were determined by immunoblotting. We found Rev-Erbβ and Rorα expression display a daily rhythmicity in the hippocampus of control rats. RXRβ transcript levels were significantly lower in the vitamin A-deficient rats compared to controls. Daily rhythms of mRNA and protein expression of Rev-Erbβ, Rorα and, consequently, Bmal1, were phase shifted in the vitamin A-deficient group. Thus, vitamin A deficiency modifies the circadian expression of core clock components in the hippocampus, probably, by reducing the availability of retinoid nuclear receptors such as RXRβ and phase shifting Rev-Erbβ/Rorα expression.

Poster Number (90) Session III

PAYING THE CIRCADIAN TOLL: THE CIRCADIAN RESPONSE TO LPS INJECTION IS DEPENDENT ON THE TLR4 RECEPTOR

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Although there is substantial information regarding the circadian modulation of immunological variables, little is known about the circadian effect of immune factors. Systemic low doses of endotoxin lipopolysaccharide (LPS) delivered at CT15 (Circadian Time 12 corresponds to locomotor activity onset) induce phase-delays of locomotor rhythm in mice. Our aim was to characterize the circadian behavior and LPS-circadian response of TLR4 (LPS receptor)-KO mice (C57bl/10ScCr), and their corresponding control strain mice (C57bl/10ScCn). We observed a free-running period and a light-pulse (100 lux, 10 min) induced phase-delay similar to the one observed in C57bl/6 mice. However, the number of wheel-turns/circadian night was much higher for TLR4KO than for controls (p0.01). LPS administration (50 ug/kg, i.p.) in C57bl/10ScCn controls induced a larger phase-delay than in C57bl/6 (-1.06+0.09 h vs. -0.52+0.21 h, p0.05). The LPS-induced phase-delay in TLR4KO mice (-0.42+0.29 h) was significantly decreased with respect to their specific controls (p0.05). In both control mice the complete inhibition of wheel-running was observed immediately after LPS injection. This inhibition, was absent in TLR4 KO mice (p=0.0038). Since stopping the wheel at CT15 did not induce circadian phase shifts, LPS effects were specific and not directly related to behavioral inhibition. The LPS-induced c-Fos and Per-1 immunoreactivity in the paraventricular hypothalamic nucleous decreased in TLR4 KO mice in comparison with control mice (p0.001). In conclusion, we found a strain dependence of the circadian LPS response, and we showed that both LPS-induced phase-delay, locomotor inhibition and c-Fos and Per-1 induction is mediated by the TLR4 receptor.

Cronobiology
Poster Number (91) Session III

SUPRACHIASMATIC NUCLEUS: NO WAY

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The NO/GC/cGMP/PKG pathway is essential for photic synchronization of the circadian clock. Phosphodiesterases (PDEs) are key regulators of intracellular cyclic nucleotide concentrations. In hamsters receiving specific PDE5 inhibitors, reentrainment to a 6h phase-advance of the LD cycle took significantly shorter than controls. PDE5 inhibitors also elicited an increase in light-induced phase advances when injected 45 min before light stimulation at CT18. No differences were observed in either reentrainment rates after a delay in the LD cycle, or light-induced phase delays after a light pulse at CT14. We have also tested natural products containing PDE inhibitors on circadian entrainment. We have studied the role of nitric oxide (NO) in the intercellular communication within the dorsal and ventral portions of the SCN. Administration of the NO scavenger PTIO blocked photic phase advances and inhibited light-induced cFos-ir, without affecting phase delays. Hamsters receiving a single dose of PTIO before light stimulation show an inhibition in the non-parametric entrainment to 23.5 h cycle and an inhibition of the light-induced Per1-ir. Preliminary results show an increase of light-induced (50lux) phase advance after the administration of the NO donor NO-Melatonin. These results demonstrate that pharmacological inhibition of PDE5 affects photic entrainment, indicating a potential benefit for circadian disorders which require an increase in light signaling to the clock. These findings could serve as a basis for pharmacological treatment for optimizing circadian adaptation to environmental changes, including transmeridian flight schedules (jet-lag). Also, a role for extracellular NO in the intra-SCN communication is suggested.

Poster Number (92) Session III

IT'S A WORM'S LIFE: CIRCADIAN RHYTHMS IN C. ELEGANS

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C. elegans is a model organism widely used in diverse areas of research but not well characterized in chronobiological studies. We have recently designed an automated system to track individual nematodes and demonstrated the existence of circadian activity rhythms in both LD (light : dark, 12 h : 12 h) and DD (constant darkness) conditions, periods were found to be of 24.2 ±0.44 h and 23.9 ±0.40 h respectively. In addition, circadian periods were temperature-compensated and could also be entrained by temperature cycles. Mutations in clock gene homologs induced circadian phenotypes with altered periodicities: lin-42(mg152) and lin-42(n1089) showed circadian periods of 25.16 ±0.45 and 25.5 ±0.50. Moreover vels26, a rescue of lin-42(mg152), exhibited a normal circadian periodicity of 24.07 ±0.26. In order to determine if the worms are able to detect different light wavelengths, we have studied phototaxic responses, and found a phototaxis index of 0.7 ± 0,09 towards the green wavelength of light (520nm). Another approach to uncover rhythmic outputs was the study of stress tolerance behaviors. We found that C. elegans showed rhythmic stress tolerance patterns for oxidative and osmotic stress with peaks at ZT 12 (lights on) and ZT 0 (lights off), respectively. Stress-related gene expression was determined by sqRT-PCR and confirmed by RealTime-PCR: gpdh-1 and gpx showed a significant diurnal variation. We have also studied circadian rhythms in metabolic variables, such as food consumption and defecation. Food consumption rate (determined by decreasing OD600 of E. coli OP50) was shown to be rhythmic and a peak was found in the evening (ANOVA, p0.01). Defecation rhythms also showed to be governed in a circadian manner. These results show that control animals have a 24 h period in the frequency of the ultradian defecation rhythm (ANOVA, p 0.01). Furthermore, the defecation behavior of the JT73 mutant strain depicts a normal rhythmic pattern on a circadian level (ANOVA, p0.01).

Finally, we have detected aaNAT activity and melatonin in this nematode. aaNAT exhibited a diurnal variation peaking at ZT12, and melatonin could serve as a possible circadian output signal. In summary, our results show that several different circadian outputs can be recorded in C. elegans; in particular, the circadian rhythm of locomotor activity can be entrained to environmental signals. These data might be a basis for the screening of putative circadian mutants in this species

Poster Number (93) Session I

REDUCING THE UNCERTAINTY ON SOLUTION EXCHANGES BY MONITORING SOLENOID VALVES ACTUATION IN REAL TIME.

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Usually, the effects of chemical compounds on biological preparations are tested using solution perfusion systems. Solenoid valves are a core component of most solution perfusion systems used in neuroscience. They control the timing and sequence of chemical stimulation. These valves have a ferromagnetic plunger which moves after the magnetization of the solenoid and which returns to its resting position by the aid of a spring. There are delays between the time of voltage application or removal and the actual aperture or closure of the valve, that are difficult to predict and have to be measured experimentally. We define as plunger signal an electric signal that is generated by the motion of the ferromagnetic plunger and that is measured over a small resistance that is set in series with the solenoid coil. We tested a 3-way pinch valve and a 2-way solenoid. In order to test on real time whether each valve was open or not we set the valve to connect a pressurized nitrogen tank to a differential pressure sensor. When the valve was open, the pressure was 0.15 bar. When the valve was closed, the pressure was equilibrated with the atmospheric pressure with a time constant of about 1 ms. We used the multifunction data acquisition card NI PCI 6229 for synchronously driving the valves and measuring both the output of the pressure sensor and the current that circulates through the valve coil at 250Khz 16 bits digitally filtered at 10KHz. The circuit driving the solenoid valves consisted of a measuring resistance in series with the solenoid valve in parallel with the series of a protective diode and a 47V Zener diode. Using signal´s plunger we detected the opening and closing of the valves with a systematic error below 2 ms. After

NEURONAL CIRCUITS INVOLVED IN VISUAL MOVEMENT DETECTION PROCESSING IN A CRAB

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Animals permanently evaluate their surroundings in order to produce an adaptive behavior. Detecting object movements is a task that visual systems need to solve rapidly to fittingly guide behavior. We study the escape response of the crab Chasmagnathus to visual stimuli. Previously, we developed an experimental preparation that allowed us to perform intracellular recordings in the intact living animal. With this methodology we found that a generic group of large motion-sensitive neurons from the crab brain respond to visual stimuli and accurately reflect the escape performance. Moreover, these neurons play a key role in visual learning and memory and in the decision to initiate an escape. In particular, we have identified 4 classes of large motion-sensitive neurons. Morphologically, all these classes consisted in large horizontal (tangential) arborizations in the deepest optic neuropile with axons projecting toward the midbrain. Because these axons are thin and a long distance separates the optic lobes from midbrain the elucidation of their projection pattern could not be accomplished in the past. Recently, we have started solving these difficulties using dextran fluorescent conjugates of high molecular weight. Here, we present the first results obtained with this technique that allow us to identify in which areas of the midbrain this neurons are projecting to. The present results open the posibility to trace these neurons with calcium sensitive dyes conjugated to dextrans of high molecular weight, which will allow to further study its physiological activity in an intact living animal.

Poster Number (95) Session II

CORTICO-SUBTHALAMIC COMMUNICATION IN EXPERIMENTAL PARKINSONISM

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The subthalamic nucleus is a key element between basal ganglia circuit that receives cortical afferents through a monosynaptic pathway (hyperdirect pathway) and a multisynaptic pathway involving the striatum and globus pallidus (indirect pathway). In Parkinson's disease the subthalamic nucleus suffers some changes in its activity that could probably explain some of the clinical manifestation observed in patients. Although it is accepted that these changes imply an abnormal synchronization with cerebral cortex, it is not clear which pathways mediate this abnormal cortico-subthalamic synchronization. As an initial approach for the study of the connectivity between cerebral cortex and subthalamic nucleus, we recorded the responses of subthalamic nucleus neurons to electrical stimulation of the motor cortex in sham and 6-hydroxydopamine lesion rats (6-hydroxydopamine destroys dopaminergic neurons), and marked subthalamic cells with neurobiotin. Preliminar results demonstrate that lesion rats show a short latency response, compatible with a monosynaptic cortical input and a delayed response compatible with activation of the indirect pathway, as it was described for normal rats. This initial work will help to design future experiments aimed at studying the role of both pathways in the functional connectivity between the cortex and the subthalamic nucleus. Funded by: UBA, CONICET, FONCYT

Neuronal Circuits Fisiology
Poster Number (96) Session II

RESEARCH PROJECT: PHYSIOLOGICAL EVIDENCE OF STRIATO-NIGRO-STRIATAL SPIRALING CIRCUITS

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Several aspects of our behavior are thought to depend on complex sensorimotor and cognitive computations performed by parallel cortico-basal ganglia circuits. Recent anatomical and behavioral evidence suggest the existence of serial cortico-basal ganglia connections linking ventral to dorsal regions of the striatum through striato-nigro-striatal spiraling loops. These connections are supposed to depend on nigrostriatal dopaminergic inputs and have been proposed to be necessary for the progression of goal-directed instrumental behavior to more habitual instrumental responses. However, physiological evidence of such connections is lacking. We speculate that cortical information would be processed within the striatum across a ventromedial to dorsolateral gradient and that such gradient should be disrupted in the absence of nigrostriatal dopamine neurons. Previous results supporting this hypothesis are presented. Striatal neurons of mice with neonatal dopamine neuron depletion exhibit a less refined tuning to localized cortical ongoing oscillations, a decreased probability of convergent responses to electrical stimulation at separate cortical sites and a disrupted transfer of experimentally induced corticostriatal long term depression to unconditioned motor cortex area after prelimbic cortex conditioning. Statistical tools allowing causal connectivity estimations have been recently applied to physiological data (e.g. Granger Causality). To study serial connectivity within the striatum and dopamine pathways influence, we show preliminary Granger Causality analysis on multisite striatal neuronal activity recorded along a ventromedial-dorsolateteral axis in mice with neonatal dopamine neuron depletion and sham controls.

Poster Number (97) Session III

COUPLING AMONG LEECH MOTONEURONS

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The leech has four types of muscles implicated in the movement: the longitudinal, the circular, the dorsoventral and the oblique muscles(lm, cm, dvm & om). Contractions of each of these muscles produce characteristic movements. All these muscles are innervated by a set of excitatory and inhibitory motoneurons. These motoneurons innervate one type of muscles and region (dorsal, lateral or ventral) of one side (left-right). The lm of one side are innervated by seven motoneurons. Among the excitatory ones the dorsal excitor 3 (MNDE-3) innervates the dorsal lm, the L motoneuron (MNL) innervates all the lm, and the ventral excitor 4 (MNVE-4) innervates the ventral lm.

Recently we have shown that the MNL and the MNDE-3 were coupled by a rectifying gap junction: the depolarizations passed from one to the other while the hyperpolarizations passed from MNDE-3 to L and almost nothing from MNL to MNDE-3. We have tried to reveal the electrophysiological coupling among the MNDE-3 and the MNL using the Neurobiotin tracer (Vector Labs) that pass through the gap junctions, and a fluorophore conjugated to a dextran that cannot pass through it.

The experiments unfulfilled the original purpose. We have also studied the coupling among MNVE-4 and MNDE-3 by intracellular recordings. The experiments of coupling among MNVE-4 and MNDE-3 have shown that there is coupling among them although there is a low one. This low coupling, however, can change the firing of the postsynaptic cell while injecting current in the presynaptic one. This coupling among ventral and dorsal motoneurons is consistent with the previous results from the lab: there is an extensive low coupling between motoneurons that is unmasked when the polysynaptic effect is abolished.

Neuronal Circuits Fisiology
Poster Number (98) Session III

DEVELOPMENT OF INTERNAL STATES OF BRAIN ACTIVITY

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Spontaneous brain activity, which represents 60-80 of brain energy expenditure at rest, is evident as stereotypic oscillations in local field potential coordinated in time and space. It depends on the history of activity during the execution of tasks and affects the behavioral responses to stimuli, regulating information flow and synaptic efficacy, and reflecting the functional architecture of underlying neural circuits. Different internal brain states are defined by the degree of synchronization of such networks, arising as periodic oscillations hierarchically organized in frequency bands. During sleep, recapitulation of neural activity patterns experienced during wake would aid the consolidation of memories or habits. Under anesthesia, it is possible to obtain activity states similar to different states of the wake-sleep cycle. Here, we analyze the development of internal brain states in anesthetized rats, using the power of characteristic frequency bands in spectrograms of local field potential recordings from prefrontal cortex and hippocampus. The results suggest that, considering the main states, the prefrontal slow wave / hippocampal large irregular activity state is well developed in pre-adolescents and adults, while the prefrontal activation / hippocampal thetha rhythm state is only well developed in the latter. The next step will be the chronic implant of electrodes in both groups of rats to confirm these results in freely moving animals.

Poster Number (99) Session III

TEMPORAL EVOLUTION OF NEURITIC CALCIUM TRANSIENTS IN A LEECH PASSIVE NEURON

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The propagation of electrical signals in neurons without action potentials (passive neurons) are primarily controlled by the passive mode of transmission, although at present there are many evidences of the presence of active conductances (i.e., voltage-dependent) on their dendrites and of their effects on the integration of signals. The NS neurons are nonspiking cells, present as pairs in each midbody ganglion of the leech nervous system, which display a very extensive arborization. They regulate the action potential frequency of all the described excitatory motoneurons and receive sensory inputs. This regulation is carried out by means of electrical synapses, rather than through gradual chemical synapses. Previous results indicate that NS neurons respond to electrical stimulation with a spike-like event. This phenomenon is basically supported by low-threshold calcium channels and TEA-sensitive potassium channels. With the aim of studying the spatial and temporal distribution of the intracellular calcium transient in the neurites of this cell which accompanies that response, we used simultaneous measurement of calcium imaging and electrophysiological recordings in the soma. Neurons were loaded with the calcium sensitive fluorescent dye Calcium Green-5N and recorded by a confocal microscope, and the spike-like event was evoked by current injection in the soma. The results suggest that the calcium channels are distributed over the whole extension of the primary neurites and the calcium transients have homogeneous kinetic properties. In addition, the entry of Ca2+ into the NS neuron seems to be simultaneous in entire studied processes.

TOGETHER IS BETTER: PHYSICAL INTERACTION OF NGF RECEPTORS TrkA AND p75.

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Nerve Growth Factor (NGF) mediates survival, differentiation and maintenance of responsive neurons through activation of signalling events from the nerve terminal plasma membrane to the nucleus. NGF engages two structurally distinct transmembrane receptors, p75 and TrkA, which have been proposed to create a "high affinity" NGF binding site through the formation of a ternary NGF-p75-TrkA complex. Evidence from a variety of systems suggests that these receptors may cooperate in NGF signal transduction. However, the mechanism by which these receptors produce synergistic effects has been difficult to discern. It has been proposed that p75 and TrkA form complexes, though an interaction through the extracellular domains has been discarded by crystallography studies. We determined that p75 and TrkA interact by their intracellular domains by Förster resonance energy transfer (FRET) and by computational modelling of protein-protein interactions. We observed energy transfer between the recombinant receptors fused to fluorescent proteins, TrkA-CFP and p75-YFP, in PC12 and COS-7 cells. In addition, we detected FRET among the endogenous receptors in PC12 cells by labelling p75 and TrkA with antibodies conjugated with the suitable fluorophores. We obtained an accurate structure of TrkA intracellular domain by homology modelling using MODELLER, and predicted three potential TrkA homodimers and several TrkA-p75 dimers with the program ClusPro. We examined the stability of selected dimers by molecular dynamic simulations using the AMBER package of programs for different homo and hetero dimers. We propose that the cooperation in NGF signal transduction is achieved by the formation of a complex between TrkA and p75 intracellular domains.

Poster Number (101) Session 1

THIOREDOXINS FAMILY PROTEINS IMMUNOLOCALIZATION IN THE RAT CENTRAL NERVOUS SYSTEM

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Glutamate excytotoxicity, oxidative stress and mitochondrial dysfunction are some of the process associated to neuronal damage and glial reaction triggered by a hypoxic ischemic injury. Although the most important function of the thiol redox proteins is the maintenance of the intracellular redox state, acting as antioxidants and reducing agents in redox signaling with oxidizing reactive oxygen species (ROS), no systematic data on the localization of these proteins in the Central Nervous System (CNS) is available until now. The aim of this work is to study the distribution of the following thioredoxins family proteins: Trx-1, Trx-2, TrxR-1, TrxR-2, Txnip, Grx-1, Grx-2, Grx-3, Grx-5, gGCS, Prx-1, Prx-2, Prx-3, Prx-4, Prx-5 and Prx-6, in Neostriatum, Hippocampus, Cerebellum, Spinal Cord, Substantia Nigra, Cerebral Cortex and Retina, which are the most vulnerable areas to hypoxic ischemic injury. While previous studies had suggested that these proteins are distributed in most of the cell types and regions of the CNS, we have observed several differences in intensity and regional distribution in these areas. The present study is the first effort to precise the localization of these proteins and could contribute to reveal new insights about the role of the oxidative pathway in the pathogenesis of the hypoxic-ischemic brain injury and neurodegenerative associated diseases. Supported by UBACYT M407, PIP 5784, PICT 15001.

A KEY ROLE FOR SPHINGOSINE-1-PHOSPHATE IN THE CROSSTALK BETWEEN RETINA GLIAL AND NEURONAL CELLS

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We have previously shown that Müller glial cells in coculture preserve the proliferative potential of neuronal progenitors and protect neurons from oxidative stress, while this stress enhances their proliferation. We have also identified the sphingolipid sphingosine-1-phosphate (S1P) as a crucial mediator in key cellular processes in photoreceptors, such as neuroblast proliferation, survival and differentiation. We have now investigated the roles played by S1P in neuroglial crosstalk. Inhibiting S1P synthesis before treating neuroglial cocultures with the oxidant paraquat blocked glial protection from oxidative stress-induced apoptosis in neurons; adding an antagonist to S1P3 receptor, a protein membrane receptor for S1P, similarly inhibited this protection. Incubation of neuroglial cocultures with exogenous S1P increased Br-deoxiuridine (BrdU) uptake in neuroblasts. An increased [3H]thymidine and BrdU uptake after S1P supplementation of glial cultures suggests S1P promoted glial cell proliferation as well. S1P also regulated neuronal differentiation and organization on neuroglial cocultures. S1P induced neuronal migration, promoted their initial aggregation and rearrangement in a radial disposition and then led to the formation of a larger number of aggregates respect to the controls. Thick bundles of neuronal axons connected these aggregates, forming an extensive network absent in controls. Concurrently, S1P increased the expression of N-CAM, a cell adhesion molecule. Our results suggest that S1P is one of the factors released by glial cells to prevent neuronal apoptosis, it promotes glial and neuronal proliferation and might also contribute to the establishment of neuronal networks.

Poster Number (103) Session 1

RELEVANCE OF OPA-1 IN THE MANGANESE INDUCED MITOCHONDRIAL APOPTOTIC PATHWAY

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Chronic manganese Mn exposition provokes a neurological disorder denominated Manganism. The astrocytic uptake of Mn is crucial in the establishment of this pathology. In previous studies, we demonstrated that Mn750M induced extrinsic apoptotic pathway by the increment of Fas-L and Caspase 8, 3 and 7 activation. In this report, we found that C6 cells astrocytic model are type II cells since they implicate the totally cleavage and activation of Bid, a substrate of Caspase 8 that establishes a cross talk between the extrinsic and intrinsic pathways. Mitochondria are dynamic organelles, which are in constant fusion and fission leading to the formation of a mitochondrial network MN. During apoptosis there is an impair fusion resulting in mitochondrial fragmentation. Using fluorescence microscopy and Mitotracker Red, we determined an increment in fission events, observed with the loss of MN. OPA-1 is a mitochondrial inner membrane protein involved in fusion and maintenance of the cristae estructure. It cleavage leads to fragmentation of MN and apoptosis increase. We found by W. Blot that Mn produce OPA-1 cleavage by the appearance of a lower MW band 71kDa respect a doublete present in control 10794kDa. Moreover, the processing of OPA-1 diminish 90 by the use of Caspase 8 inhibitor 10M.This confirm the existence link between the apoptotic pathways mentioned. Our findings lead to the elucidation of signalling involved in the Mn neurotoxicity.

Molecular And Cellular Neurobiology
Poster Number (104) Session I

NF-B INHIBITION AFFECTS SURVIVAL OF CORTICAL NEURONS IN A MODEL OF SLEEP APNEA BY INTERMITTENT HYPOXIA.

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Sleep apnea (SA) is a human pathology that produces important alterations in the cognitive performance. Using an experimental model of SA by intermittent hypoxia (IH), we previously demonstrated early severe alterations and neuronal death in hippocampus and brain cortex. However, neuronal loss was limited. To analyze the NFKB role in the neuronal survival in IH conditions, we blocked NFKB activation in IH animals by daily intracerebral infusions of sulphazalazine (SFZ). Three days after the surgery to fix the needle, male Wistar rats were infused with 1.25mM sulphazalazine and exposed to IH cycles (alternating 10 - 21 O2) every 6 min during 8h/day (sleep phase) for 3 days. Then, rats were anaesthetized and fixed by perfusion. Immunohistochemistry with neuronal specific nuclear marker (NeuN) and dendritic marker MAP-2 was performed to evaluate the integrity of the neuronal cells. Nuclear p65 NFKB abundance was used to verify the effectiveness of SFZ infusion and to determine the area were NFKB activation was blocked. SFZ infusion induced a persistence of cytoplasmic p65 immunostaining, indicative of NFKB blockage in the area surrounding the needle tip. NFKB blockage induced decreased neuronal survival and induced a further retraction in neuronal dendrites in brain cortex compared with animals that were also exposed to IH but received only vehicle. Our results showed that NFKB activation is necessary for neuronal survival to IH exposure. Further studies are necessary to confirm if the observed NFKB dependence of neuronal survival is a consequence of neuro-glial interaction mediated by S100B-RAGE. Grants CONICET PIP6063, PIP1728, PICT jovenes 33735, IBRO RHF

Poster Number (105) Session 1

NOTCH PATHWAY AND THE EFFECT OF APOTRANSFERRIN ON REMYELINATION

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Escobar Cabrera et al., (1994, 97) demonstrated that a single intracranial injection of apotransferrin (aTf) in 3-day-old rats produces an increase in myelin constituents. These promyelinating effects of aTf were clearly shown in animals suffering demyelination after cuprizone feeding (Adamo et al., 2006). In this study we evaluated the effect of aTf and the possible participation of the Notch receptor pathway in remyelination on lysolecithin (LPC)-induced focal demyelination in the corpus callosum (CC). Adult rats were anaesthetized and positioned in a stereotaxic frame in order to be injected 2 LPC in saline solution (SS). LPC was injected unilaterally into the CC (2mm anterior and 1mm lateral to bregma with 2.5mm deep from skull surface). Controls were injected SS. The day of LPC injection was designated as day 0 (0 DPL). Seven days later animals were injected a single dose of 350 ng of aTf or SS in the subventricular zone (SVZ) (3 mm posterior and 3 mm lateral to bregma and 3 mm dorsoventral from skull surface). After aTf or SS injections, animals were sacrificed at different times (2, 6 and 24 h or 3 and 7 days depending on experiments). A subgroup of animals received one intraventricular injection of the -secretase inhibitor (DAPT 1 mM) 5 min before the injection of aTf. To evaluate whether the effects of aTf were due to the protein or to iron, experiments were carried out in the presence of desferroxamine (DFX 10 ng). We observed significant demyelination in the injected area in the CC at 7 DPL and a spontaneous reversion 21 DPL. The injection of aTf induced remyelination 10 DPL. We observed an increase in oligondendrocyte (OL) APC+ population concomitantly with a decrease in OL precursors NG2+ in the CC and SVZ. The injection of DAPT blocked aTf's effect on remyelination. Experiments with DFX showed no differences in the promyelinating effects of aTF. In this model of toxic demyelination, results seem to indicate the involvement of the Notch pathway in the aTf effect on remyelination.

Molecular And Cellular Neurobiology
Poster Number (106) Session 1

REACTIVE GLIOSIS AFTER BRAIN ISCHEMIA IS REDUCED IN ANIMALS PREVIOUSLY EXPOSED TO AN EXPERIMENTAL MODEL OF SLEEP APNEA BY INTERMITTENT HYPOXIA

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Cerebral ischemia has a major impact on public health. Sleep apnea syndrome (SA) is also a serious public health problem in adult population. A common complication of SA is brain ischemia; however SA patients usually succeed in the post-stroke recovery. In an attempt to understand the clinical observations, we exposed adult male Wistar rats (230-250g) to an experimental model of sleep apnea by intermittent hypoxia (IH) by cycling oxygen level every 6 min from 21 to 10O2 for 5 days, 8 h/day, during the sleep phase. Another set of animals were exposed to the same chambers but in normoxic conditions (Nx). On the sixth day both groups were subjected to brain ischemia induced by cortical desvascularization (CD). Animals were sacrificed at 3 and 7 days post lesion (dpl), and brains were processed for immunocytochemistry and image analysis. Glial Fibrillary Acidic Protein (GFAP) and Vimentin immunostaining showed that reactive gliosis was restricted to the ischemic hemisphere, being maximal in the penumbra area that surrounds the ischemic core. To analyze the intensity of reactive gliosis, morphometric parameters of penumbra astrocytes were studied in IH and Nx animals located at differents distances from the ischemic core. Our results showed that reactive gliosis normally induced by brain ischemia was significantly diminished in animals previously exposed to IH compared with Nx animals. These preliminary results raise the hypothesis that probably IH exposed brain develop a degree of adaptation or tolerance to a subsequent ischemic injury, thus supporting clinical observations from SA patients. Supported by CONICET PIP6063, PIP1728, PICT jovenes 33735, IBRO RHF
Keywords: Sleep apnea, hypoxia, ischemia, hypoxic preconditioning, GFAP, cortical desvascularization

Poster Number (107) Session 1

EXTRACELLULAR ADP REGULATES LESION-INDUCED CELL PROLIFERATION AND DEATH IN THE ZEBRAFISH RETINA

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Persistent neurogenesis in the adult fish retina has been a valuable tool to study cell proliferation and differentiation processes. Damage of the mature retina activates tissue regeneration from intrinsic germinal cells within different pools of precursors. We have previously demonstrated that endogenous purinergic signals regulate cell proliferation induced by a partial lesion with ouabain. The aim of this study was to elucidate which of the endogenous extracellular nucleotides regulate cell proliferation and whether they have an effect on cell death. Zebrafish were lesioned by intravitreal injections of ouabain. Then, apyrase (an enzyme that hydrolyses extracellular nucleotides) or different antagonists of purinergic receptors were injected daily for 6 days in the ouabain-treated eyes. On day 7 cell proliferation or death were determined by using 5-Bromo-2-deoxyuridine or TUNEL respectively. We demonstrated that cell proliferation is regulated by ADP via P2Y1 metabotropic receptors since the ADP-activated P2Y1 receptor antagonist MRS2179 completely blocked lesion-induced increases in cell division. In contrast, the ADP-activated P2Y12, 13 receptors antagonist MRS2211 did not affect cell proliferation. Likewise, the injection of an antagonist of adenosine P1 receptors (8-SPT) or a mixture of antagonists for ATP-activated P2Y11 or P2X1, 2, 3 receptors did not modify lesion-induced cell division. We also found a role for purinergic signals in regulating injury-induced cell death. Extracellular nucleotides scavenging by apyrase significantly increased cell death in injured retinas. This effect was partially reproduced by blocking P2Y1 receptors. This study demonstrates a crucial role for extracellular ADP in the repair of retina following injury.

Molecular And Cellular Neurobiology
Poster Number (108) Session I

ALTERED HIPPOCAMPAL NEUROGENESIS IN A TRANSGENIC MOUSE MODEL OF ALZHEIMER'S DISEASE (AD). CHANGES INDUCED BY LONG TERM EXPOSURE TO AN ENRICHED ENVIRONMENT (EE).

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Evidence from the literature suggests that cognitive stimulation can be protective in some neurodegenerative diseases, including AD. Our aim was to explore the effect of environmental enrichment on different steps of hippocampal neurogenesis in a model of AD, and their potential correlation with cognitive function. Female transgenic mice (tg) carrying the Swedish and Indiana Familial AD-associated mutations in the amyloid precursor protein and their siblings (non-tg) were housed in special cages containing tubes, nesting material, a house and toys, or in standard conditions (SC) for 3 months (5 to 8 months of life). Proliferation rates measured by Ki67 labeling in the dentate gyrus were lower in tg mice compared with controls with no effects of EE. Tg mice showed a decrease in doublecortin cells in the dentate gyrus. Survival of newborn cells was examined by administration of bromodeoxyuridine (BrdU) 21 d before euthanasia. EE induced a marked increase in BrdU+ cells in both groups (non-tg SC 59.8±11.4; tg SC 21.3±7.05; non-tg EE 135.2±16.9p0.01 vs non-tg SC; tg EE 64±11.3p0.05 vs tg SC BrdU+cells). Ratios of BrdU+NeuN+/ BrdU+cells -calculated on the basis of colocalization of BrdU labeling with the neuronal marker NeuN using confocal microscopy- were low for tg mice housed in SC but EE strongly increased this ratio, suggesting that more neurons were produced in the dentate gyrus from stimulated tg mice. Working memory was evaluated in the Y maze: spontaneous alternation was clearly improved in tg mice after EE exposure. However, no differences in numbers of Aβ plaques in CA1 were observed in tg groups. Our results suggest an important role for social, sensory and cognitive stimuli in the pathogenesis of AD.

Poster Number (109) Session 1

RAPID ENDOCYTOSIS IN MOUSE CHROMAFFIN CELLS

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Endocytosis is critical for maintaining membrane homeostasis and secretion reliability in neuroendocrine cells. We studied rapid endocytosis in mouse chromaffin cells using patch clamp-whole cell capacitance measurements. Single or repetitive depolarizations were applied, but the process was only consistently activated with unique pulses lasting ≥0.5s. Two patterns were identified: (1) the amount of membrane retrieved was the same than the one added by exocytosis (compensatory endocytosis, CE), or (2) membrane retrieval was bigger than endocytosis (excess retrieval, ER). CE occurred at relatively low Ca2+ entry, but ER was triggered by higher Ca2+ influx (45.3±9.2 vs 114.23±15.3pC, $p<0.005$). To evaluate if the measured endocytosis is carried out by more than one component, multiexponential fittings were performed. A frequency histogram showed three time constant populations: two components associated to rapid endocytosis, tR1<2.5s and tR2 between 2.5 and 16s; and one to slow endocytosis tRL>16s. ER showed a faster tR1component (0.40±0.06 vs 1.20±0.43s, $p<0.01$) and a bigger contribution of the two rapid endocytosis components to the whole process tR1:21.9±5.1 vs 6.7±4.7%, $p<0.05$; tR2: 68.6±6.7 vs 41.8±9.9%, $p<0.05$) in comparison with CE. Our data suggest that endocytosis is a complex phenomenon, in which ER is favored by a high Ca2+ entry and is driven by both fast components. Finally, in order to study the fate of the internalized membrane we performed experiments with FM1-43. We found that after high K+ depolarizations that induced an excess retrieval (Endo-Exo) of 12.2±4.0% (capacitance gave a similar value: 10±2.5%), approximately 50% of the endocytosed membrane was recycled to releasable vesicles.

Molecular And Cellular Neurobiology
Poster Number (110) Session I

MICE LACKING PRESYNAPTIC DOPAMINE D2 AUTORECEPTORS DISPLAY HYPERACTIVITY AND INCREASED MOTIVATION FOR FOOD REWARD

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The dopamine D2 receptor (D2R) is expressed postsynaptically in most dopamine (DA) target areas where it participates in the extrapyramidal control of locomotor activity, spatio-temporal organization of goal-oriented behaviors and the reinforcing properties of natural rewards. Also, D2Rs are present in DA neurons where they act as autoreceptors controlling cell firing and DA release. Selective in vivo blockade or stimulation of D2 autoreceptors has been hampered by the fact that active compounds on these receptors also interact with those located on postsynaptic non-DA neurons. To circumvent this difficulty, we created transgenic mice lacking D2 autoreceptors by cell-specific conditional gene targeting. Homozygous mutant mice carrying loxP sites flanking Drd2 exon 2 (Drd2flox/flox), overtly indistinguishable from Drd2+/+ mice, were crossed with knockin mice expressing Cre from the dopamine transporter gene Dat+/IresCre. An in situ hybridization analysis performed on compound Drd2flox/flox. Dat+/IresCre mice (autoDrd2-/-) showed a total loss of Drd2 expression within midbrain dopaminergic neurons while retaining expression in forebrain postsynaptic neurons and pituitary cells. AutoDrd2-/- mice displayed increased locomotor activity and were insensitive to low doses of the D2R agonist quinpirole. Motor coordination on a rotarod, approach/avoidance behavior on an elevated plus maze and conditioned place preference for cocaine were normal in autoDrd2-/- mice. Interestingly, autoDrd2-/- mice showed increased motivation for food reward in a progressive-ratio operant test. Altogether, our results indicate that loss of presynaptic D2 autoreceptors impairs behaviors dependent in locomotor and emotional functions.

Poster Number (111) Session I

CG6115, A GENE INVOLVED IN PROGRESSIVE NEURODEGENERATION

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About 64 of unique genes involved in neurodegeneration in humans have orthologs in Drosophila. A misexpression screen to identify genes involved in this process has been carried out in our laboratory. It consisted in examining locomotor behavior in young and aged flies. Flies that showed a progressive loss of rhythmic activity were chosen as candidates to reveal novel genes involved in neurodegenerative mechanisms. One of the mutants is 100B, where, as a result of the P element insertion, there is a striking downregulation of CG6115 expression. CG6115 encodes a gene of unknown function, with a putative zinc finger domain predicted in its protein sequence, thus implying that CG6115 may function as a transcription factor. The P element is also localized near another predicted gene: CG15133, whose expression levels remain unchanged by the insertion. A severe downregulation of CG6115 is likely the cause of the lethality observed when the mutation is present in homozygosis. Homozygous mutants cannot progress from larvae to pupae. Mutant larvae are reduced in size and display an indifferent behavior towards food earlier than wild type or heterozygous larvae, despite clear indications of starvation at the molecular level. However, when homozygous larvae are raised in the presence of liquid food (a much more accessible food source than the typical solid one) a proportion can progress to pupae and even adults. Restricted expression of a RNAi directed towards CG6115 caused progressive arrhythmicity in adult flies, thus confirming a dependence of CG6115 levels for neuronal viability. This mutant provides a venue to investigate a possible link between a gene relevant for neuronal survival in circuits involved in feeding control.

Molecular And Cellular Neurobiology
Poster Number (112) Session I

AXOGENIC EFFECT OF WNT-3A FACTOR IN CULTURED HIPPOCAMPAL NEURONS.

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Neuronal development, from the establishment of neuronal polarity to axon guidance and maturation are controlled by a combination of an intrinsic program of gene expression and by extrinsic factors (such as Wnts, BMPs, IGF-1, BDNF, and NGF). Wnt factors are secreted signalling molecules implicated in important developmental processes, as embryonic patterning, tissue polarity and cell movement. Recent works have shown that Wnts also regulate neuronal maturation as they have been implicated in axon guidance, dendritogenesis and synapses formation. Wnts through Frizzled (Fz) receptor activate Dishevelled (DVL), a first effector. Wnt-DVL signalling can signal through three different pathways: the canonical or b-catenin pathway, the planar cell polarity pathway and the calcium pathway. In this work, we study the role of WNT-DVL signalling during neuronal differentiation, particularly during axon outgrowth and the establishment of neuronal polarity. Neurons cultured in the presence of Wnt3a or expressing DVL show multiple and more complex axons. Wnt3a seems to regulate axon formation through a non-canonical pathway and this effect is blocked by sFRP (a Wnt antagonist). Importantly, Wnt3a activates PI3K in neurons and in purified growth cones particles suggesting that Wnt3a may act through the same pathway as IGF-1 (previously defined as an essential for neuronal polarity). In addition, we found that Wnt3a cross-activates the receptor of IGF-1 in neurons and in growth cones and this effect is blocked by an IGF-1R blocking antibody. These findings suggest that Wnt proteins are essential for neuronal polarity and suggest a possible parallelism between the two signalling systems: Wnt-Fz-DVL and IGF-1-IGFR-PI3K on axon formation.

Poster Number (113) Session 1

MUTATIONAL ANALYSIS OF THE AGONIST BINDING SITE OF THE α9α10 NICOTINIC CHOLINERGIC RECEPTOR.

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The agonist binding site of nicotinic cholinergic receptors (nAChR) is a pocket of aromatic and hydrophobic residues arranged in six loops at the interface of two adjacent subunits. One of the subunits containing loops A, B & C forms the principal component of the binding site and the adjacent subunit containing loops D, E & F forms the complementary component. Loop C has a disulfide bond between two conserved neighboring cysteines. Loop B has a conserved W149 (Torpedo numbering) associated to agonist binding through cation-pi interactions. Finally, W55 in loop D is one of the few conserved residues in the complementary component. The aim of this study was to analyze the importance of these residues in the α9α10 nAChR and to characterize the contribution of each subunit to the binding site. Site directed mutagenesis of W149F, W55H and C192S/C193S was carried out in both subunits by using QuickChangeII (Stratagene). ACh-gated currents were recorded in two-electrode voltage-clamped X. laevis oocytes injected with the mutant subunits cRNAs. C192S/C193S mutations showed a similar shift in EC50 for ACh when present in α9 or α10 (α9α10: EC50 = 14μM; α9α10*: EC50 = 145 ± 1μM, n=17; α9*α10: EC50 = 147 ± 1μM, n=8; α9*α10*: EC50 = 402 ± 1μM, n=6). W149F mutations had a stronger effect on EC50 when present in α9 (α9α10*: EC50 = 24 ± 1μM, n=6; α9*α10: EC50 = 110 ± 1μM, n=5). This was also seen in W55H mutants (α9α10*: EC50 = 96 ± 1μM, n=3; α9*α10: EC50 = 717 ± 1μM, n=3). W149F and W55H mutations show that both subunits are able to form principal and complementary components, but that α9 is more efficient. C192S/C193S mutations, when compared to W149F ones, may indicate that the former are influencing agonist binding and/or gating.

CHEMOTACTIC EFFECTS OF UROKINASE-TYPE PLASMINOGEN ACTIVATOR (UPA) ON POSTMITOTIC NEURONS AND GROWTH CONES IN THE DEVELOPING CENTRAL NERVOUS SYSTEM

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Several signalling molecules have been implicated in controlling neuronal migration and a number of these same molecules play important roles in axonal guidance. These molecules regulate the cell motility by promoting or inhibiting this process. The growth cones at the tip of the neurites sense the concentration gradients of these same molecules and translate them into changes in the rate and/or the direction of axonal outgrowth, and are able to promote axonal branching. The aim of this study was to investigate the possible chemotactic effect of uPA on neuronal migration and neuritogenis Optic tectum explants from chicken embryos of 6 days, were grown in DMEM/F12 and incubated at 37ºC for 20 hours. After that, the explants were exposed to a gradient of uPA using acrylic beads embedded in 20 nM of uPA. After 15 or 30 minutes, the explants were photographed. The images were assembled and the explants were divided in two halves, in order to compare the side next to the beads with the opposing side. Three different variables were measured: pattern of cell migration, number of filopodia and size of growth cones. After the treatment, the explants were fixed in paraformaldehyde 4 in 0.1M phosphate buffer, and incubated with primary antibody anti-b3tubulin. After that the explants were incubated with secondary antibody Alexa Fluor 488 and phalloidin-rhodamine to detect microtubules and actin cytoskeleton. The region exposed to the gradient showed a significant increase in the number of neurons that left the explants and in the number of axonal filopodia in comparison with the control condition. The submitted to the uPA gradient halves showed large growth cones with microtubule loops whose area were bigger than in the control conditions. The results indicate that uPA acts as a chemotactic molecule promoting the directional neuronal migration and the formation of large growth cones by regulating the axon outgrowth. This work was supported by grants from UBA-CONICET.

Poster Number (115) Session 1

DEVELOPMENTAL PATTERN OF EXPRESSION OF EPHA/ EPHRINA SYSTEM IN THE CHICKEN RETINOTECTAL SYSTEM

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Introduction EphAs and ephrinAs play a key role in the establishment of retinotopic projections onto the optic tectum (OT). Still, their developmental pattern of expression has not been described in detail. Objective Our objective was to describe the developmental pattern of expression of EphA3 and ephrinA2 in the chicken retinotectal system. Methods We used immunocytochemistry in cultured retinal explants and in paraffin sections since 3 days embryos (E3) to postnatal day 2 (P2). Results EphA3 and ephrinA2 are expressed in the plasma membrane of neuroepithelial cells of the retina and the OT since E5. As lamination process occurs, they are seen along all the radial retinal and tectal extension. The differential expression patterns of the EphA3 and the ephrinA2 in the retinal ganglion cells (RGCs) and in the intermediate and superficial layers of the OT might lead to the opposed gradients observed along the temporo-nasal axis in the retina and along the rostro-caudal axis in the OT, respectively. EphA3 gradients are noticed since E6 to E18 while ephrin-A2 gradients are evident since E6 to P2 in the retina and between E5 and P2 in the OT. In both organs differentiated postmigratory neurons present a patch-like expression pattern of EphA3 and ephrinA2 whereas ephrinA2 presents the same pattern in premigratory cells. Discussion EphA3 and ephrinA2 present differential developmental patterns of expression, but both of them are high when axon guidance of RGCs takes place over tectal surface. The disappearance of EphA3 gradient could be one of the reasons of lack of regeneration in adult chicken retinotectal system. Hence, manipulation of this system could be useful in regenerative strategies. Funded by CONICET and UBA.

Molecular And Cellular Neurobiology
Poster Number (116) Session I

PROTECTIVE ACTIONS OF GROUP II METABOTROPIC GLUTAMATE RECEPTORS IN CULTURED RAT ASTROCYTES

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Metabotropic glutamate receptors (mGluR) are implicated in neuroplasticity and neuroprotection. In the present assay, we investigated the effect of group II mGluR on cell death and NF-κB activation in cultured rat astrocytes treated with LPS+IFN-γ and analyzed the expression of these receptors after such inflammatory stimulus. Treatment with LPS (1 µg/ml)+IFN-γ (50 ng/ml) for 24 h augmented the percentage of TUNEL-positive astrocytes (p0.01). In the presence of a selective agonist of group II mGluR (LY379268 100 µM) this effect was abrogated (p0.05). The mGluR antagonist EGLU (300 µM) reverted the effect of LY379268 (p0.001). An inhibitor of NO synthesis, NMA (1 mM), reduced almost completely the percentage of apoptotic cells increased by LPS+IFN-γ (p0.001), suggesting that NO is the major mediator of LPS+IFN-γ-evoked astrocyte death. Since NF-κB mediates inflammatory responses and survival signaling, we determined its translocation to the nucleus and the expression of its inhibitor IκB. Exposure to LPS+IFN-γ for 30 min incremented the NF-κB protein levels in the nuclear fraction (p0.05). No significant changes were observed in the presence of LY379268. However, cytosolic IκB levels were significantly reduced by LPS+IFN-γ (p0.01) whereas LY379268 reverted this effect. Protein expression of group II mGluR was induced by LPS+IFN-γ (p0.05), whereas exposure of astrocytes to LY379268 significantly reduced their expression (p0.05), suggesting the involvement of auto-regulatory mechanisms in the control of mGluR activity. Our results indicate that selective activation of group II mGluR could play a neuroprotective role on inflammatory processes in the CNS, by preventing astrocyte degeneration.

Poster Number (117) Session 1

REGULATION OF MBP FUNCTION BY ITS INTERACTION WITH CA2+-CALMODULIN AND POST-TRANSLATIONAL MODIFICATIONS

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Myelin basic protein (MBP) is essential for formation of myelin compact membranes in central nervous system. The interactions of MBP with different cell components are regulated by Ca2+-calmodulin and by various post-translational modifications. Since calmodulin (CaM) reverses the actin polymerisation and bundling effects of MBP, it might be a regulatory element, in concert with modifying enzymes such as kinases and deiminases, of the putative signaling role of MBP in vivo. In this regard, we study the MBP-CaM interaction by immobilized peptide arrays. There are six variants of MBP encoded by a single gene and generated by alternative splicing. The MBP isoform 1 contains peptide sequence encoded by all seven exons of the MBP gene representing the longest variant. For this reason, we performed the peptide array with this amino acid sequence and we find that CaM binds to three distinct domains that lay in exons involved in splicing and exon 7, common to all the isoforms. These CaM binding-sites differ in the strength of interaction. The strongest CaM binding-site is located in the C-terminal of 1, 2, 3 and 5 MBP isoforms. To analyze the relevance of these sites for the interaction of MBP with CaM we generated constructs that contain three, two, one or none CaM-binding site. Thus, we cloned the cDNA that codify to 1, 3, 4 and 6 MBP isoforms in a mammalian expression vector, plus their C-terminal deleted versions, to study their interaction with CaM in an oligodendroglial cell line that do not express MBP. In addition, each CaM binding-site has three serines and two arginines that can undergo the most common post-translational modifications of MBP such as phosphorylation or deimination respectively. Deimination of MBP has been correlated with early development, demyelination process and

disease severity in multiple sclerosis (MS). Further study of the regulation of MBP by Ca2+-calmodulin and post-translational modifications will help to understand its role in signaling for oligodendrocyte differentiation and myelin formation, and its involvement in the pathogenesis of MS.

Poster Number (118) Session 1

SIGNAL TRANSDUCTION OF CRFR1 IS ALTERED IN AN ANIMAL MODEL OF DEPRESSION

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Corticotrophin releasing factor (CRF) has been shown elevated in depressive patients as well as in animal models of depression. In the hippocampus, one of the brain structures involved in this pathological condition, it exerts its action mainly through activation of type one CRF receptor (CRF1). CRF activates, trough CRF1, the extracellular signal-regulated kinases 1 and 2 (ERK1/2) in the area CA3 of the hippocampus. However, the level of the ERK1/2 signaling under chronic CRF exposition is unclear. It has been proposed that the signaling produced by the coupling of CRF to CRF1 would be altered and could be responsible, in part, for the depressive symptomatology. We evaluated the levels of CRF1 and the activation of ERK1/2 (pERK1/2) in the hippocampus of rats after 21 days of exposure to the learned helplessness (LH) paradigm. The levels of expression of CRF1 were measured by in situ hybridization using a cRNA digoxigenin-labeled probe. pERK1/2 was measured by immunofluorescence. The non activated form was also measured to discard differences in the levels of the protein. We compared three groups: C (rats not exposed to stress), LH+ (rats that develop the behavioural despair after exposure to stress) and LH- (rats that fail to develop the behavioural despair after exposure to stress). LH+ showed a decrease in the CRF1 expression versus LH- or C, both in CA3 and in dentate gyrus (p0.01). This result was accompanied with the decrease in the activation of ERK1/2 in the area CA3 (p0.05). In dentate gyrus there was no activation of ERK1/2. We conclude that in animals with a model of chronic depression the MAPK signaling triggered by CRF is reduced and is area specific. Supported by: PICT 31953, PIP 5870, UBACYT M013

Molecular And Cellular Neurobiology
Poster Number (119) Session I

CDK5 MODULATES MORPHOLOGICAL PLASTICITY OF DENDRITIC SPINES INDUCED BY AMPHETAMINE IN HIPPOCAMPAL PYRAMIDAL NEURONS

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Experience-dependent changes in behavior are thought to involve structural modifications in the central nervous system, especially alterations in patterns of synaptic connectivity. However, little is known about the morphological plasticity occurring during exposure to drugs of abuse. One of the targets of such structural plasticity are dendritic spines, which are dynamic, actin-rich protrusions. Recent reports have suggested that cdk5 plays an important role in drug addiction. In this study, we tested the role of cdk5 in amphetamine (Amph)-induced dendritic spine formation. Hippocampal slices maintained in organotypic tissue culture were biolistically-transfected with cDNAs coding for eYFP and exposed to different Amph doses (50 and 100μM) for 48h. Quantitative analyses of dendritic spine density and morphology were carried in CA1 and CA3 hippocampal pyramidal neurons. Our results demonstrate that Amph exposure increased spine density in apical dendrites of both regions and changed the proportion of morphological spine types. Interestingly, cdk5 inhibition by expression of a dominant negative mutant during Amph exposure, decreased spine density. These results suggest that Amph-induced spine formation require intact cdk5 activity and encourage us to propose cdk5/p35 as an excellent candidate that might mediate the regulation of actin cytoskeleton, through the phosphorylation of specific substrates that interact with actin biding proteins. PAK1 is a cdk5 substrate to test in future experiments, since it is a key protein that switch from an active to an inactive state and thereby mediate the rapid and dynamic regulation of the actin cytoskeleton, essential in dendritic spine morphogenesis.

Poster Number (120) Session 1

CHOLESTEROL DEPLETION BY METHYL-β-CYCLODEXTRIN ALTERS AXONAL BEHAVIOR OF RETINAL GANGLION CELLS.

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We have previously demonstrated that EphA3 stimulates axons of retinal ganglion cells to grow toward caudal tectum. We suggested that ephrin-As act as receptors for EphA3 and it is known that ephrin-As are located in cholesterol-rich membrane microdomains (rafts). Our objective was to examine if membrane-cholesterol microenvironment is necessary for axon growth and guidance. We used cultures of chicken embryos retinal explants exposed to methyl-β-cyclodextrin (MCD) at different concentrations and/or aggregated EphA3Fc. We analyzed the axonal length and morphology, and studied the expression pattern of EphAs and ephrin-As by immunocytochemistry. Explants exposed to MCD presented an early significant increase in the number of axonal varicosities and of collapsed growth cones followed by a significant decrease in the axonal length. Ephrin-A2 was reduced in the growth cones and was increased in the axonal varicosities. Explants exposed to EphA3Fc presented a significant increase in the number of expanded growth cones. Exposure to EphA3Fc and MCD together produced intermediate results than those produced by them separately. Results obtained with MCD suggest that cholesterol depletion decreases the ephrin-As located in growth cones and the axonal growth by stimulating endocytosis. The substractive effects of EphA3 and MCD suggest: a) axonal growth mediated by EphA3 is reduced by MCD for resting membrane by endocytosis and/or reducing the ephrin-As in the growth cones, and b) the interaction between ephrin-As and EphA3 reduces the endocytosis mediated by MCD. These data suggest that cholesterol environment is necessary for regulating the axon guidance mediated by EphA/ephrin-A system. Funded by CONICET and UBA.

Molecular And Cellular Neurobiology
Poster Number (121) Session II

HETEROCHRONY AND POSITIVE SELECTION IN THE LINEAGE LEADING TO ANTHROPOIDS OF A NEURONAL DLL1 ENHANCER INVOLVED IN TELENCEPHALIC DEVELOPMENT

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The neocortex, the most prominent structural and functional innovation of the mammalian brain, has expanded independently in several mammalian lineages. In anthropoid primates this expansion reached a maximum in the human lineage composing around 80 of the entire brain mass. We hypothesize that uncovering the genetic basis of primate brain enlargement and functionality will shed light to understand human brain evolution. We have detected a highly conserved sequence showing signatures of rapid evolution in the lineage leading to anthropoids upstream of Delta-like 1 (Dll1), a gene involved in the proliferation/differentiation switch of neuronal precursors during brain development. Transgenic mouse studies showed that mouse and human orthologs of this conserved region are nervous system-specific enhancers active between E8.5 and E16.5 in the developing nervous system. Swapping the six anthropoid-specific nucleotides into the mouse enhancer produces an extension of the expression territory at E14.5 and E15.5 whereas swapping the ancestral nucleotides back into the human enhancer impaired proper expression of the reporter gene. These results indicate that positively selected substitutions in a neuronal Dll1 enhancer induced heterochronic gene expression that could have contributed to increase the number of neural precursors in the telencephalon of anthropoids and, ultimately, to shape a larger brain.

Poster Number (122) Session II

ENA/VASP DOWNREGULATION TRIGGERS CELL DEATH BY IMPAIRING AXONAL MAINTENANCE IN HIPPOCAMPAL NEURONS

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Neurodegenerative diseases encompass a broad variety of motor and cognitive disorders that are accompanied by death of specific neuronal populations or brain regions. Cellular and molecular mechanisms underlying these complex disorders remain largely unknown. In a previous work we searched for novel Drosophila genes relevant for neurodegeneration and singled out enabled (ena), which encodes a protein involved in cytoskeleton remodelling. To extend our understanding on the mechanisms of ENA-triggered degeneration we now investigated the effect of silencing ena ortholog genes in mouse hippocampal neurons. We found that ENA/VASP downregulation led to neurite retraction and concomitant neuronal cell death through an apoptotic pathway. Remarkably, this retraction initially affected the axonal structure, showing no effect on dendrites. Reduction in ENA/VASP levels blocked the neuritogenic effect of a specific RhoA kinase (ROCK) inhibitor, thus suggesting that these proteins could participate in the Rho-signaling pathway. Altogether these observations demonstrate that ENA/VASP proteins are implicated in the establishment and maintenance of the axonal structure and that a change on their expression levels triggers neuronal degeneration.

Molecular And Cellular Neurobiology
Poster Number (123) Session II

CHARACTERIZATION OF THE SYNAPTIC NF-KAPPAB POOL

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The transcription factor NF-kappaB is involved in the gene expression regulation that follows a neuronal plasticity event. In memory models, it activates in a biphasic fashion, translocating to the cellular nucleus immediately after a long term memory inducing training (LTMIT) and 6 hours after. The sub-cellular localization of this transcription factor shows not only a cytoplasmatic perinuclear localization but also a synaptic pool of NF-kappaB, that activates, also after a LTMIT . This work characterizes the NF-kappaB containing synapses as a way of investigating the molecular pathways involved in its activation and its function in the synapse during neuronal plasticity.

Poster Number (124) Session II

NITRIC OXIDE SYNTHASE IN THE BRAIN OF WILD BEES

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Nitric oxide (NO) is a established signaling molecule in the insect nervous system. Several experiments in Apis mellifera suggest an important role of this molecule in the processing of olfactory information, as well as in learning and memory formation. To localize the presence of the enzyme producing NO, nitric oxide synthase (NOS), we carried out immunocytochemistry experiments using universal NOS antiserum. However this methodology gave unreliable results in our bee model. NADPH-diaphorase histochemistry was further chosen to study the distribution of NOS in bee species belonging to the family Apidae. Members of this family show differences in social structure and food source preference. We dissected female brains from different species: Apis mellifera workers (social, generalist); Bombus atratus workers (social, generalist); Centris trigonoides (solitary, specialist); Diadasina distinta (solitary, specialist). The brains were fixed in paraformaldehyde, and serially sectioned with a cryostat and incubated with the appropriate reagents.In A. mellifera, B. atratus and C. trigonoides, the neuropils of the antennal lobe, optic lobe and lateral protocerebrum were labeled. In both A. mellífera and B atratus the peripheral layers of medial and lateral calyces of the mushroom bodies exhibited staining. Instead, in C. trigonoides the vertical lobe, the pedunculus and the basal ring of the calyces were only stained. In B. atratus we observed positive somata in the optic lobe as well as in neighbouring neuropilar areas. D. distinta exhibited no staining at all. In conclusion, differences in the staining pattern of NADPH diaphorase were observed between social and solitary bees. Within social bees, B. atratus, showed ample staining in cell bodies and fibers, while solitary species displayed either a restricted pattern or no labeling at all. The fact that NADPH-diaphorase staining is present in the optic and antennal lobes of social and solitary bees suggests a role for NO in visual and olfactory primary processing centers.

MODULATION BY IRON OF THE EXPRESSION OF TRANSCRIPTION FACTORS INVOLVED IN THE PERIPHERAL NERVOUS SYSTEM MYELINOGENESIS

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Schwann cells (SCs) are responsible for myelination in the peripheral nervous system (PNS) and derive from neural crest cells. During the development of SC lineage there are SCs precursors (SCPs; E13-E14), immature SCs (E16-E17) and, after birth, mature myelinating and nonmyelinating SCs. Transcription factors involved in this process include Sox10, SCIP (crucial for temporal control of myelination) and Krox-20, vital for myelinogenesis and myelin maintenance. We have previously demonstrated the expression of transferrin (Tf) mRNA in SCPs and immature SCs. The aim of this work is to demonstrate a negative correlation between the expression of these factors and Tf mRNA and to study if the prodifferentiating effect of iron on SCs is mediated by the upregulation of these factors. We isolated SCPs and immature SCs from embryonic sciatic nerves (embryonic days 14, 16, 18 and 20, E14-E20) and mature SCs from 4 day old pups (P4). The cells were cultured for 3 hours (E14-E18) or 24 hours (E20 and P4) and either proteins or RNA were obtained. We have detected SCIP in E20, Krox-20 in P4 and S100 in all phases by Western blot. The presence of Krox-20 mRNA was evaluated by semiquantitative RT-PCR. It was found at all stages but its expression was stimulated by Fe3+ or fetal calf serum only in E18 and E20, suggesting that in previous phases the mechanisms by which Fe3+ or serum stimulate its expression are missing. Our results suggest that the expression of Tf is followed by the that of promyelinating transcription factors. These consecutive events would modulate myelinogenesis in the PNS. This also suggests that the prodifferentiating effect iron has on SCs could be mediated by the activation of the expression of these factors.

Poster Number (126) Session II

AMYOTROPHIC LATERAL SCLEROSIS AUTO-ANTIBODIES AND ABSENCE OF P/Q-TYPE CALCIUM CHANNELS

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Background: Amyotrophic Lateral Sclerosis (ALS) is an invariably fatal neurodegenerative disease characterized by a gradual loss of superior and inferior motoneurons. Approximately 90 of ALS cases belongs to a sporadic form of the disease, whose etiology is still unknown. Objectives: Previous results from our laboratory (J. Neurosci. 26(10):2661, 2006) favor an autoimmunity hypothesis as a potential cause for sporadic ALS. In order to gain knowledge about the possible antigens that interact with Immunoglobulins G from sporadic ALS patients (ALS-IgG), we studied their immunoreactivity against NMJ of normal mice and those lacking P/Q- and N-type calcium channels. Methods: We purified Immunoglobulins G (IgGs) from sera of ALS patients by affinity chromatography and characterized them by immunofluorescence with a confocal microscope. Results: In approximately 50 of cases (5 out of 9), ALS-IgGs presented a strong immunoreactivity against neuromuscular junctions of mouse diaphragm, colocalizing with Acetylcholine Receptor, a post-synaptic membrane marker of that structure. The representative fluorescence intensity (rfi) for ALS-IgGs was 3.97+/-0.76 whereas for control patients it was 1.76+/-0.54 (p0.01, N=3). Additionally 4 out of 5 of these sera showed a significant decrease in their interaction with NMJ of mice lacking P/Q-type calcium channels (rfi: 2.72+/-0.29, p0.001, N=2), reaching levels comparable with the isotype control (rfi: 2.31+/-0.38). This difference in reactivity was completely absent when N-type calcium channel wild-type and knock-out mice were used (rfi: 16.47+/-1.18 for WT and 17.35+/-1.27 for KO, N=2). Conclusions: The results found in this work add evidence in favor of

the autoimmunity hypothesis as one of the possible causes of ALS. They also suggest that auto-antibodies which are present in the serum of some patients would interact with proteins whose expression is diminished in mice lacking P/Q-type calcium channels.

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DIFFERENTIAL CONSEQUENCE OF GAIN-OF-FUNCTION FHM1 MUTATION ON NEURONS IN KNOCK-IN MICE DEPENDING ON THE DURATION OF THE ACTION POTENTIAL.

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Familial hemiplegic migraine type-1 (FHM1) is caused by missense mutations in the CACNA1A gene that encodes the α1A pore-forming subunit of Cav2.1 P/Q-type Ca2+ channels. We have used knock-in (KI) transgenic mice harbouring the pathogenic FHM1 mutation R192Q to study the physiology of neurotransmission at the calyx of Held glutamatergic synapse. Using whole cell patch clamp in brainstem slices we confirmed that KI P/Q-type Ca2+ channels activate at more hyperpolarizing potentials and have smaller activation time constants. In spite of that, presynaptic calcium currents (IpCa) evoked by presynaptic action potentials (APs) in these neurons are similar in their amplitudes and kinetic parameters. Since migraine is closely related to altered properties of cortical circuits, we extended our studies to cortical layer 2/3 pyramidal neurons. These have longer durations and smaller amplitude APs than those at the calyx of Held, thus allowing us to compare different APs waveforms to elicit Ca2+ currents. We observed the same shift in the voltage activation of calcium currents (ICa) but in contrast to the calyx of Held IpCa, P/Q-type ICa evoked by APs of cortical pyramidal neurons showed increased amplitudes in KI compared to WT mice. Instead, when P/Q-type ICa were evoked in pyramidal neurons by calyx of Held APs waveforms, we found no amplitude differences between WT and KI mice. Our results suggest that the longer depolarizing time course of APs is an important factor for the expression of a synaptic gain of function in KI mice. In addition, they show that the consequences of FHM1 mutations may vary in different excitatory neurons (glutmatergic neurons in the calyx of Held vs glutamatergic neurons in the cortex), which adds to the complexity of the pathophysiology of migraine.

THE LYSOSOMAL PATHWAY: A NEW STRATEGY IN MANGANESE-INDUCED CELL DEATH

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Manganese Mn is an essential element for normal development and corporal function in mammals. However, overexposure to this metal produces accumulation mainly in astroglia, followed by permanent and progressive neurodegenerative damage. On the cellular level, lysosomes take up manganese to a greater extent than mitochondria, a fact that suggests that this organelles may play an important role in Mn metabolism and its toxicity. Citotoxicity of MnCl2 750M in rat C6 glioma cells was assessed at different times. Cellular viability measured by mitochondrial dehydrogenases activity MTT assay diminished 6 ± 2 and 40 ± 2 for 6 and 24h treatment, respectively. When viability was assayed by neutral red staining, a vital dye that accumulates in lysosomes, a raise was measured for 6h 45 ± 4 and a decrease 39 ± 4 for 24h treatment. For this reason, lysosomes integrity was analized using acridine orange AO, a weak base that accumulates in acid compartments. An increase in positive cells to AO was found after a 6h Mn treatment 144 ±28. Using monodansylcadaverine, it was confirmed that changes on the lysosomal level were no due to autophagy induction. Bafilomycin A1 0,1nM, which is a lysosomal proton pump inhibitor and Pepstatine A 10M, a Cathepsin D inhibitor, protected cells from Mn citotoxicity leading to a viability recovery of 21 ± 2 and 17 ± 2, respectively. Therefore, our results suggest a role of lysosomal pathway in Mn-induced cell death in glioma C6 cells.

Poster Number (129) Session II

Aβ-TOXICITY IN NEURONS REQUIRES APP-DEPENDENT SIGNALING THROUGH Gβγ SUBUNIT OF GO PROTEIN

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Amyloid β (Aβ) is a metabolic fragment of the Amyloid β precursor protein (APP). Aggregation and deposition of A β in the brain play a central role in neuronal degeneration in Alzheimer´s disease (AD). Previously, we showed that interaction of A β with APP induce neurodegeneration by a mechanism that involves heterotrimeric Go protein activation, suggesting an Aβ-receptor-like role of APP in neuronal degeneration. In this presentation, we analyzed different point mutations within the Go-interacting domain of APP, and found that these mutations abolish Aβ-toxicity. In addition, we found that over-expression of Gα subunit of Go protein inhibits Aβ-toxicity in a dose-dependent manner, suggesting that APP/Go-dependent toxicity of Aβ is not mediated by Gαo subunit-signaling. Moreover, over-expression of both, the c-terminal fragment of the β adrenergic receptor-kinase (βARKct), and a prenylation-deficient mutant form of Gγ-subunit, inhibit APP-dependent toxicity of Aβ. Altogether, these results suggest that Aβ toxicity in neurons requires interaction of APP with Go protein, and signaling is mediated by Gβγ subunit (rather that Gα) of Go protein. Thus, Aβ and its parental protein APP might be key targets for halting neurodegeneration in AD.

EARLY ENDOGENOUS MODIFICATIONS DURING THE NEUROPROTECTION OF PARKINSON'S DISEASE INDUCED BY ENRICHED ENVIRONMENT

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Enriched Environment (EE), which includes social, physical and cognitive stimulation, has proved to be neuroprotective in several animal models of neurodegenerative diseases. Our group has shown that EE protects the nigrostriatal system from dopaminergic neuron damage 21 days after 6-hidroxidopamnie (6-OHDA) administration. However, the underlying mechanisms of this neuroprotection and when they are initiated are still unknown. We previously determined that at an early time period (4 days after lesion) the anterior but not the posterior Substantia Nigra (SNa, SNp) has neurodegenerating cells. At this time EE induces a remarkable reduction of the neurodegeneration and coincidently a strong increase of Glial Fibrillary Acidic Protein (GFAP) levels. Given that EE modifies Trophic Factors' (TFs) levels in several brain areas, and that these proteins have shown to be neuroprotective in different models of neurodegeneration, they might be implicated in the neuroprotection of EE from 6-OHDA cell death. We analyzed by Western Blot if EE per se modifies Brain Derived Neurotrophic Factor (BDNF) Glial Derived Neurotrophic Factor (GDNF) and Fibroblast Growth Factor (FGF-2) levels both in the SN and the Striatum, and if these TFs are modified by the toxin and/or the EE 4 days post-lesion. No change was observed in TFs levels neither by EE nor by 6-OHDA in both of the areas studied. However, using inmunofluorescence technique, an increase of FGF-2+ cells was observed in the SNa but not in the SNp of lesioned animals. This increase did not occur in lesioned animals maintained in EE.

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INTERACTION OF AB AND APP ANALYSED BY USING DIFFERENT CELL TYPES.

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Amiloide Aβ (Aβ) is a soluble metabolic product of the Amyloid β precursor protein (APP), a transmembrane type-I glycoprotein. Aggregation and deposition Aβ of in the brain cause neuronal degeneration in Alzheimer´s disease (EA). Previously, we showed that aggregated Aβ binds APP eliciting neuronal degeneration in vitro, suggesting a role for APP in AD-neurodegeneration.Here we further analysed the interation of APP with Aβ, by expressing human-wild type APP and deletion-mutant forms of APP in different cell types, including mammalian cells and yeast. The data suggest that interation of Aβ with APP is mediated by two different APP-domains, which are the juxtamembrane Aβ -domain, and the n-terminus of APP-ectodomain. The particular relevance of these two APP-domains for binding to Aβ appears to depend on the glycosilation state and the insertion of APP into the membrane. Secreted APP binds Aβ through the n-terminus domain, while membrane-anchored holo-APP interact with Aβ through the juxtamembrane Aβ -domain. Glycosilation and appropriate folding of APP appears to prevent the bilding of membrane-anchored holo-APP to Aβ through the n-terminus domain, allowing binding only through the juxtamembrane Aβ -domain, selectively. Finally, neuronal toxicity of Aβ requires the juxtamembrane Aβ -domain but not the n-terminus domain. Altogether, the data suggest that binding of Aβ to APP is critically dependent on APP-conformation/folding rather that on specific aminoacid sequences of APP.

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NPSAX: A NOVEL STRUCTURE FOR MRNA REGULATION AT SYNAPSE

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Local regulation of mRNAs is instrumental for synapse plasticity. Neurotransmitters and neurotrophins provoke distinct effects on mRNA transport and translation at synapses. Ionotropic receptors stimulation causes a transient inhibition of global protein synthesis at synapse, whereas metabotropic receptors activation provokes an increase of local translation (Steward et al, J.N., 2006). The contribution of mRNA stability to the transient mRNA activation and subsequent decay is unknown. Processing Bodies (PBs) are cytoplasmic structures involved in mRNA decaping and decay as well as mRNA storage that have been described in several cell types. PBs contains structural and enzymatic components: XRN1 exoribonuclease 5′-3′; Dcp1a, a subunit of decaping enzyme; and P54/RCK and GE-1/Hedls, that are self-aggregating molecules. We are aimed to investigate whether PBs are relevant to mRNA regulation at synapses. We found that there are a number of distinct foci containing PB components located at the somato-dendritic compartment of hippocampal neurons. As in other cell types, neuronal PBs are in dynamic equilibrium with polysomes, and recruit silenced transcripts. Strikingly, XRN1 forms large foci closely associated to the post-synaptic density, that do not contain DCP1a and that we termed NPSAXs (Non PB- Synapse Associated XRN1). We found that NPSAX respond distinctly to different synaptic stimuli. NMDAR activation, known to provoke a global translational silencing induced the formation of NPSAX. NPSAX assembly upon NMDAR activation requir.

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ALFA -SYNUCLEIN TRANSLOCATION TO MITOCHONDRIA ENHANCES FREE RADICAL FORMATION

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Parkinson´s disease (PD) is the second most common neurodegenerative disease, affecting 1 of the population above the age of 65. PD clinical manifestations include Bradykinesia, rest tremor, rigidity and postural instability. The characteristic pathology is the degeneration of dopamine neurons in the substantia nigra and the presence of Lewy bodies which are mainly composed of a-synuclein (AS). Mutations in the AS gene or AS overexpression are causal for familial PD. AS might be damaging to neurons because it is inherently prone to aggregation; mutations or increased concentration of the protein intensify this tendency. Otherwise, small oligomers derived from AS may damage key processes within the cell. Several biochemical abnormalities have been described in the brains of patients with PD, including oxidative stress and mitochondrial dysfunction, although the mechanisms remain unclear. We found AS in the mitochondria of rat brain and liver and of HeLa cells. Incubation of AS with the isolated organelle caused its entrance into the organelle. Both AS monomers and oligomers were found in mitochondria. The incubation of AS with mitochondria caused an increase in mitochondrial H2O2, NO and O2- concentration. It was recently described that AS regulates mitochondrial NO production by an activation of mtNOS (Parihar et al., Cell. Mol. Life Sci., 2008). An increase in mitochondrial NO may block electron transport chain and increase O2- production by ubisemquinone auto-oxidation, and further H2O by O2- dismutation catalyzed by MnSOD. Therefore, it is plausible that an increase in free radicals may cause modifications on AS and impact oligomer formation, aggregation, and eventually cause cell death.

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DE-DIFFERENTIATION OF SCHWANN CELLS AND IRON UPTAKE. A CLOSER LOOK.

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Schwann cells (SCs) are responsible for the myelination of the peripheral nervous system. During SCs development, precursors migrate along with the growing axons and proliferate rapidly. Loss of axonal contact, such as occurs after nerve injury or in isolated SCs in vitro, leads to down regulation of myelin genes expression. We have described that cultured SCs become de-differentiated acquiring a phenotype similar to SCs precursors and non-myelin forming SCs. Holotransferrin (hTf) prevented this de-differentiation while apotransferrin (aTf) was unable to avoid such effect. This prodifferentiating effect suggests that iron or hTf are involved in the axonal signal that occurs physiologically during SCs maturation and enables their survival. Whereas Tf-mediated iron uptake is considered the main route in most cells, there is evidence for Tf independent mechanisms. In the present work we measured 59Fe uptake by liquid scintillation counting in cultured SCs and evaluated the cells' intracellular iron content by atomic absorption. No 59Fe uptake was detected in cells incubated in the presence of serum or aTf. However, cells treated with iron or hTf showed an increase in the uptake, in agreement with intracellular iron content results. We evaluated TfR and Tf intracellular levels by Western blot (WB) analysis and observed that the expression of TfR increased in serum deprived SCs, but decreased in the aTf (66) and hTf (30) treatments. Finally we chose DMT1 among the iron transporters described and evaluated its presence by WB analysis; which was demonstrated in nerve homogenate, isolated adult-rat myelin and cultured SCs. These data allow us to strongly consider the existence of a Tf independent iron uptake mechanism in SCs.

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A NOVEL TRANSLATIONAL REGULATION PATHWAY THAT INVOLVES SMAUG1 AND NANOS1 REGULATES SYNAPSE BIOGENESIS AND FUNCTION IN MAMMALS.

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Local translation at the synapse is an important mechanism for synaptic plasticity. Several mRNA binding proteins and microRNAs are involved in translation regulation upon neurotransmitter or trophic factor stimulation. Smaug is a translational repressor initially identified in Drosophila. It regulates the stability and/or translation of hundred of maternal mRNAs that contain specific motifs termed Smaug-Recognition-Element (SRE). We have previously shown that mammalian Smaug1 represses the translation of reporter mRNAs with SRE motifs (Baez and Boccaccio, JBC 2005). Mammalian Smaug1 is expressed specifically in mature neurons, and occurs simultaneously with the synaptic markers Synapsin and PSD95. Smaug1 forms granules containing silenced mRNAs located at the post-synapse. Smaugl foci disassemble upon NMDA receptor activation, releasing mRNAs for their translation (submitted). Here, we show that mammalian Smaug1 has an important effect on synaptic plasticity. Smaug1 knockdown provokes the formation of smaller and more numerous synapses. Correlating this defect on synapse morphology, Smaug1-depleted neurons respond defectively to a repetitive depolarizing stimulus, as indicated by a reduced induction of ARC, an early gene marker of activity. Finally, we found that mammalian Nanos1 is a potential target of Smaug1. Nanos1 mRNA has SREs and is expressed in hippocampal neurons. We found that a double knockdown Smaug1 Nanos1 partially revert the Smaug1-KD phenotype. Our results suggest that the Smaug1-Nanos1 pathway is an important mechanism for local mRNA regulation that affects synapse biogenesis and plasticity. Supported by ANPCyT, CONICET, UBA, Argentina and NIH-USA

ROLE OF IMMUNE SIGNALS ON THE SURVIVAL, DIFFERENTIATION AND PROLIFERATION OF TRANSPLANTED ANSC

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Adult neural stem cells (aNSC) from the subventricular layer in the lateral ventricles (SVZ) have the potencial to differentiate into neural cells. Their plasticity and lack of ethical problems have made aNSC an attractive source of cells for cell-based therapies for neurodegenerative disease. Inflammatory response is known to affect transplanted cell survival, differentiation and proliferation. As a first approximation to study the role of immune signals on transplanted aNSC, we have characterized the inflammatory response to an aNSC transplant in the striatum. Before transplantation, the percentage of aNSC, astrocytes or neurons in the aNSC culture was determined by immunocytochemistry using specific markers (Nestin, GFAP and Tuj, respectively). Survival and inflammatory response after striatum transplantation of undifferentiated aNSC were determined 1, 3 and 6 weeks after grafting. At that time points animals were perfused intracardially, brains were dissected out and Nissl staining and GFAP or GSA immunohistochemistry were performed to analyze the inflammatory response to the transplant and cell survival. Although a large portion of grafted cells underwent cell death, 31 of them were identified after 6 weeks and the inflammation was only evident in the grafted area. The percentage of GFAP-positive grafted cells increased at 6 weeks post-transplantation, while Nestin-positive cells decline over time. These results indicate that without any stimulus grafted cells in the striatum diverted to glial differentiation. These data show that aNSC could become an important source of cells for cell-based therapies because of the survival percentage and the low inflammatory response against the transplant.

Poster Number (137) Session II

CERAMIDE-1-PHOSPHATE: A NEW MEDIATOR OF PROLIFERATION AND DIFFERENTIATION OF RETINA PHOTORECEPTOR NEURONS

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During the past two decades, key roles have been established for several sphingolipids in essential cellular processes; however their functions in retina photoreceptors were virtually unknown. Recent work from our laboratory has demonstrated that diverse sphingolipids play important roles in the development in vitro of these neurons. We determined that ceramide and sphingosine are mediators of their apoptosis during development in vitro and upon oxidative stress. We also showed that sphingosine-1 phosphate (S1P) is an intracellular signal activated by Glial Derived Neurotrophic Factor and by Docosahexaenoic Acid, two photoreceptor trophic factors, to promote proliferation and differentiation, respectively. We now investigated the role of ceramide-1-phosphate (C1P), which has been shown to promote survival and proliferation in some cellular types, in the regulation of photoreceptors development. Supplementation of rat retina neuronal cultures (PN0) with C1P 1, 5 and 10 M increased the amount of mitotic figures and BrdU uptake in photoreceptor progenitors, indicating an enhanced proliferation. Adding of C1P (1M) increased the expression of opsin and peripherin, two outer segment specific proteins, stimulated the formation of apical processes, which resembled rudimentary outer segments, and promoted the localization of those proteins in these structures. In addition, C1P had a protective effect, decreasing the apoptosis of photoreceptors occurring during their development in vitro. These results suggest that C1P, as S1P, acts as a mediator in the proliferation, survival and differentiation of photoreceptors.

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MELATONIN PREVENTS APOPTOSIS OF PHOTORECEPTORS DURING DEVELOPMENT IN VITRO

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Apoptosis a key process in the nervous system development, is required for establishing the final number of neurons and removing neural precursors that form inappropriate synapses. Abnormal apoptosis has been also involved in several neurodegenerative diseases, including those occurring in the retina, like retinitis pigmentosa and age related macular degeneration. In these diseases, apoptotic photoreceptor (PR) death leads to vision loss. Hence, finding exogenous factors that prevent PR apoptosis is relevant for treating these pathologies. Considering that oxidative stress is involved in inducing photoreceptor death and that melatonin (Mel), is a potent antioxidant, we investigated the effect of Mel on PR apoptosis. For this purpose, pure retinal cultures from newborn rats were incubated for six days with or without 40 nM Mel, and finally fixed. Cell viability was determinated by propidium iodide assay; apoptotic cell death was evaluated by TUNEL assay and DAPI staining; and mitochondrial integrity was analyzed using MitoTracker Red. In control conditions, in the absence of trophic factors, PRs initiate an apoptotic process after 4 days in vitro. Mel improved cell viability and reduced the number of apoptotic PRs after 6 days in vitro, with a parallel increase in the amount of PRs preserving mitochondrial membrane integrity. Moreover, Mel decreased about 75 the production of lipid peroxidation products (thiobarbituric acid reactive species, TBARS) and by 50 that of reactive oxygen species (ROS). These results suggest that Mel prevents PR apoptosis in vitro, probably by acting as an antioxidant, decreasing ROS accumulation.

Poster Number (139) Session II

ISOLATION AND CHARACTERIZATION OF ADULT NEURAL STEM CELLS FROM THE SVZ FOR CELL-BASED THERAPY FOR PARKINSON'S DISEASE

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Parkinson's disease is a neurodegenerative disorder characterized by a progressive loss of dopaminergic neurons. The adult neural stem cells (aNSC) are an alternative for regenerative therapies because these cells are able to differentiate into neural cell in vitro and in vivo. Our group observed that the TGF-β is pro-neurogenic on hippocampus aNSC. The aim of our work is to study the use in regenerative and protective therapies of aNSC obtained from the subventricular layer in the lateral ventricles (SVZ). In order to prove the therapeutic potential of these cells is important the standardization of the isolation protocol and the characterization of the cells in culture. We performed primary cultures dissecting the SVZ from adult Wistar rats. These cultures were characterized after 2, 4 and 6 weeks in culture with undifferentiated cells (Nestin), astrocyte (GFAP), and neural (Tuj) marker by immunocytochemistry. The effect of TGF-β on aNSC was analyzed by treatment of cultures with this cytokine for five days and characterized by immunocytochemistry. Preliminary results showed that Nestin and Tuj positive cells in culture increases from week 2 to 6 (41% to 58 % and 31% to 70% for Nestin and Tuj markers respectively). In contrast, the fraction of GFAP cells remains relatively constant over 6 weeks (3%). On the other hand, the treatment with TGF-β increases 10% the Tuj cells. This approach shows that the culture is mainly form by Tuj positive cells. This result indicates that these cells are already committed toward a neural phenotype, so it could become an important source for cell based therapies for neurodegenerative disease. In addition TGF-β might be a promising tool to increase neural differentiation.

Molecular And Cellular Neurobiology
Poster Number (140) Session II

CHARACTERIZATION OF ADULT NEURAL STEM CELLS FROM THE SVZ AFTER DIFFERENT CULTIVATION TIMES: DIFFERENTIATING ROLE OF TGF-BETA

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Adult neural stem cells (aNSC) are able to differentiate into neural cells and are regarded as a potential source of neurons for future regenerative therapies. One main requirement to achieve clinical impact is to develop efficient and reproducible differentiation protocols. Variable such as cultivation time could be affecting the differentiation potential of the cells. Interestingly, our group observed that TGF-β is pro-neurogenic on hippocampal aNSC. The aims of our work were: 1. to characterize the effect of the time in culture on the stability of cell phenotypes in aNSC obtained from the subventricular layer in the lateral ventricles (SVZ) and 2. test the pro-neurogenic effect of TGF-β on these cells. We characterized aNSC cultures dissected from the SVZ from adult rats after 2, 4 and 6 weeks in culture with undifferentiated (Nestin), astrocyte (GFAP), and neuronal (Tuj) markers by immunocytochemistry. The effect of TGF-β on aNSC was analyzed by treatment of cultures with this cytokine for five days and the different populations were determined by immunocytochemistry. Preliminary results showed that the percentage of Nestin and Tuj positive cells in culture increases from week 2 to 6 (41 to 58 and 31 to 70 for Nestin and Tuj markers, respectively). In contrast, the fraction of GFAP+ cells remains relatively constant over 6 weeks-period (3). On the other hand, the treatment with TGF-β increases 10 the percentage of Tuj+ cells. This study shows that, under our experimental conditions, the aNSC culture is already committed towards a neuronal phenotype, so it might become an important source for cell-based therapies for neurodegenerative disease. In addition TGF-β might be a promising tool to increase neuronal differentiation.

Poster Number (141) Session II

IMMUNOHISTOCHEMICAL CHARACTERIZATION OF CORTICAL DEVELOPMENTAL STAGES IN THE CHICK OPTIC TECTUM

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The present work analyzes the developmental pattern of Notch1, Hes5, NeuroD, βIII-tubulin and Synaptotagmin1 immunolabeling in the developing optic tectum (OT) from E2 (neuroepithelium) until E12 (end of basic laminar organization). During the early developmental stages (DS1-3) Notch expression is restricted to progenitor neuroepithelial cells bodies of the generative zone (GZ). This zone is surrounded by NeuroD-, βIII-tubulin- and Syt1-positive postmitotic premigratory neurons. Hes5 is intensely positive at the marginal zone indicating the existence of a Notch-independent phase of Hes5 expression. The beginning of neuritogenesis (DS2-4) is characterized by the appearance of Neurofil- and Syt-positive fascicles. As neuronal differentiation progresses (DS4-5), larger differentiating neurons acquire Notch and Hes5 cytoplasmic labeling and NeuroD nuclear labeling. From DS6 onwards the larger differentiating neurons start displaying Notch1 nuclear staining indicating an increasing nuclear translocation. The neuropile differentiation typically involves the sequential expression of Notch followed by Hes5. Synaptotagmin1 staining allows following the temporal and spatial pattern of synaptogenesis. The GZ Notch reactivity decreases during DS5 but from DS6 onwards an intense and homogeneous Notch and Hes5 reactivity reappears probably indicating their participation in gliogenesis. Although the expression of these developmentally active molecules displays a complex and dynamically changing pattern most of these changes temporally and spatially correlate with different developmental cell behaviors that take place at particular developmental stages and at defined positions along the OT radial axis.
Grants from CONICET(Arg)

Molecular And Cellular Neurobiology
Poster Number (142) Session III

DAILY VARIATIONS IN THE PROLIFERATION OF PROGENITOR CELLS ARE REGULATED BY EXTRACELLULAR NUCLEOTIDES IN THE ADULT ZEBRAFISH RETINA

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Teleost retina can regenerate and grow during the animals life span. Fish retina is endowed with a rim of tissue called margin germinal zone (MGZ) which contains proliferative (PC) and differentiating cells. We have recently described variations in the number of PC during a 24 h light/dark cycle. We found a peak at the middle of the light phase (L-14 h) and a minimum in the first half of the dark phase (from I-21 to I-02 h). On the other hand, we have described the presence of NTPDase enzymes that control extracellular nucleotide levels by immunohistochemistry in the zebrafish retina. Our aim was to study the role of extracellular nucleotides in regulating cell proliferation during a 14/10 h light/dark cycle. Zebrafish (Danio rerio) were separated in 2 groups. Group I was maintained under a light/dark cycle with an inverted phase respect to Group L. Three different treatments were performed by intravitreal injections of either apyrase (an enzyme that hydrolyzes nucleotides), MRS2179 (an antagonist of P2Y1 receptor), or ARL67156 (an NTPDase inhibitor). Saline or inactivated-apyrase were injected to control eyes. 20 h post-treatment, at L-14, I-21 and I-02 h, eyes were treated with 5-bromo-2'-deoxiuridine (BrdU) for 2 h. BrdU-labeled cells in the MGZ were quantified in 15 µm slices. NTPDases mRNA from retinal homogenates was assessed by RT-PCR. We found that at L-14 h apyrase-, MRS2179- or ARL67156-treatment significantly inhibited light-induced PC numbers increase. At I-21 and I-02 h apyrase-treatment also significantly decreased PC counts. Moreover, we described the presence of NTPDase1, 2 and 3 by RT-PCR. Our results suggest that nucleotides in the extracellular environment regulate daily variations of PC numbers in the MGZ of the zebrafish retina.

Poster Number (143) Session III

CORTICO-ANGIOGENESIS DYNAMICS IN THE DEVELOPING CHICK OPTIC TECTUM CORTICOGENESIS

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This work analyzes the temporal-spatial correlation between angio- and corticogenesis in the developing chick optic tectum (OT) by means of the NADPH-diaphorase method. Qualitative and quantitative parameters were used to analyze new vessels formation and growth of preexisting ones as a function of time and space. Angiogenesis begins with the radial ingression of capillary-like vessels, at the cephalic-basal mesencephalon, which by terminal anastomosis form a subventricular plexus (SVP). The tangential expansion of the SVP is accompanied by the simultaneous ingression of additional vessels originated as radial branches from the external plexus overlying the pial surface. As corticogenesis progresses by the addition of concentric neuronal layers, new vessels, with different spatial orientation, sprout from the previously formed radial vessels. A clear temporal correlation was observed between sprouting of new branches and formation of new neuronal layers. Besides, there is a remarkable spatial correlation between the increase in complexity of the OT cortex and that of the vascular beds. At least four vascular beds with different spatial patterns and specific positions respect to the successively appearing cortical layer were identified at the end of development. Angio- and corticogenesis progress as a function of time and space from the cephalic to the caudal OT ends. Our results could advantageously help to analyze the signaling networks involved in regulating the cortico-angiogenesis. Supported by grants from CONICET (Argentina)

Molecular And Cellular Neurobiology
Poster Number (144) Session III

INTERACTION OF Aβ AND APP ANALYSED BY USING DIFFERENT CELL TYPES.

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Amiloide Aβ (Aβ) is a soluble metabolic product of the Amyloid β precursor protein (APP), a transmembrane type-I glycoprotein. Aggregation and deposition Aβ of in the brain cause neuronal degeneration in Alzheimer´s disease (EA). Previously, we showed that aggregated Aβ binds APP eliciting neuronal degeneration in vitro, suggesting a role for APP in AD-neurodegeneration.Here we further analysed the interation of APP with Aβ, by expressing human-wild type APP and deletion-mutant forms of APP in different cell types, including mammalian cells and yeast. The data suggest that interation of Aβ with APP is mediated by two different APP-domains, which are the juxtamembrane Aβ -domain, and the n-terminus of APP-ectodomain. The particular relevance of these two APP-domains for binding to Aβ appears to depend on the glycosilation state and the insertion of APP into the membrane. Secreted APP binds Aβ through the n-terminus domain, while membrane-anchored holo-APP interact with Aβ through the juxtamembrane Aβ -domain. Glycosilation and appropriate folding of APP appears to prevent the bilding of membrane-anchored holo-APP to Aβ through the n-terminus domain, allowing binding only through the juxtamembrane Aβ -domain, selectively. Finally, neuronal toxicity of Aβ requires the juxtamembrane Aβ -domain but not the n-terminus domain. Altogether, the data suggest that binding of Aβ to APP is critically dependent on APP-conformation/folding rather that on specific aminoacid sequences of APP.

Poster Number (146) Session III

POTENTIAL ROLE OF ANGIOTENSIN II AT2 RECEPTORS IN PURKINJE CELLS MIGRATION.

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Angiotensin II (Ang II), the active component of the renin–angiotensin system, binds and activates two major subtype of receptors, namely AT1 and AT2. In the fetus, AT2 receptors predominate in all tissues and decline shortly after birth, being restricted to a few organs including brain. Interpretation of the function of Ang II in cerebellum necessitates a thorough understanding about the localization of Ang II receptors. A clear complementary pattern of AT1 and AT2 binding labeled by [125I]Ang II was observed on adjacent layers in young rats within the cerebellar cortex. By using specific markers of the Purkinje cells (PCs) (Zebrin II and calbindin), we demonstrated that Ang II AT2 receptors co-localized with the PCs as a monolayer, in correspondence with the well-defined layer observed by binding autoradiography at differential developmental stages (P8 to P60). Blockade of AT2 receptors with PD12319 during late pregnancy caused a lost of AT2 binding in the external granular layer (EGL) in P0 pups. A detailed histological analysis evidenced an enlarged EGL in the cerebellar cortex. It is well known that PCs migrate early during fetal stage (E14) toward the cerebellar cortex. Cote et al. 1999, showed a role of Ang II AT2 receptors in cerebellar neuron migration. PCs regulate proliferation of the granulose cells (Carletti, 2008). The lack of receptor stimulation during prenatal period by pharmacological blockade altered developing cerebellum. The enlarged EGL in the cerebellar cortex and the lack of binding at the EGL, suggest a potential role of Ang II AT2 receptors during PCs migration. Cote et al. 1999. J Biol Chem 274: 31686–31692. Carletti et al. 2008.The Neuroscientist 14; 91-100.

Molecular And Cellular Neurobiology
Poster Number (147) Session III

PREGNANCY AND OPIOID ADDICTION TREATMENT: BUPRENORPHINE AFFECTS MYELINATION IN THE DEVELOPING BRAIN

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To avoid "street" drug use and withdrawal symptoms, pregnant opioid addicts are treated with the opioid analogue buprenorphine. Unfortunately, this treatment is associated with increased risk of sudden infant death syndrome as well as child learning disabilities and behavioral problems. The underlying causes for these conditions are unclear; however, they may in part involve alterations in myelination since oligodendrocytes express opioid receptors in a developmentally regulated manner. To investigate this possibility, pregnant rats were implanted on day 7 of gestation with minipumps to deliver buprenorphine at 0.3-1 mg/kg/day, doses covering the range used in humans. Analysis of their pups at different postnatal ages (12-26 days) indicated that exposure to 0.3 mg/kg/day buprenorphine caused an accelerated and significant increase in the expression of all myelin basic proteins (MBPs) in the brain. In contrast, treatment with the higher dose caused a developmental delay in MBPs expression. EM analysis of corpus callosum at 26-days of age indicated that buprenorphine cause changes in the caliber and number of myelinated axons which is accompanied by a thinner myelin sheath. Analysis of myelin associated glycoprotein (MAG) expression and glycosylation suggests that this molecule may play a crucial role in mediating these buprenorphine effects. Co-immunoprecipitation studies also point to a mechanism involving a MAG-dependent activation of the tyrosine kinase Fyn. These results show for the first time that opioid signaling plays an important role in regulating myelination in vivo and provide cellular and molecular clues that may help to understand the neurological problems affecting children exposed to opioids in utero.

Poster Number (148) Session III

MELATONIN INDUCES APOPTOSIS IN C6 GLIOMA CELLS. THERAPEUTIC IMPLICATIONS.

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Malignant gliomas are resistant to various proapoptotic therapies, such as radiotherapy and conventional chemotherapy. Melatonin is a hormone synthesized by pineal gland with widespread functions. Several evidences indicate an antiproliferative action of melatonin in tumor cells. However, no definitive intracellular pathway has been described to explain this antineoplasic effect. In this study, we demonstrated that melatonin induces a dose-dependent decrease in cell viability. Melatonin (2mM, 24hs) induced cell cytotoxicity in the presence and absence of FBS, measured by both MTT (18±1%, 57±1%) and Neutral Red (27±4%, 41±2%). Additionaly, cell death was visualized by phase-contrast microscopy as a dramatic disruption of the cell monolayer with retraction of astrocytic processes. In this conditions, caspase 3 activity, a marker of apoptotic cell death, increases 81±23% and 208±40% in the presence and absence of FBS, respectively. A correlation between ERK phosphorylation and p53 levels was detected by Western Blot analysis. Incubations with PD98059 (25µM), a MEK activity inhibitor, resulted in a total recovery of viability in absence of FBS; however, in the presence of serum, PD98059 enhances melatonin-induced injury. Our results suggest that melatonin may be an important endogenous cell death modulator and a potential therapeutic agent in glial tumors.

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Poster Number (149) Session III

NEUROPROTECTIVE EFFECTS OF 17 BETA ESTRADIOL ON CA1 HIPPOCAMPAL AREA OF PERINATAL ASPHYCTIC RATS

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Perinatal asphyxia (PA) is an important cause of neonatal mortality and subsequent serious consequence such as motor and cognitive deficits and seizures. To our best knowledge few reports describe long-term alterations and neuronal cytoskeleton changes after PA. In this work we studied the effects of a late treatment with 17B estradiol as a neuroprotective strategy over the effects of PA on the astrocytes, estrogen receptor alfa localization and neuronal cytoskeleton of the hippocampus of 4 mouth old rats. Hippocampus was reported to be one of the most hypoxia-sensitive areas. Staining with GFAP followed by confocal microscopy analysis showed an astrogliosis in Stratum radiatum of CA1 hippocampal area of AP Vhi animals. MAP2 staining revealed a focal swelling and a markedly fragmented appearance of distal dendrites in AP Vhi group in this area. Axonal alterations were evaluated with neurofilaments immunostaining. We did not observed a significant difference 160Kd neurofilaments staining in AP Vhi rats respect to controls groups. However, neurofilaments phosphoforms staining was more intense in CTL groups respect to AP Vhi animals. When a late treatment was administrated (AP 17B), the changes observed in AP Vhi animals were reverted. All the groups treated with 17 beta estradiol differ from to non treated ones in estrogen receptor alfa localization and colocalization with astrocytes. These results suggest that hippocampal alterations observed in asphyctic animals could be related with a neurodegenerative changes, and a late treatment with estradiol could reverted these alterations. IBRO Studentship 2008; Beca MAE-AECID; UBACYT M407; PIP 5784.

Poster Number (150) Session III

M6A GLYCOPROTEIN IS INVOLVED IN NEURONAL PLASTICITY AFTER PERINATAL ASPHYXIA

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During perinatal asphyctic episode produces a synaptic dysfunction that has been related to neuronal death, although this mechanism is not fully understood yet. Previously, we showed in 30 days old rats, that asphyxia increased actin cytoskeleton in hippocampal post-synaptic densities. In additiion, using electron and confocal microscopy, we observed an increase in dendritic spine number in Stratum radiatum of CA1 area from asphyxiated animals. Moreover, newly formed filopodia were observed in those animals probably as a consequence of neuronal plasticity induced by asphyxia. In addition we also demonstrated that the glycoprotein M6a is involved in hippocampal neuronal plasticity by promoting filopodium/spine formation and is regulated by stress. Taken together all of these previous observations, the main aim of this work is to investigate the expression of M6a in 30 days old rats that were subjected to perinatal asphyxia (PA) by real time RT-PCR and immunocytochemistry. Real time PCR assays revealed an over expression of M6a mRNA in hippocampal formation from asphyxiated animals in comparison to control animals. Immunocytochemistry also showed an increase in M6a staining in hippocampus CA1 area from treated animals. These results suggest that M6a glycoprotein could be involved in the dynamic of dendritic spines changes in asphyctic animals. Therefore, these observations indicate that perinatal asphyxia could affect neuronal plasticity mediated for the changes in the expression of M6a glycoprotein.
UBACYT M407; PIP 5784.

Molecular And Cellular Neurobiology
Poster Number (151) Session III

GENETIC IDENTIFICATION OF A NOVEL GATA2/3+ CELL POPULATION IN THE DEVELOPING MOUSE SPINAL CORD

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In spite of the progress made in understanding early events in cell specification, the mechanisms that lead to the diversity of neuronal types remain to be elucidated. In the developing neural tube, distinct populations of neurons arise at specific dorso-ventral positions. In order to analyze how early embryonic population contribute to different cell types, we used Cre/loxp labeling systems to fate map descendents of V2b cells, one ventral group of embryonic neurons that express the transcription factors Gata2/3. By performing cell lineage tracing in the Gata3-Cre and in the Gata2-GFP mouse, we identified a novel population of cells in lamina X of the spinal cord, which is distinct to V2b-derived interneurons that locate in lamina VII. These cells, termed cerebrospinal fluid-contacting neurons (CCNs), have a unique morphology, with a dendritic-like process through the ependyma into the central canal. We found that CCNs are born from ventral progenitors at E13-14, when neurogenesis in the neural tube is almost completed. The late birthdate of CCNs contrasts with the earlier progenitor cell cycle exit that generates lamina VII Gata2/3 neurons. The genetic mechanisms that control the development of early-born V2b cells requires the activity of the transcription factor Foxn4 and Notch signaling pathway. On the other hand, the differentiation of CCNs appears normal in Foxn4-/- and in Presenilin1 mutant mice, indicating that different genetic mechanisms are involved in the genesis of distinct subsets of Gata2/3 spinal neurons. These results show that restricted populations of precursors in the developing tube can sequentially differentiate into separate neuronal subtypes, contributing to the diversification of neuronal fates.

Poster Number (152) Session III

ROLE OF MULLER GLIAL CELLS IN THE GENERATION OF NEUROBLASTS AND PHOTORECEPTOR-LIKE CELLS. APOPTOSIS PREVENTION BY SPHINGOSINE 1 PHOSPHATE

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Apoptosis of photoreceptors (PR) is the main cause of blindness in retinal neurodegenerations. Since the finding of stem cells in the retina, a promising strategy to avoid vision impairment is to regenerate lost PR. Using Muller glial cells (MGC), which display stem cell properties, requires establishing how MGC might generate neuroblasts (NB), how to induce these NB to further differentiate into mature neurons and how to avoid apoptosis of the regenerated neurons. To investigate these issues we used pure neuronal and glial primary and secondary cultures, and neuro-glia cocultures. NB, characterized as round, undifferentiated cells that took up Bromodeoxyuridine and expressed Nestin and Pax6, were only preserved in long-term primary and secondary neuro-glia cocultures, since they were absent or rapidly disappeared in pure neuronal or pure glial cultures. NB comprised about 63 of the total small, round cells in primary neuro-glia cocultures but dropped to 1 in secondary cocultures; concomitantly, nearly 70 and 10 of round cells in secondary cocultures expressed the PR markers Crx and opsin, respectively; these cells also showed high affinity glutamate uptake, a feature of functional PR. Apoptosis of PR-like cells increased during culture time but addition of sphingosine-1-phosphate (S1P), recently shown to prevent PR apoptosis, decreased their death. Our results suggest that neuron-MGC interactions might be relevant in the preservation or generation of NB and in their further differentiation as PR, while S1P might provide a useful tool to prevent apoptosis in newly generated PR.

Molecular And Cellular Neurobiology
Poster Number (153) Session III

STUDY OF PROGENITOR CELLS FROM AVIAN RETINA

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Retinal progenitor/stem cells from hot-blood vertebrate eyes have become quite significant for retinal regeneration research. These cells were found in the ciliary-circumferential marginal zone (CMZ) in embryos and postnatal birds. The layering of CMZ has been immunoanalyzed, but little is known about the proliferation and differentiation of retinal progenitor cells in culture. Thus, the purpose of this study was to analyze their morphological and immuno profile under basal conditions and trophic stimulation. Briefly, these cells were obtained as primary culture after mechanical dissociation from specific small pieces removed from CMZ of chick and quail embryos at E13 to E19. Isolated cells were then cultured in DMEM-F12, bFGF, EGF. Cells clumped together and formed typical neurospheres a few hours later. To characterize these we performed a tridimensional neurosphere bioassay inside a gelified collagen I. They were studied, during 4 days, under the action of NGF, NT-3, and NTN, factors known to be very active in retinal development. Progenitors could be identified by their clumping behavior forming neurospheres, a long preservation period in basal quiescent state for at least nine to ten months, by assaying for the expression of proliferate markers (PCNA, KI67), neural progenitor markers (A2B5, Foxn4, Pax6), and by the incorporation of BrdU. In the 3-D-bioassay, trophic stimulated cells generated outgrowths in which most cells were glial and a discrete number of neurites emitted by neurons. Several cells expressed calbindin and vimentin. Our bioassay of trophic stimulation allowed us to conclude that isolated progenitors were able to proliferate and differentiate, and clearly generate large glial cells and neurons.

Molecular And Cellular Neurobiology
Poster Number (154) Session III

TROPHIC STIMULATION OF EMBRYONIC CELLS FROM RAT CORPUS STRIATUM

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Neural Stem Cells (NSC) from the sub ventricular zone of mammalian brain have become essential for neural regeneration research. Progenitors in the Corpus Striatum (CS) were discovered a few years ago, but little is known about their proliferation and differentiation. The purpose of this study was to analyze CS morpho-immune profiles using bioassays under basal and different trophic stimulation conditions. Briefly, primary cells obtained from CS of rat embryos at E13-14 were cultivated floating in DMEM-F12, bFGF, and B27. After forming neurospheres they were then placed inside gelified collagen I, and cultured under basal conditions or with the addition of NGF, NT-3, or NTN. We obtained optimum growth of neurites that were measured in number and length after 24 and 48 hours. The expression of proliferation markers (PCNA, Ki67) and neural progenitor markers (GFAP, Nestin, Vimentin, O4, A2B5, Pax6, S100, TubIII, and NeuN) were also analyzed. The initial behaviour of CS primary cell cultures showed distinguishable neurospheres, that when placed in collagen gels generated neurites, depending on the trophic support. Also, glial cells grew out from the neurospheres. Antibody staining was strongly positive with the exception of NeuN and O4 that were faint. The bioassay system allowed us to conclude that CS cells can generate neural progenitors useful for research on proliferation and differentiation. Our assay showed high reproducibility, short culture time and high resolution to trace neurites growing out from neurons in a few hours or visualize glial cells outgrowth.

AN ACTIVITY-DEPENDENT ANATOMICAL GRADIENT FOR NEURONAL DEVELOPMENT IN THE ADULT HIPPOCAMPUS

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The dentate gyrus of the mammalian hippocampus generates neurons through life. In the adult hippocampus, neural progenitor cells develop, mature and integrate to become functional neurons capable of information processing. Each of those steps is modulated by physiological and environmental factors. In the present work we sought to investigate whether the marked anatomical and functional segregation along the longitudinal (septotemporal) axis of the hippocampus may regulate the development of adult-born neurons. We labeled newborn neurons of the adult mouse dentate gyrus using a retroviral construct expressing GFP and analyzed their morphology, marker expression and function at different ages. At the septal pole of the hippocampus, three-week-old neurons expressed mature markers and exhibited complex spiny dendrites, repetitive spiking and high frequency of miniature glutamatergic postsynaptic currents (minis~1Hz). In contrast, neurons of the same age at the temporal pole were highly immature, displaying immature neuronal markers, simple dendrites with fewer spines, single action potentials, and low mini frequency (0.2Hz). These observations reflect a slower pace of neuronal maturation in the temporal hippocampus. Interestingly, housing mice with a running wheel enhanced network activity in the temporal dentate gyrus as seen by Arc expression, and accelerated neuronal maturation, minimizing the regional difference. Therefore, we propose that the septotemporal gradient in the timing for neuronal maturation in the adult hippocampus might render a different time window for the time associations during episodic memories. Interestingly, the temporal resolution of this window could be determined by network activity.

Poster Number (156) Session III

MIGRATION OF BONE MARROW MONONUCLEAR CELLS TO THE CRUSHED SCIATIC NERVE. ITS EFFECT ON REMYELINATION

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We have previously described in a reversible model of Wallerian degeneration the demyelination of the distal stump of the crushed sciatic nerve in terms of P0 and MBP levels. During the same period we have also demonstrated the migration of transplanted bone marrow mononuclear cells to the distal stump of the injured nerve. The aim of the present work is to study the remyelination of the crushed sciatic nerve and to evaluate whether BMMC migrate to the injured nerve in order to participate in the demyelinating and/ or in the remyelinating process. For this purpose, adult Wistar rats were submitted to the crush of the right sciatic nerve and sacrificed at different survival times. BMMC isolated from the bone marrow extruded from tibia and femur bones were dyed with a fluorescent probe and injected intravenously immediately after crushing the sciatic nerve in order to evaluate their migration to the injured area. IHC analyses were done to evaluate the demyelination-remyelination of the nerve, the endogenous migration of BMMCs and the phenotype of BMMCs once they reached the nerve. Our results clearly demonstrate that the remyelination process begins 28 days post injury, reaching normal values by 60 days. The endogenous migration of CD34+ cells exclusively to the distal stump of the injured nerve was observed from 3 days to 14 days post injury. Our results also show the colocalization of CD34+ cells, a BMMCs marker, with S100, a universal SC marker, exclusively in the crush area and the distal stump of the ipsilateral nerve. More experiments are necessary to confirm the role of BMMCs in the degeneration-regeneration process and to choose the population of BMMC that works best for future transplantation therapies.

Poster Number (157) Session III

A PUTATIVE RELATIONSHIP BETWEEN PROTEIN AGGREGATES AND STRESS GRANULES

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Cytoplasmic aggregates of misfolded proteins are frequent in several neurodegenerative disorders. These inclusions are a pathological hallmark of neuronal disease. Neurodegeneration is linked to cellular stress. This is a survival response that includes a number of mechanisms. One of them implicates the formation of novel structures known as Stress Granules (SGs). SGs are cytoplasmic aggregates that sequestrate silenced mRNA along with proapoptotic factors, all this helping recovery. SGs are transient and are induced upon acute stress stimuli. Similar to neuropathological protein aggregates, SGs contain ubiquitinated proteins, require the molecular motor dynein for aggregation and chaperons for dissolution. SGs contain RNA binding proteins with RNA recognition motives (RRM) and protein aggregation domains that mediate self-aggregation. These proteins are very similar to TDP43, which was identified as the major component of cytoplasmic inclusions characteristic of Frontotemporal Lobar dementia (FTLD) and amyotrophic lateral sclerosis (ALS). TDP43 is a conserved protein that contains two RRM and a glycin-rich domain at the C-terminal that mediates protein aggregation. These striking similarities lead us to wonder if TDP43 C-terminal aggregates may affect SGs physiology. We are currently analyzing whether the presence of TDP43 inclusions in the cytoplasm facilitates or inhibits SG formation and dissolution, thus affecting neuronal survival upon a stress insult. Supported by ANPCyT; CONICET and UBA, Argentina, and NIH, USA.

Poster Number (158) Session III

AUTOMATIC AND QUANTITATIVE ANALYSIS OF NGF RECEPTORS CO-ENDOCYTOSIS

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Spatial colocalization analysis of two fluorescently labeled molecules in optical microscopy is of major importance in cell biology. Qualitative colocalization analysis is generally visual-based and therefore highly prone to random error and bias. New methods to quantitatively analyze colocalization through the evaluation of overlapping pixels, based on global statistic analysis of pixel intensity distributions have been recently developed. Still, the majority of colocalization situations demand customized approaches. We developed an algorithm that quantitatively and automatically tracks colocalization without the bias of visual interpretation and simultaneously overcomes definite inconvenients not contemplated by former algorithms: i) it detects colocalization in images where fluorophore distribution is mainly anticolocalizing and thus are negative correlated; ii) it distinguishes colocalizing pixels in images with high density of fluorescent molecules; iii) it can be applied to the whole images or to a definite region with the same level of accuracy. In addition, we redefined the utility of the colocalization coefficients by constructing informative maps of the distribution of these coefficients throughout the image. In this way we could directly observe the regions inside the image where colocalization is relevant. With this new method we determined the endocytosis characteristics of the NGF receptors TrkA and p75 when co-expressed in PC12 cells. We observed that upon overexpression of TrkA-CFP and p75-YFP three populations of endosomes arose: those containing only p75, only TrkA or both receptors. This finding may shed light on the mechanism that underlies the cooperation of these receptors on NGF signal transduction.

Molecular And Cellular Neurobiology

Poster Number (159) Session III

ERYTHROPOIETIN DIFFERENTIAL ACTION ON MATURE AND IMMATURE SH-SY5Y CELL CULTURES

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Erythropoietin (Epo) has emerged as a multifunctional factor that could play an important role in tissues outside the hematopoietic system. In previous works, we found an Epo antiapoptotic action on undifferentiated neuronal SH-SY5Y cells against cytotoxicity induced by stauroporine (STP) or TNF-alpha. Then, we investigated whether the protective effect of Epo could be detected in neuronal cells differentiated by retinoic acid (RA). Immature and mature stages of SH-SY5Y cells were exposed to proapoptotic agents. In immature cell cultures, STP, TNF-alpha or hypoxia significantly reduced cell viability (MTT assay) and increased apoptosis (Hoechst staining) (STP 49±3, TNF 49±3, H 28±2, P0.05 vs. Control). However, cell resistance was observed after RA differentiated cells (RA-STP 28±3, RA-TNF 15±3, RA-H 7±2, P0.05 vs. Control). Pretreatment of undifferentiated cells with Epo significantly (P0.05) prevented cell death against STP (23±3), TNF (20±6), or hypoxia (7±2). These effects can be partially explained by Bcl-xL and Bcl-2 upregulation (RT-PCR and Western Blotting). Instead, no additional effect of Epo was observed upon differentiated cells. Inhibition of Jak-2 pathway and ARNm analysis of the erythropoietin receptor (Real time PCR) suggest that this lack of response could be associated to receptor downregulation. In conclusion, Epo is able to protect immature SH-SY5Y cells from cell death induced by STP, TNF-alpha or hypoxia but is uncapable to affect RA-differentiated cells. A close dependence of the Epo neuroprotective action on the degree of cell differentiation could be one explanation. This differential behavior of immature and mature neuronal cells could be important in the pharmacological effect of Epo. Key words: Erythropoietin, Neuroprotection, Differentiation.

Molecular And Cellular Neurobiology
Poster Number (160) Session III

RECOVERY OF OLFACTORY FUNCTION AFTER MASSIVE DEGENERATION OF OLFACTORY NEURONS IN AMPHIBIAN LARVAE: A POSSIBLE ROLE FOR BRAIN-DERIVED NEUROTROPHIC FACTOR.

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Amphibian larvae represent an excellent experimental model to study the ability of the olfactory epithelium (OE) to regenerate its neuronal population continuously throughout life. We have developed an experimental design consisting in immersion of Rhinella arenarum larvae in zinc sulphate (ZnSO4) that provokes a massive degeneration of the olfactory tissue. We have previously observed that the normal architecture of the OE is restored by the third day after ZnSO4 treatment. However, the functionality of this recovered epithelium remained to be analyzed. Thus, we designed a simple and reliable method to test larvae behavior that consists in analyzing their responsiveness to an olfactory stimulus that indicates the presence of food. Our data show that shortly after treatment there is no response to the olfactory stimulus, whereas since the second day and thereafter the responsiveness is restored and exhibits the same timing that the response registered for control animals. These results suggest that the sensorial ability of the OE recovered after injury is, at least for this kind of stimulus, as efficacious as that achieved during the normal physiological turnover of the olfactory neurons. We next addressed the issue of which factor(s) are involved in this re-establishment of olfactory functionality. As we had previously observed that a strong brain-derived neurotrophic factor (BDNF) immunostaining is present in specific regions of the OE and in the olfactory nerves immediately after ZnSO4 treatment (in contrast to control animals in which it is absent) we screened the evolution of this staining pattern during recovery of the OE. Here we show that BDNF staining in the olfactory nerves fades away by the second day of recovery, whereas staining in the OE remains unchanged during this time lapse. These results suggest that BDNF plays some role during the reconnection of the olfactory nerves to the olfactory bulb that allows restoration of the responsiveness to olfactory stimuli, whereas in the OE it may have a longer term effect.

Molecular And Cellular Neurobiology

Poster Number (161) Session III

CHARACTERIZATION OF A M6 HYPOMORPHIC MUTANT IN THE FRUIT FLY

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Neuronal remodeling is a fundamental process by which the brain responds to environmental influences during stress. The glycoprotein M6a, member of the 'Proteolipid proteins' (PLP), has recently been identified as a stress-responsive gene in the hippocampus of stressed animals. Our findings indicate that M6a plays an important role in neurite outgrowth and filopodium/spines formation. Evolutionary studies showed that m6 is the only member of the PLP family in Arthropods and bioinformatics analysis of the protein sequences revealed that M6a and M6 have structural homology. Based on this information we decided to characterize M6, the ortholog of M6a, in D. melanogaster. M6 hypomorphic mutant flies with reduced M6 expression level (40) were subjected to behavioral tests (climbing, locomotor activity, life span, rest/activity cycles) and exposed to stressful conditions (extreme temperatures, an oxidative agent and starvation). Interestingly, M6 mutant flies specifically exhibited reduced global locomotor activity. Next, we examined M6 expression in the fly brain employing a GFP enhancer trap line expressing GFP fused at the N-terminal of M6C isoform. M6 is expressed in the mushroom bodies, optic lobes and central body complex, but a more detailed analysis including specific structural markers is still required. During the characterization of the M6 hypomorph mutant we noticed that females are sterile. Eggs laid from M6 mutant flies showed severe defects, collapsing soon after they are laid. Immunohistochemistry is underway to shed light on this issue. In depth characterization of such phenotypes will enable us to study M6 function at the cellular and molecular level in both reproductive and nervous systems.

Molecular And Cellular Neurobiology
Poster Number (162) Session III

DIACYLGLYCEROL KINASE EPSILON (DAGKEPSILON) PRESENCE IN BOVINE ROD OUTER SEGMENTS.

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Vertebrate retinal photoreceptor cells have an active phosphoinositide metabolism and several steps in the PI cycle are stimulated by light. Previous research from our lab has shown a peripherally-associated DAGK in bovine ROS that changes its association to membrane in response to light (Ilincheta de Boschero and Giusto, 1992). A DAGK activity, up-regulated by transducin subunits dissociation was also proposed on the basis of GTPgammaS and fluoride action. In ROS obtained from bleached bovine retina (B-ROS), a DAGKgamma isozyme was reported to be photoassociated and activated by light (Huang et al, 2000). The presence of DAGKepsilon and DAGKgamma in ROS obtained from dark bovine retina (D-ROS), B-ROS and D-ROS exposed to brief light (ROS-L) was analyzed by immunofluorescence microscopy (IM) and western blot (WB). Rabbit polyclonal DAGK antibodies (anti-DAGKepsilon or anti-DAGKgamma and goat anti-rabbit secondary antibody coupled to FITC were employed to isoform detection by IM. Interestingly, positive DAGKepsilon labeling was found in ROS with a granular distribution and membrane localization of this isoform is thus suggested. Positive ROS-DAGKgamma labeling homogenously distributed was found, which seems to indicate a soluble localization. DAGKepsilon predominantly phosphorylates DAG with an arachidonate in sn2 position, thus giving support to the notion that in ROS, DAGKepsilon could play a role in enriching inositol phospholipid synthesis.

Computational Neuroscience

Poster Number (163) Session 1

LOW-DIMENSIONAL DYNAMICAL MODEL FOR THE DIVERSITY OF PRESSURE PATTERNS USED IN CANARY SONG

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During song production, oscine birds produce large air sac pressure pulses. During those pulses, energy is transferred to labia located at the juncture between the bronchii and the trachea, inducing the high frequency labial oscillations which are responsible for airflow modulations, i.e., the uttered sound. In order to generate diverse syllables, canaries Serinus canaria use a set of air sac pressure patterns with characteristic shapes. In this work we show that these different shapes can be approximated by the

subharmonic solutions of a forced normal form. This simple model is built from identifying dynamical elements which allow to reproduce the shape of the pressure pattern corresponding to one syllable type. Remarkably, integrating that simple model for other parameters allows to recover the other pressure patterns used during song. Interpreting the diversity of these physiological gestures as subharmonic solutions of a simple nonlinear system allows us to account simultaneously for their morphological features as well as for the syllabic timing and suggests a strategy for the generation of complex motor patterns.

Computational Neuroscience
Poster Number (164) Session 1

NONTRIVIAL FEATURES OF SENSORIMOTOR SYNCHRONIZATION PREDICTED BY A MATHEMATICAL MODEL FOR FINGER TAPPING

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Time estimation is critical for survival and control of a variety of behaviors, both in humans and other animals. Time estimation in the hundred-milliseconds range, known as millisecond timing, is involved in motor control, speech generation and recognition, and sensorimotor synchronization (like playing music or finger tapping to a beat). We have developed a mathematical model for finger tapping and made a prediction on a nontrivial feature of this behavior, namely on the amount and asymmetry of the overshoot after a recovering from a perturbation in the stimulus period. In this work we report an experimental validation of our mathematical model based on that prediction.

Poster Number (165) Session 1

INTERACTION BETWEEN INTRINSIC DYNAMICS AND STDP LEARNING RULES IN IMPROVEMENT OF SIGNAL TRANSMISSION IN A NOISY NEURAL NETWORK

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In the learning rules associated with the spike timing dependent plasticity (STDP) phenomenon, the synaptic connection between neurons increases or decreases accordingly to the precise temporal ordering of presynaptic and postsynaptic action potentials. In this work we analyze the interaction between the intrinsic dynamics of neurons and the STDP rules produces one interesting network properties, namely improvement in signal transmission. We use models of conductance and reduced models in order to simulate a feed-forward architecture of neural network, and three different rules of Spike-Timing Dependent Plasticity: one with even symmetry, other with odd symmetry and the last one asymmetric with synaptic depression larger than potentiation. We consider different types of neural behavior associated with different shapes in the Phase-Response Curve (PRC). This curve is shaped by the ionic conductances and the external currents, and documents the changes in timing of action potentials as a result of a small perturbation in a firing neuron (1). We find that the symmetrical rules favor the improvement of the reliability of signal transmission in a noisy environment, through the effect of stochastic resonance. The outcome is larger for the cases in which the Phase-Response Function has a maximum for small deviations from the neural oscillation period. This result allow us predict the effect of different synaptic conductances over the information transmission properties of the network. (1)Pfeuty B., Mato G., Golomb D., Hansel D. Electrical Synapses and Synchrony: The role of Intrinsic Currents. The Journal of Neuroscience, 23(15):6280–6294, July 16, 2003.

Computational Neuroscience
Poster Number (166) Session II

A COMPUTATIONAL MODEL OF THE RIBBON SYNAPSE

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Inner hair cells (IHC) in the cochlea transduce sound into graded electrical responses. These responses are relayed to the brain with exquisite temporal precision via the coordinated release of vesicles from the ribbon synapses to the auditory nerve fibers. Fibers can be locked to the phase of the stimulus up to frequencies of 5 kHz. It is thought that this can be achieved through the unique features of the ribbon synapses of the IHC. They provide sustained release with minimum latency and high reliability. Some recent research suggest that the existence of a readily releasable pool of vesicles and the coordinated release of many vesicles can be determinant for the synapses temporal precision. However, the detailed mechanism of exocytosis is still unknown and several hypotheses has been proposed so far. In this work we propose a computational model of the IHC ribbon synapse that takes into account current research and explore different exocytotic mechanisms. A significant increase in temporal precision was obtained when the release events were not independent (coordinated release). The critical size of the RRVP and the replenishment rate are also explored and compared with experimental measures.

Poster Number (167) Session II

NEURAL CODIFICATION MODEL FOR BASILAR MEMBRANE EXCITATION PATTERNS.

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It is well known that the basilar membrane (BM) has the capacity to segregate the frequency components of a complex stimulus. In this way each site of the BM has a maximal response to a given frequency. This organization (called tonotopic), is preserved all along the auditory route. In the other hand each site of the BM is innervated with auditory nerve fibers (AF) that fire in synchrony with the oscillation of the membrane (transduced by the inner hair cells). Thus, the frequency information is coded also by the interspike time in the bunch of AF. Under the hypothesis that the brain takes advantage of this redundancies, this work proposes a minimal neural net that extracts the spatial-temporal information of the activation pattern of the BM, whit special focus on: (a) the synchronization of the AF with the stimulus (temporal coding); (b) the activation of a crescent number of AF on different frequency bands with stimulus raising intensity (population and place coding); (c) a coincidence detectors net whose activities are sensitive to the temporal coherence of spike patterns of adjacent fibers. This last characteristic would allow besides being biologically plausible a mechanism to detect stability recently proposed to explain the tonal perception on frequency modulated sounds. [1] Mesz, B. A. y Eguia, M. C. Ann. N.Y. Acad. Sci. 1169: 126–130 (2009).

Computational Neuroscience
Poster Number (168) Session II

HEBBIAN PLASTICITY AND HOMEOSTASIS IN A MODEL OF HIPERCOLUMN OF THE VISUAL CORTEX

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Neurons in the nervous system display a wide variety of plasticity processes. Among them are covariance based rules and homeostatic plasticity. By themselves, the first ones tend to generate instabilities because of the unbounded potentiation of synapses. The second ones tend to stabilize the system by setting a target for the post-synaptic firing rate. In this work we analyze the combined effect of these two mechanisms in a simple model of hipercolumn of the visual cortex. We find that the presence of homeostatic plasticity together with non-plastic uniform inhibition stabilizes the effect of Hebbian plasticity. The system can reach non-trivial solutions, where the recurrent intracortical connections are strongly modulated. The modulation is strong enough to generate contrast invariance. Moreover, this state can be reached even beginning from a weakly modulated initial condition.

Poster Number (169) Session III

EXPLORING THE ZEBRA FINCH SONG PRODUCTION MECHANISMS

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The basic mechanism of birdsong production resembles the generation of voiced sounds by humans: expiratory airflow drives sustained oscillations of the membranes - vocal folds in humans and labia in birds. Recently, a modified model (containing nonlinear elastic restitution for the labia) has been proposed to account for a mathematical relationship between fundamental frequency and its spectral content in zebra finch song. This model analyses the interaction between the pressure, the flow thought the labia and the upper vocal tract filtering. If syringeal muscles function similarly to those of other songbirds (i.e., ventral syringeal muscles control the tension of the labia, dorsal tracheobronchial muscles affecting gating), we hypothesize that the synergistic action of the parameters representing the activity of the muscles within the framework of this model allows generating the diversity of complex syllables found in zebra finch song. This system is an example of the emergence of complex behaviour due to the interaction of the nervous system with nonlinear effectors in the peripheral system. This mathematical model has also been implemented in an electronic syrinx capable of generating song by transducing physiological instructions into acoustic output for zebra finches with high similarity in syllable structure between the synthetic and natural sounds. The electronic syrinx acts as a real time integrator of the differential equations using DSP technologies. One of our future objectives is to use this technology to develop altered feedback experiments. These experiments will be essential to understand the songbird learning process.

Computational Neuroscience
Poster Number (170) Session III

RESPONSE OF POISSON NEURAL MODELS DRIVEN BY SLOW STIMULI

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The coding properties of cells with different types of receptive fields have been studied for decades. ON-type neurons fire in response to positive fluctuations of the time-dependent stimulus, whereas OFF cells are driven by negative stimulus segments. Biphasic cells, in turn, are selective to up/down or down/up stimulus upstrokes. In this paper, we explore the way in which different receptive fields affect the firing statistics of Poisson neuron models, when driven with slow stimuli. We find analytical expressions for the time-dependent peri-stimulus time histogram and the inter-spike interval distribution in terms of the incoming signal. Our results enable us to understand the interplay between the intrinsic and extrinsic factors that regulate the statistics of spike trains. The former depend on biophysical neural properties, whereas the latter hinge on the temporal characteristics of the input signal.

Poster Number (171) Session III

THE EFFECT OF ADAPTATION ON THE NEURAL CODE

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Adaptation processes are ubiquitous in the brain. Cortical neurons are endowed with a variety of ionic currents that are activated upon spike generation. These currents provide negative feedback to the cell, thus reducing its excitability after intense firing periods. Hence, sustained stimulation results in a gradual decrease of the response. The functional role of negative feedback was initially believed to enable neurons to dynamically adjust their maximum firing rate, in order to represent stimuli of variable dynamic range. However, recent studies have demonstrated that the effect of adaptation is even more complex. Here we show that adaptation significantly alters the correlations between successive inter-spike intervals (ISIs). In consequence, the response of an adapting neuron becomes more rigid: the ISI at a given time partially conditions the ISI at subsequent times. Thereby, dynamic flexibility of the response is diminished. On the other hand, adaptation reduces the steady-state variability, so the rate response is more reliable. Here we explore the tradeoff between these effects, and characterize how adaptation impacts on the neural code. By using both abstract and realistic neuron models, we show how adaptation influences (a) the output dynamic range, (b) the output variability, and (c) the temporal correlations.

THE INFLUENCE OF LEARNING ON THE EVOLUTION OF ANIMAL PERSONALITIES: A COMPUTATIONAL MODEL

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Though the existence of animal personalities has been observed through experiments, its neurobiological and psychological substrates have not been explained yet. There is a general agreement that suggests that learning capability increases the chances of a species adaptation and survival, despite the fact that sometimes this notion is against the evidence on behavioral tendencies. On the other hand, perhaps genetically determined, these tendencies seem to deny the law of effect. Wolf et al (2007) introduces a model in which animal personalities could be explained based on the trade-off between current and future reproduction. This paper presents an adaptive model where coexistence of different personalities and learning capability are not opposite characteristics. In fact, we show that learning capabilities could emphasize behavioral tendencies, previously assigned to inherited personalities. Our model shows that the observation of extreme behavior does not imply extreme personalities. Moreover, this learning ability promotes individual adaptation to environments where extreme personalities are stable, therefore preserves genetic diversity.

REPRODUCTIVE HIERARCHY DYNAMICS IN MALES OF THE CICHLID FISH CICHLASOMA DIMERUS (HECKEL, 1840) UNDER LABORATORY CONDITIONS

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Social status or dominance may be a determining factor on mating success. Cichlids are a group of fish with complex social behaviors that are being intensively studied in the area of social control of reproduction. The SouthAmerican species Cichlasoma dimerus has been widely studied in our laboratory. During the reproductive season, this species presents a dominance hierarchy in which only some males have access to territories that they defend and where they reproduce in monogamy. In the present work the access to reproductive territories and females in relation to the social status of each male were studied in two conditions: when there were no territories established and when they where established and a reproductive opportunity was generated by the removal of the dominant male. Four males and a female were placed in a neutral tank (53 litres) in order to establish the social hierarchies. Once the reproductive couple is formed, the dominant male was removed before spawning to study the social dynamic (N=4). Dominance indexes were calculated and males were sacrficed afterwards. For each individual, its reproductive strategy was registered and correlated with organo-somatic indexes, body coloration patterns, weight and body length. Plasma cortisol levels where about three-fold higher in the most subordinated individuals and gonadotropins pituitary content showed a reduction in those males with a lower hierarchy. Body color patterns were related with dominance status. Overall, our findings highlight a complex association between social behaviour and hierarchies, pituitary hormones (β-FSH and β-LH) and adrenal steroids related to stress (cortisol).

Neuroendocrinology And Neuroimmunology
Poster Number (174) Session 1

EFFECTS OF HYPO- AND HYPERTHYROIDISM ON NEUROPEPTIDE GLUTAMIC ACID-ISOLEUCINE (NEI) IN BRAIN REGIONS RELATED TO REPRODUCTION

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NEI is a peptide derived from ppMCH that is capable of regulating the release of TSH and LH. Aim: To analyze if hypo- or hyperthyroidism can modify the content of NEI at different stages of the rat estral cycle, late pregnancy (day 19: G19 and 21: G21) and early lactation (postpartum day 2: L2), in brain areas related to reproduction. Methods: Female Wistar rats weighing between 180 and 250 g were divided into control (C) and treated (T) groups. Hypo- and hyperthyroidism were induced with PTU and T4, respectively. The studied brain areas were OVLT + AVPV (vascular organ of the lamina terminalis + anteroventral periventricular nucleus), POA (preoptic area), HLA (lateral hypothalamic area), ZI (zona incerta), PeN (periventricular nucleus), ME + Arc (median eminence + arcuate nucleus) and PP (posterior pituitary). NEI concentrations in samples were assessed by RIA. Results: Cycling females: OVLT +AVPV: the differences were observed in T, with the highest values found in T4 P12. POA (area related to sexual behaviour): the lowest values were for PTU and T4 P19h. HLA, higher concentration of NEI in C E12 that decreased in T. ZI: the pattern between C and PTU was very similar with lower values in the latter; the peptide was hardly modified in T4. No differences in C and T were observed for PeN, and were minimal in ME +Arc. PP: there was a significant increase in T E12h. Pregnant females: A significant increase of NEI was observed in pregnant rats: in OVLT + AVPV were found in T4 G19 compared to PTU, in T4 G21 compared to C and PTU, and in C L2 compared to all other groups; in POA, in PTU G21 compared to C and T4; the content of NEI in HLA for C L2 was greater than in T; increases in ZI were observed in C and T4 G19 compared to PTU, in T4 G21 compared to C and PTU, and in C L2

compared to all other groups; in POA, in PTU G21 compared to C and T4; the content of NEI in HLA for C L2 was greater than in T; increases in ZI were observed in C and T4 G19 compared to PTU, and in C L2 compared to T; PeN showed increases in T G21 compared to C; increases in ME + Arc were found in C L2 compared to PTU and T4 L2; and in PP, there were increases in T4 G21 compared to C and PTU. Conclusion: The content of NEI in different brain regions related to reproduction is modified by hypo- or hyperthyroidism in cycling, pregnant and early lactation females.

INVOLVEMENT ANDROTENEDIONE IN SUPERIOR MESENTERIC GANGLION IN THE PHYSIOLOGY ACTIVITY IN RAT OVARY

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Most of the fibers that constitutes the innervation of the ovary, make synapses in the coeliac ganglion (CG) and superior mesenteric ganglion (SMG). The ovarian nervous plexus (ONP) is originated in fibres posganglionic the of SMG. The objective of this work was to investigate at the oestrous stage in the rat and in an ex–vivo sistem, if the addition of androstenedione (A2) and its antagonist Flutamide (Flut) in SMG, modify through ONP the progesterone (P), (A2) and estradiol (E2) release in ovary and the enzymatic activities of the P síntesis ((3- HSD) and degradation (20- HSD) enzymes. Previously was standardized the integrated system SMG-ONP-Ovary. This sistems were incubated with/without A2 10-6M and A2 + Flut (both in concentration 10-6M) in the ganglion compartment. In all cases a specially designed cuvette was used with Krebs Ringer solution, pH 7.4 at 37 °C in metabolic bath .Student´s t-test was applied with a significance of p0.05. The results show that A2 stimulated P, A2 0.001). A2 + Flut do not produce changesand E2 release in all time the incubation (p 0.05) and A2 + Flut did not make signifficant changes at any case in refference with control group. The results show that the pressence of ganglionic receptors for A2 in the SMG and evidenciates the fisiological relevance in the control of ovarian functions by neurons of the peripheral nervous sistem.In the other side A2 increased 3- HSD activity but lowed 20- HSD activity (p

Poster Number (176) Session 1

EFFECT OF DIPHENYL DISELENIDE (DPDS) ADMINISTERED BY DIFFERENT VIA ON THE DEVELOPMENT OF EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS (EAE)

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EAE is a T cell-mediated inflammatory and demyelinating disease of the central nervous system with clinical and pathological similarities with multiple sclerosis (MS). It can be induced in susceptible animals by a single injection of myelin homogenized in an adequate adjuvant. The oxidative stress is one of the major mediators of demyelination and axonal damage in both, MS and EAE. Therefore, several studies are being performed to assess whether treatment with antioxidants prevents the progression of these diseases. Some organic forms of Se that exhibit glutathione peroxidase-like activity have become good candidates for disease prevention and therapy since they catalytically remove oxidative stressors. Particularly, DPDS exerts antioxidant activity and has neuroprotective effects in several systems. The aim of the present study was to prove the therapeutic activity of DPDS on the development of EAE. DPDS given orally (25 mg/ml in 60 ethanol, 1 ml/kg body weight) produced a significant inhibition of EAE (from 90 to 54 the incidence) without any toxic effect. Intraperitoneally administered DPDS (0.03-7.80 mg/ml in 50 ethanol, 1 ml/kg body weight) reduced also the incidence of the disease but at concentrations higher than 1.5 mg/ml begun to be deleterious for the animals. In addition, there was a higher reactivity of sera from the suppressed animals and diminished DTH and proliferation of mononuclear cells against the encephalitogenic myelin basic protein, indicating a shift from a Th1 to Th2-type milieu. Although more investigation is needed, these results show an effective suppression of the autoimmune response that could be the base for future developments of successful antioxidants therapies in EAE as well as in MS

TWO FACES OF TNF OVER THE VIABILITY OF DOPAMINERGIC NEURONS IN THE SUBSTANTIA NIGRA

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Tumor necrosis factor-alpha (TNF) has been implicated in several human neurodegenerative diseases of the central nervous system, such as Parkinson's disease. In order to understand the functional role of chronic TNF on dopaminergic neurons in the substantia nigra (SN), we utilized a combination of adenoviral vectors, the CRE/loxP system and hypomorphic mice to express three different levels of TNF in the SN of adult mice: basal, low and upregulated levels of TNF. The expression of low level of TNF did not produce inflammatory infiltrate or microglial activation, although astrocytosis has been observed in the SNr of k-in mice. Low TNF expression induced TNF-R1, GDNF and IGF-1 in the SN and increased SOD activity in the Striatum (ST). Low TNF reduced the nigral neurodegeneration mediated by intrastriatal 6-hydroxydopamine administration without an inflammatory response. The injection of the adenovirus which express CRE recombinase, allowed us to upregulate the TNF level due to the excision of an interference cassette. In consequence, the SN of k-in mice injected with AdCRE showing high TNF expression level induced progressive neuronal loss, glial activation and an inflammatory response composed almost exclusively by monocyte/macrophages. This approach allowed us to clarify the functional role of TNF in the SN according to its levels of expression and characterize its cellular and molecular environment, supporting the concept of a dual role of TNF on several CNS diseases. Protective effects of low TNF level may be mediated by TNF-R1, GDNF, IGF-1 and SOD activity. On the other hand, neurodegenerative effects could be mediated, at least in part, by activated glia.

Poster Number (178) Session II

THE NEURONAL GABAERGIC SYSTEM IN HUMAN LYMPHOCYTES

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γ-Amino butyric acid (GABA) is an ubiquitous neurotransmitter in the central nervous system but it is also present in non neuronal cells. The goal of this study was to determine the neuronal components of the GABAergic system in lymphocytes and their functional significance. Using RT-PCR we determined mRNA expression of different components of this system in resting and mitogen activated lymphocytes (PHA 10 µg/mL): i) GAD67, an isoform of the enzyme that synthetizes GABA; ii) VIAAT, the vesicular protein involved in GABA storage; iii) GABA transporters (GAT1 and GAT2); iv) GABA-T, the enzyme that catabolizes GABA; v) alpha subunits (α1-6) of GABAA receptor; and vi) rho 2 subunit of the GABAC receptor. The functionality of the transporters was evaluated by measuring the uptake of radioactive GABA. The results demonstrated that the 3[H]GABA uptake is 5-fold higher in activated lymphocytes than in resting ones. Using 3[H]thymidine incorporation, we established that GABA and muscimol are able to modulate lymphocyte proliferation. Finally, we demonstrated that these GABA receptor agonists are capable to elicit macroscopic currents in activated lymphocytes. Our results revealed that lymphocytes have most of the essential components needed to constitute a GABAergic system. Pharmacological modulation of this system may provide new approaches for regulation of T cell response.

"SENSITIZATION" OF NITRIC OXIDE SYNTASE ACTIVITY IS CRITICAL FOR BEHAVIORAL COCAINE SENSITIZATION AND THE ASSOCIATED ENHANCEMENT OF HIPPOCAMPAL SYNAPTIC PLASTICITY.

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Nitric oxide (NO) is a neuromodulator which influences synaptic transmision and promotes synaptic plasticity. The hippocampus is a brain structure that participates in learning and memory processes, and it has been implicated in the neuropathological mechanisms that underlie drug addiction. It has been shown that repeated cocaine (COC) administration induces behavioral sensitization in a ≈ 50 of treated animals. NO could be involved in the adquisition and maintenance of behavioral effects of cocaine because inhibition of the enzyme NO synthase (NOS) attenuates the development of sensitization. We have previously demonstrated that repeated COC administration induced an increase in hippocampal synaptic plasticity, which is more pronounced in COC sensitized (S) rats . Moreover, the rol of NO in the mechanisms involved in COC sensitization related to hippocampal synaptic plasticity have not been described. In the present work we combined behavioral, electrophyisiological and neurochemical experiments in order to examine the impact of NOS inhibition on: 1- Development of COC sensitization, 2- The hippocampal synaptic plasticity associated to COC sensitization, and 3- The NOS activity after COC sensitization. Our results demonstrated that inhibition of NOS during repeated COC treatment reduced the percentage of S rats and this reduction is related to the values observed in synaptic plasticity. Furthermore, the inhibition of NOS prevented the "sensitized" NOS activity observed after COC sensitization. These findings indicate that NO may have an important role in the changes induced by COC in hippocampal synaptic transmission contributing to the development of sensitization.

Poster Number (180) Session II

ADRENERGIC AGENTS MODIFY OVARIAN P450 AROMATASE EXPRESSION IN THE RAT FIRST OESTRAL CYCLE.

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We have showed that peripheral innervation participate in ovarian oestradiol release. The purpose of this work was to analyze the effects of Norepinephrine (NE), α and β adrenergic antagonists, Phentolamine (PHE) and Propranolol (PROP) respectively in coeliac ganglion (GC) on the ovarian release of androstenedione (A2) and P450arom expression during the first proestrous (PE), estrous (E) and diestrous (D) in rat. We used the ex vivo GC-superior ovarian nerve-ovary system. Witch was incubated in Krebs Ringer at 37°C in atmosphere of 95O2-5CO2. The groups were: a- Control, b, c and d, NE, PHE and PROP at the same concentration 10-6 M. Aliquots from the ovarian compartment were taken at 15, 30, 60 and 120 min. A2 was measured by RIA. After 120 min, ovaries were separated and the total RNA was extracted by the method of TRIzol and levels of P450arom mRNA were semiquantified using RT-PCR. Was utilized ANOVA 1 followed by Tuckey test with a significance of p0.05. The results shown that in PE, PROP decreased ovarian A2 release at 30 min. In E, NE increased A2 release at 60 min and decreased its levels at 30 min, while PHE increased A2 at 30 and 60 min and PROP at 60 and 120 min. In D, NE and PHE increased ovarian A2 levels at all studied times. Ganglionic NE addition would have a differential effect on the P450arom mRNA enzyme expression depending on the oestral cycle stage. FEN stimulation antagonized adrenergic effects only in PE, where P450arom mRNA control levels are higher in comparison to E and D. The results suggest that the mechanism of adrenergic ganglion stimulation underlying on ovarian steroidogenesis would be, at least in part, mediated by α and/or β adrenergic receptors.

Neuroendocrinology And Neuroimmunology
Poster Number (181) Session II

POSTNATAL PROGRAMMING OF ANXIETY AND DEPRESSION RELATED BEHAVIORS: MATERNAL CARE AND EARLY INFLAMMATION CONTRIBUTIONS.

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The development of the central nervous system and its interactions with endocrine and immune systems can be altered by events occurring early in life. This plasticity is part of an adaptive mechanism in mammals that contributes to the organism survival. However, these changes could lead to disorders in the adulthood. In this context, "programming" is defined as a process in which stimuli that occur early in life have long term effects in the animal physiology and behavior. Previous data show that maternal care and postnatal inflammation can induce long term changes in anxiety and depression related behaviors. Our hypothesis is that both events act on the same neural system. Our aim is to study how these stimuli can interact to program adult behavior. To reach this aim, we caused an acute inflammatory response on postnatal day 3 in mice, injecting different doses of LPS or saline solution. In addition, we used two mice strains (C57BL/6J and BALB/c) to generate a F1 with different mothers, and consequently, different maternal care. We analyzed the adult offspring through a battery of behavioral tests, that evaluate anxiety and depression related behaviors. We analyzed the data using a principal components analysis of the most significant variables of different tests. This analysis gave us more comprehensive information and allowed to identify behavioral profiles. We observed a maternal care effect mostly in males and an inflammation effect mostly in females. We did not observe a strong interaction between maternal care and inflammation in the anxiety or depression components, suggesting that both stimuli are affecting the postnatal programming through different pathways

REPEATED PRO-INFLAMMATORY STIMULI: HOW DOES IT AFFECT DEMYELINATION AND REMYELINATION

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MS is a neurodegenerative disease characterized by demyelination, inflammation and axonal loss. Remyelination occurs in the early stages of the disease, but as the disease progresses remyelination fails. The most predominant type of MS exhibits relapsing-remitting episodes, and remyelination is less efficient after every relapse. Patients in relapsing phase show high levels of IL-1β in the CSF, and blocking it reduces the severity of the disease. We have observed that chronic expression of IL-1β in the striatum produces reversible demyelination, BBB breakdown and axonal damage. Our hypothesis is that repeated pro-inflammatory stimulus in the brain could exacerbate demyelination and/or impair remyelination in animals which have received a previous demyelinating stimulus. To contrast this hypothesis, we administered either adenoviral vectors expressing IL-1β (AdIL-1β), or other inflammatory stimulus (LPS). At different time points, we re-administered the AdIL-1 β. Animals receiving pro-inflammatory stimuli twice had less inflammation and demyelination if the second stimulus was administrated during the resolution phase. However, when the second pro-inflammatory stimulus was given after the lesion´s resolution, inflammation and demyelination levels were similar to control group. We observed that the glial activation followed the pattern of inflammation in all cases. We also found up-regulation of oligodendrocyte lineage marker Olig2 21 days after the AdIL-1β injection, that decreased at day 30, and even more at 51. In conclusion, a previous pro-inflammatory stimulus may reduce the inflammatory and demyelinating effect of a second pro-inflammatory stimulus, when administered in a specific point of the injury's resolution.

MORPHOLOGICAL PARAMETERS AND TESTOSTERONE SERUM LEVELS OF MALE RATS EXPOSED TO PRENATAL STRESS

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Stress during gestation has been reported to alter the neurobiological, immune and endocrine development of the progeny inducing long term behavioral and biochemical abnormalities in the offspring. Among other impairments, maternal stress was shown to suppress testosterone (T) surge that occurs in the male embryo between gestational days 17 and 18, responsible for the brain sexual differentiation. In a first approach to evaluate the pituitary-testicular axis in our model of prenatal stress we analyzed the anogenital distance, testicular descent and T levels in serum in prenatally stressed male offspring. Pregnant dams were subjected to three 45 min period sessions of restraint stress per day, between days 14 and 21 of gestation. Anogenital distances were measured at postnatal day (PND) 1, 10 and 21. Analysis of testis descent, defined as the day when both testes fully descended into the scrotal sac, was initiated on PND 21. T levels were quantified by radioimmunoassay employing blood serum from 28, 45, 60 and 75 days old offspring. Prenatally stressed (PS) animals showed reduced anogenital distance at PND 1 and 21, compared to control (C) animals. Moreover, while C animals complete their testis descent at PND 23, PS animals showed a 2-day delay (i.e. PND 25). T serum levels analysis revealed a similar temporal pattern in both PS and C groups: T levels started to increase at PND 45, reaching the maximal serum concentrations at PND 60. However, prenatally stressed animals showed higher T concentrations in comparison with C ones at PND 28 and 75. These results support the idea that prenatal stress alters offspring pituitary-testicular axis, modifying masculine morphological patterns and T serum levels.

POSSIBLE INVOLVEMENT OF MELANIN-CONCENTRATING HORMONE IN SOMATIC GROWTH IN CICHLASOMA DIMERUS

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In vertebrates, hypothalamus produces neuropeptides that stimulates (orexigenic) or inhibits (anorexigenic) food intake. Melanin-concentrating hormone (MCH) is a neuropeptide synthesized in the hypothalamus and is related to body color regulation in non mammals. In mammals, it is implicated in feeding behaviour and energy homeostasis. In teleost fish, contradictory results were found, while in goldfish MCH has an anorexigenic function, in barfin flounder has an orexigenic one. The aims of the present study were: 1) To examine the distribution of MCH in relation to two classical orexigenic neuropeptides: orexin and neuropeptide Y (NPY), 2) To examine the effect of fasting over on MCH brain expression and 3) To examine the effect of background colour (white background (WB): high MCH levels and black background (BB): low MCH levels) on somatic growth. C. dimerus was chosen as experimental model since shows dramatic colour changes under different environmental and physiological conditions. The full length sequence of MCH (GQ253057) and the phylogenetic analysis shows that C. dimerus is close similar to barfin flounder and is high distant to goldfish. The MCH, orexin and NPY neurons and fibers show and overlap distribution in some regions of the hypothalamus suggesting interactions among them. The fasted fish showed an increased MCH expression compared with the fed fish suggesting an orexigenic function. Finally juvenile animals reared in WB showed an augment in somatic growth compared with BB-reared animals ($p < 0.05$). These results suggest that MCH, together with orexin and NPY, regulates appetite leading to an augment in somatic growth.

Neuroendocrinology And Neuroimmunology
Poster Number (185) Session III

THE ROLE OF ARGININE VASOTOCIN IN REPRODUCTION AND SOCIAL BEHAVIOR IN THE CICHLID FISH CICHLASOMA DIMERUS

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In non-mammalian vertebrates, the nonapeptide arginine vasotocin (AVT) is involved in the regulation of social behavior related to reproduction, aggression and parental care. The cichlid fish Cichlasoma dimerus is a monogamous species with biparental care of larvae and complex social hierarchies. In this work we studied the location and morphometry of AVT immunoreactive neuronal populations in dominant and non-dominant males, and the effect of AVT treatment on testicular steroidogenesis. Using an antibody against AVT that was previously tested for specificity, we examined the three well-established preoptic area nuclei: parvocellular, magnocellular and gigantocellular. Axonal projections were mainly observed in the pituitary and pineal gland. The effect of AVT on testicular steroidgenesis was analyzed by culture of testicular fragments with different concentrations of AVT. Testosterone synthesis and secretion were significantly increased by AVT (54.54 ng/dl control vs 139.83 ng/dl 50nM AVT treated. N=5, p0.01). Finally, 2 adult couples (N=4) were placed in community tanks (53 liters) under constant temperature and a 14: 10 hs photoperiod. Once social hierarchies were established, individuals were sacrificed and their brains processed for number, cellular and nuclear diameter of AVT neurons. Results show that preoptic AVT neuronal populations present a similar distribution compared to other cichlid fish species, that AVT (probably as a neurohypohyseal hormone released into the bloodstream) stimulates testosterone secretion from the testes, and the presence of morphometric differences in AVT neuronal populations between dominant and non-dominant males.

Poster Number (186) Session III

CAN ANDROSTENEDIONE REVERSE THE LUTEAL REGRESSION THROUGH NEURAL PATHWAY

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Working with the coeliac ganglion-superior ovarian nerve-ovary (CG-SON-Ovary) system, androstenedione (A2), through neural pathway, stimulated the liberation of luteal progesterone (P) and nitric oxide (NO), gaseous neurotransmitter, in late pregnant rat. This effect may be mediated by androgen receptors present in CG. On day 4 post partum, when the luteal regression is advanced, the same effect was observed respect to P, A2 and estradiol, but inhibited NO. The aim of this work was to investigate on day 4 post partum the possible molecular mechanisms at the ovary level involved in the neural action of A2. The ex vivo CG-SON-Ovary system was incubated in Krebs Ringer-glucose-albumin (0.1 mg/ml) at 37°C, keeping CG and ovary connected by the SON, in separate cuvettes. A2 (10-6M) was added in the CG compartment, Controls were not stimulated. At the end of total incubation period (180 minutes), luteal RNA was extracted to determine the expression levels of the progesterone synthesis (3β-HSD) and degradation (20α-HSD) enzymes, bcl-2, bax (genes involved in the regulation of apoptosis) and inducible nitric oxide synthase (iNOS) by RT-PCR. The addition of A2 to the CG did not modify neither 3β-HSD, 20α-HSD, Bcl-2 nor Bax expression but increased iNOS expression respect to the Control group. A2 from CG only affected the iNOS expression without modifying functional and structural regression parameters.

HYDROCORTISONE ACTS AS A NEGATIVE ALLOSTERIC MODULATOR OF 5-HT3 RECEPTORS

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5-HT3A receptor is a member of the Cys-loop family of ligand-gated ion channels. Due to its low conductance, kinetic analysis of this receptor has been restricted to the macroscopic level. We introduced mutations in the 5-HT3A subunit to obtain a high-conductance form so that single-channel currents can be detected. We used electrophysiological techniques to study the effect of the neuroactive steroid, hydrocortisone (HC), in the high-conductance form of the 5-HT3A receptor. At the single-channel level, currents triggered by 1 μM 5-HT appear as a series of long opening events of 4.7±0.4 pA (-70 mV) grouped in long clusters. A low-conductance population of opening events occurs at a very low frequency (relative area 0.1, amplitude ~2.7 pA). Open-time histograms show three components. In the presence of HC, a reduction in the duration of the slowest open component (~100 ms) is observed, suggesting an open channel block that can be interpreted on the basis of a simple linear blocking scheme. In addition, an increase in the frequency of the low-conductance events occurs in a dose-dependent manner. The relative area of the low-amplitude population is 4-fold higher at 400 μM HC than in the absence of the steroid. Macroscopic currents evoked by 100 μM 5-HT decay slowly and decays are well fitted by two exponential components (tfast = 60 ± 30 ms and tslow = 400 ± 190 ms). In the presence of HC, the peak current is reduced (~50 at 400 μM HC), and decay rates are increased. The results reveal that the neuroactive steroid hydrocortisone negatively modulates 5-HT3A receptors and shows a novel mechanism which involves the stabilization of a sub-conductance form.

Poster Number(188) Session 1

GLUTAMINE 57 AT THE COMPLEMENTARY BINDING-SITE FACE IS A KEY DETERMINANT OF MORANTEL SELECTIVITY FOR α7 NICOTINIC RECEPTORS

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Nicotinic receptors (AChRs) play key roles in synaptic transmission. We explored activation of neuronal αlpha7 and mammalian muscle AChRs by morantel and oxantel. Our results revealed a novel action of morantel as a high-efficacy and more potent agonist than ACh of αlpha7 receptors. The EC50 for activation by morantel of both αlpha7 and αlpha7- 5HT3A receptors is 7-fold lower than that determined for ACh. The minimum morantel concentration required to activate αlpha7-5HT3A channels is 6-fold lower than that of ACh, and activation episodes are more prolonged than in the presence of ACh. By contrast, oxantel is a weak agonist of αlpha7 and αlpha7-5HT3A, and both drugs are very low-efficacy agonists of muscle AChRs. The replacement of Gln57 in αlpha7 by glycine, which is found in the equivalent position of the muscle AChR, decreases the efficacy for activation and turns morantel into a partial agonist. The reverse mutation in the muscle AChR (εG57Q) increases 7-fold the efficacy of morantel. The mutations do not affect activation by ACh or oxantel, indicating that this position is selective for morantel. In silico studies show that the tetrahydropyrimidinyl group, common to both drugs, is close to W149 of the principal face of the binding site, whereas the other cyclic group is proximal to Q57 of the complementary face in morantel but not in oxantel. Thus, position 57 at the complementary face is a key determinant of the high selectivity of morantel for αlpha7. These results provide new information for further progress in drug design.

Neurochemistry and Neuropharmacology
Poster Number (189) Session I

EVIDENCE OF AN AMPA/KA AND GABA-A-MEDIATED MECHANISM OF NMDA ANTAGONIST- INDUCED NEURONAL DEATH IN ADULT RATS.

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Drugs with NMDA-antagonist properties have multiple uses such as animal model of psychotic disorders, anesthetics, and drugs of abuse. In animals, high doses of NMDA antagonists induce neurodegeneration in retrosplenial cortex (RSC) but their mechanism remains unclear. Here, to test if an imbalance of synaptic inhibition and excitation would mediate the neurodegenerative effect of MK801 (a selective NMDA-antagonist), the participation of GABA-A, NMDA and AMPA/KA receptors were evaluated. Female adult rats were administered intraperitoneally with 2,5 mg/kg of MK801 and, locally in RSC, with muscimol (GABA-A agonist), DNQX (AMPA/KA antagonist), NASPM (calcium permeable AMPA/KA antagonist) and MK801 at several times (0.5, 5, 10, 24 hours) post systemic MK801 administration. Neuronal death was evaluated 48 hours after MK801 injection by fluoro jade-b and amino-cupric-silver techniques. The results showed that intra-RSC administration of muscimol, DNQX and NASPM (but not MK801) significantly decreased the MK801-induced neuronal death, even when applied ten hours later. The data suggest that a prolonged (more than 10 hours) GABA-A hipofunction and/or AMPA/KA hiperfunction are involved in the mechanism of NMDA antagonists induced neurodegeneration.

Poster Number (190) Session 1

CROSSTALK BETWEEN CHOLINERGIC AND GABAERGIC SYSTEMS

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Cys-loop receptors are pentameric neurotransmitter-activated ion channels that mediate fast synaptic transmission throughout the nervous system. They include excitatory receptors, such as the nicotinic cholinergic (AChR) and serotonin type 3 receptors (5-HT3), and inhibitory receptors activated by GABA or glycine. Given the homology between members of this family we evaluated if GABAergic agonists can activate nicotinic cholinergic receptors. In the presence of GABA (1 µM), single-channel openings from the muscle AChR are readily detected. Even at high GABA concentrations, openings do not appear in typical clusters as observed in ACh-activated channels, indicating that GABA is a low-efficacy agonist. The presence of GABA does not affect the channel properties of ACh-activated channels. We also studied activation by GABA of muscle AChRs carrying a mutation in alfaG153, which has been shown to decrease the dissociation rate of ACh (Sine et al., 1995). GABA activation is enhanced in the alfaG153S and alfaG153E mutants, indicating that this residue is involved in the activation by both neurotransmitters. In silico studies show that in the muscle AChR, GABA docks into the ACh-binding site, though it interacts with different residues when compared to ACh. However, no docking into the binding site is observed in the alfa7 AChR, in agreement with the lack of activation. In conclusion, we determine that GABA is not capable of activating neuronal alfa7 AChRs but it acts as a partial agonist of the muscle AChR.

PRENATAL STRESS INDUCES ABNORMALITIES IN CEREBELLAR OXIDATIVE MECHANISMS OF RAT'S OFFPRING

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Stress during early neurodevelopmental stages induces both early and later alterations. We have previously described behavioural abnormalities in stressed rats` offspring. The objective of this work was to evaluate possible changes in cellular oxidative mechanisms. For this purpose pregnant Wistar rats were individually restrained three times a day, 45 minutes each, since gestational day 14, until delivery. The offspring's cerebellum were analysed for Nitric Oxide Synthase (NOS) activity, and neuronal NOS (nNOS), caspase 3 and extracellular signal-regulated kinase 1/2 (ERK 1/2) mRNA and protein levels by RT-PCR and western blot, respectively. We found an increase in total NOS activity (pmol/gtissue/30min) in cerebellum at PN7 and PN15. We also detected an increased protein profile of nNOS at PN15 together with an alteration in the expression of its mRNA. Immunoblot analyses revealed an increase in caspase 3 at PN7 and a decrease in ERK1/2 at PN15. We conclude that stress during early development stages induces alterations in cerebellar oxidative mechanisms. Taking these results together with the behavioural abnormalities previously described, we hypothesise that the oxidative alterations might be primary events during development, which reflects in adulthood as significant changes in animal behaviour.

Poster Number (192) Session 1

NEUROPROTECTIVE EFFECT OF 17 β-ESTRADIOL ON LEARNING AND MEMORY PROCESSES AFFECTED BY NEONATAL X-RADIATION

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Developing Central Nervous System (CNS) is vulnerable to radiation-induced reactive oxygen species (ROS). The consequent oxidative stress has been shown to produce behavioral, biochemical and morphological changes. The aim of the present work was to test if 17 β-estradiol (βE) a potential neuroprotector, was able to counteract radiation-induced changes in the hippocampus (Hip). Since a relationship between dendritic spines and memory processes has been postulated, the density of dendritic spines was assessed in irradiated Hip as well as an hippocampal-related memory test. Neonatal male Wistar rats were X-irradiated (5 Gy) in their cephalic end and a group of these animals (E2) was treated with βE (5 µg/g). Inhibitory avoidance (IA) and ROS levels, as well as the levels of PKC -a protein involved in the memory mechanism- were evaluated in the Hip. A morphological assessment of dendritic spines was also performed at 30 postnatal days. The increase in the number of dendritic spines in CA1 region of the irradiated group was partially restored with the administration of βE. However, it was not able to modify the improvement in the performance in the IA test observed in irradiated animals. The PKC activity in the E2 group remained increased after the treatment, although a decrease in PKC translocation to the membrane was observed, indicating an attempt to restore control PKC activity. Finally, the increase in basal ROS levels induced by X-rays was restored. These results suggest that βE was able to counteract, at least in part, the effects of X-rays on the Hip at behavioral, biochemical and morphological levels. Since ROS have been involved in PKC dynamics, an antioxidant mechanism for βE could be postulated.

FUNCTIONAL STUDIES ON THE MECHANISMS UNDERLYING REDOX MODULATION OF GABAC RECEPTORS.

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Redox mechanisms can regulate the activity of many neurotransmitter receptors including the members of the cys-loop receptor family. In a previous work we showed that, like GABAA receptors, GABAC receptors can be redox modulated. Two extracellular sulfhydryl groups (-SH), C 207 and 221, form the characteristic cys-loop in GABAC receptors and are promising targets for redox modulation. To test this hypothesis we studied if chemical manipulation of these aminoacidic residues can affect GABAC receptor modulation by redox agents. Homomeric GABArho1 receptors (GABACR) were expressed in X. laevis oocytes and GABA-evoked Cl- currents recorded by two-electrode voltage clamp. The application of N-ethylmaleimide (NEM), an irreversible thiol alkylating agent that forms covalent bonds with free -SH and prevents further chemical reactions with these sites, modulated GABAC responses, shifting to the left D-R curves and significantly increasing maximal responses. Meanwhile, -SH reducing agent DTT also potentiates GABACR (Calero, et al., 2008). In order to study if NEM effects were due to the chemical modification of C 207 and 221, we examined DTT actions on GABAC responses before and after the application of NEM. NEM treatment prevented DTT-induced potentiation of GABAC responses. Similar experiments were performed using redox agents, ascorbic acid (Asc) and GSH, which modulate GABACR. Redox modulation of GABAC responses induced by Asc and GSH was only partially prevented by NEM. Our results indicate that redox agents can induce at least two types of alterations at the GABACR: 1) Modifications of the -SH that form the cys-loop; 2) Reaction with redox-sensitive/NEM-insensitive residues. Supported by CONICET and FONCyT.

Poster Number (194) Session 1

MELATONIN PREVENTS APOPTOSIS TRIGGERED BY OXIDATIVE STRESS IN RETINAL GANGLION CELL CULTURE.

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Glaucoma is one of the main causes of vision loss. The reactive oxygen species (ROS), associated with apoptosis of retinal ganglion cells (RGCs), play an important role in the pathogenesis of this optic neuropathy. Melatonin (MEL), known by its circadian properties, is synthesized by photoreceptors and RGCs, but the specific role in the retina remains unknown. The aim of this work was to study the apoptotic mechanisms, triggered by increment of ROS on RGCs and to elucidate the role of MEL on those apoptotic processes. We obtained RGCs from 8 day-old chicken embryos by Thy-1 antibody immunopurification. We induced cytotoxicity by glutamate administration (20 mM, GLUT) and oxidative stress by L-buthionine, S-R-sulfoximine (0.5 mM, BSO) treatment. The following experimental groups were used: 1) RGC Controls 2) RGCs treated with BSO+GLUT and 3) RGCs treated with BSO+GLUT+MEL and the respective controls for 24, 48 or 72 hours. The survival of RGCs was studied by crystal violet technique and apoptotic death by TUNEL method. The glutathione content (GSH) was assayed by spectrophotometry. The results showed that RGCs treated with BSO+GLUT decreased their survival and increased the number of TUNEL positive cells respect to the control groups both 48 and 72 h postreatment. This effect was counteracted by MEL administration (0.5mM). The decrease in the GSH content caused by BSO or BSO+GLUT at 24 h was not reversed by MEL. These results indicate that MEL would use a different antiapoptotic mechanism to reestablish GSH levels. It is possible that MEL plays an important protective role to retard the apoptotic processes, being a potential pharmacological agent to prevent the retinal damage produced by glaucoma.

Neurochemistry and Neuropharmacology
Poster Number (195) Session I

PARTICIPATION OF THE GABAERGIC SYSTEM ON THE GLUTAMATE RELEASE OF SYNAPTOSOMES FROM ANIMALS WITH EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS (EAE)

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Recent reports have been showed a deficit in expression of proteins associated with GABAergic neurotransmission in neocortex of Multiple Sclerosis (MS). Interestingly, it had been described that the activation of GABAA receptors led to an inhibition of glutamate release. Recently, we found in synaptosomes isolated from cerebral cortex that the glutamate release was decreased during of EAE, the animal model of MS. In order to evaluate the potential events that may affect neuronal function in EAE synaptosomes, we analyzed the possible participation of the GABAergic system on the glutamate release. For this, synaptosomes from CFA and EAE animals were incubated in the presence of GABA followed by the addition of 4AP to trigger release. In synaptosomes from CFA rats, the glutamate release was decreased by GABA. To confirm that the observed inhibition of glutamate release from CFA synaptosomes was indeed mediated by GABAA receptors, we incubated synaptosomes with a GABAA antagonist, prior to the addition of GABA. The inhibition of glutamate release by GABA was abolished by the antagonist in CFA synaptosomes. However, the glutamate release was unaffected when EAE synaptosomes were incubated with GABA prior to induction of the release. On the other hand, GABAA R density was measured ex vivo in neocortex cerebral synaptosomes by 3[H]-flunitrazepam binding assay at 4° C. The Bmax in synaptosomes from EAE rats was 591 fmol/mg proteins, whereas the Bmax fmol/mg proteinsin CFA syanptosomes was 1101 fmol/mg proteins. Ours results suggest that the diminution of the flunitrazepan sensitive GABAA R density could explain the observed failure in the GABAergic regulation on the glutamate release of synaptosomes of neocoxtex from EAE rats.

Poster Number (196) Session 1

KINETIC SCHEME FOR ACTIVATION AND DESENSITIZATION OF HOMOMERIC 5-HT3A RECEPTOR.

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The 5-HT3A receptor is a member of the Cys-loop family of ligand-gated ion channels. To perform kinetic analysis, we introduced the mutations R432Q/R436D/R440A in the 5-HT3A subunit to obtain a high-conductance form (5-HT3A-HC), in which single-channel currents can be detected. At all 5-HT concentrations (0.1 µM) channel activity appears as openings of ~4.7 pA (-70 mV) in quick succession forming bursts, which coalesce into clusters. By combining single-channel and macroscopic data we generated a kinetic model that perfectly describes activation, deactivation and desensitization. The model shows that full activation arises from receptors with three molecules of agonist bound. It also reveals an earlier conformational change of the fully-liganded receptor that occurs while the channel is still closed. From this pre-open closed state the receptor enters into an open-closed cycle involving three open states, which conforms the cluster whose duration parallels the time constant of desensitization. This suggests that at a synapse the lifetime of the elementary response of 5-HT3A receptors is determined mainly by desensitization. Since the desensitized state is a stable state, the inter-response latency is expected to be prolonged. A similar model but lacking the pre-open closed state can describe the data only if the opening rates are fixed to account for the slow activation rate. Thus, our kinetic model provides a foundation for studying structure-function relationships as well as molecular mechanisms of drug action in 5-HT3 receptors.

PRO-OXIDANT EFFECT OF VANADIUM IN WISTAR RAT'S BRAIN AREAS

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Vanadium V is a catalytic metal, which has been reported to induce reactive oxygen species ROS generation in vitro, as well as lipid peroxidation and oxidative damage in a great variety of biological systems. We have shown that i.p. administration of 3 mgkg body weight of sodium metavanadate NaVO3 to adult rats produced high lipid peroxidation levels, astrogliosis, heat shock protein expression Hsp 70 and NOS activation in hippocampus Hc and cerebellum Cer. In the present work, in vivo ROS formation in NaVO3 treated rats brain was studied. 24 rats were randomly distributed into 3 groups and, for 5 consecutive days, 8 were i.p. injected with 3 mgkg body weight bw of NaVO3 V1 group; 8 were injected with 7.2 mgkg bw of NaVO3 V2 group and 8 were injected with saline C group. For salicylate trapping and hplc assay of hydroxyl radical OH Floyd et al. -1984, 6 rats per group were injected with salicylic acid 100mgkg bw, i.p. and 30 min after, they were guillotined and Cer and Hc were removed and processed. For in situ ROS detection with the DAB-Mn-Co histochemical method Kerver et al, 1997, entire brains of 4 animals per group were used. Cer OH levels were significantly increased 0.37 ± 0.08 in V2 group with respect to control 0.21 ± 0.04. Moreover, in situ ROS histochemical staining was positive in V2 group Cer. Although lipid peroxidation in Hc and Cer was determined with the lowest dose, vanadium-induced OH production was detected only in Cer and with the highest dose.

Poster Number (198) Session 1

ANTIOXIDANT STATUS IN RAT'S BRAIN AREAS AFTER EXPOSURE TO SODIUM METAVANADATE

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Endogenous protective enzyme systems, such as superoxide dismutase SOD and catalase Cat and scavengers as well as reduced glutathione GSH can remove harmful free radicals from the cell. As we have shown, the main areas affected by vanadium-mediated peroxidation and free-radical generation were the hippocampus Hc and the cerebellum Cer. So, the aim of the present work was to study the antioxidant status in those rats brain areas after exposure to sodium metavanadate NaVO3. 42 rats were randomly distributed into 3 groups and for 5 consecutive days 14 were i.p. injected with 3 mgkg body weight bw of NaVO3 V1 group; 14 were injected with 7.2 mgkg bw of NaVO3 during 5 days V2 group and 14 were injected with saline solution C group. 36 rats were guillotined and Hc and Cer were removed and processed for biochemical studies. Histochemical studies were performed in six rats whole brain.Biochemical studies CuZn superoxide dismutase Beauchamp and Fridovich-1971 and catalase Beers and Sizer-1952 activities as well as total and oxidized glutation Tietze-1983 levels were measured. Histochemical studies In Situ SOD detection Viggiano y col., 2003. In both areas, GSH/GSSG ratio was significantly decreased in V1 and V2 groups independently of the dose, while neither Cat nor Cu-Zn SOD activity show any change.

ANTIOXIDANTS ARE UNABLE TO REVERSE APOPTOSIS PROVOKED BY MENADIONE ON RETINAL GANGLION CELLS

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The oxidative stress induces ocular pathologies such as diabetic retinopathy and glaucoma. Menadione (MEN), a quinone employed with different pharmacological purposes, produces cellular oxidative stress. The aim of this study was to investigate the effect of MEN on retinal ganglion cells (RGC) and the possible neuroprotector role of different antioxidants. The primary cultures of RGC were performed from retina of 8 days chick embryos using anti-Thy1 antibody for immunopurification. After 24 h of culture, the cells were treated with MEN at different doses and cell survival was evaluated at different times by the crystal violet technique. The neuroprotector role of the antioxidant quercetin (QC), melatonin (MEL) and the active metabolite of vitamin D (1,25(OH)2D3) was evaluated. Total glutathione (GSH) content was determined by enzymatic method. The apoptotic death was measured employing the TUNEL technique. The results revealed that death of RGC began 15 h after MEN treatment, which was dose dependent, being 12.5µM the LD50. The content of GSH diminished 1 h after treatment and returned to control values 2 h later. GSH monoester addition to the cell culture prevented cell death caused by MEN. The number of positive TUNEL cells increased in the cultures treated with MEN as compared to the control values. The treatments with QC, MEL or 1,25(OH)2D3 did not prevent the cell death provoked by MEN. The decrease in the GSH content suggests that the MEN treatment induces oxidative stress in the RGC, which leads to cellular death by an apoptotic mechanism. These effects are not prevented by QC, MEL or 1,25(OH)2D3 in the doses and times used.

Poster Number (200) Session 1

D2 AND D4 DOPAMINE RECEPTOR MRNA DISTRIBUTION IN PYRAMIDAL NEURONS AND GABAERGIC SUBPOPULATIONS IN PRIMATE PREFRONTAL CORTEX: IMPLICATIONS FOR SCHIZOPHRENIA TREATMENT

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D2 and D4 dopamine receptors play an important role in cognitive functions in the prefrontal cortex and they are involved in the pathophysiology of neuropsychiatric disorders such as schizophrenia. The eventual effect of dopamine upon pyramidal neurons in the prefrontal cortex depends on which receptors are expressed in the different neuronal populations. Parvalbumin and calbindin are two GABAergic interneuron subpopulations that differently innerve pyramidal cells. Recent hypotheses about schizophrenia hold that the root of the illness is a dysfunction of parvalbumin chandelier cells that produces disinhibition of pyramidal cells. In the present work we report double in situ hybridization histochemistry experiments performed in monkey prefrontal cortex to determine the prevalence of D2 receptor mRNA and D4 receptor mRNA in glutamatergic neurons, GABAergic interneurons and both parvalbumin and calbindin GABAergic subpopulations. We found that around 54 of glutamatergic neurons express D2 mRNA and 75 express D4 mRNA, while GABAergic interneurons express around 34 and 47 respectively. Parvalbumin cells mainly expressed D4 mRNA (65) and less D2 mRNA (15-20). Finally, calbindin cells expressed both receptors in similar proportions (37). Our data suggest that D4 receptor is a preferential target in designing new antipsychotics, mainly because of its predominance in parvalbumin interneurons.

AC4-ASA, A NOVEL HETEROBIFUNCTIONAL PROBE AND COMPETITIVE AND ALLOSTERIC LIGAND OF THE MUSCLE NICOTINIC ACETYLCHOLINE RECEPTOR

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The probe was developed as a tool for the study of cholinergic receptor binding sites. In order to achieve that, acetylcholine was derivatized at its alkyl end and through a short spacer, with a photoactivatable aryl-azide group susceptible to radioiodination. The synthesis and purification procedures were simple and the probe proved to be stable in the dark. Besides, it was able to interact specifically with muscarinic and muscle nicotinic receptors showing to be an agonist of the former and having selectivity for the α/δ binding site of the latter. The ligand presented the capability of modifying the affinity of (-)-[3H]-nicotine by the muscle-type nicotinic receptor. Competition experiments between AC4-ASA and (-)-[3H]-nicotine revealed that the ligand could perform its modulating activity through, at least, a new allosteric binding site, different from the typical orthosteric binding sites. Future photolabelling experiments will display its location at the receptor. Moreover, we would like to point out the ligand potential use for the study of the structural changes undergone by the nicotinic receptor interfaces during activation.

Poster Number (202) Session II

REALLY GREEN CHEMISTRY: PHOTORELEASE OF CAGED NEUROTRANSMITTERS USING A LOW POWER GREEN LASER POINTER

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Caged neurotransmitters are a very convenient technique for application of an increasing diversity of small molecules. Aminoacids, neurotransmitters, nucleic acids and even some hormones and oligopeptides have been caged. Good properties for the photorelease reaction are high quantum efficiency ({phi}) and long photon wavelength ({lambda}). Our group has been working on a cageing technology, based on ruthenium bipyridine coordination bonds, that allows for the tuning of the spectral and chemical properties of the compound. We demonstrate the photorelease of neurotransmitters with a 5 mW, 532 nm (green) laser pointer.

Neurochemistry and Neuropharmacology
Poster Number (203) Session II

DOPAMINERGIC D1 AND GLUTAMATERGIC AMPA RECEPTORS COOPERATION IN THE LONG-TERM SENSITIZATION TO COCAINE INDUCED BY ACUTE STRESS

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Several evidences indicate that the administration of the D1 agonist receptor, SKF increased AMPA receptor insertion in the extra synaptic cell surface, phenomenon associated with the sensitization to cocaine. The aim of the present study was to demonstrate the cooperation between D1 and AMPA, in the sensitization induced by stress. Specifically we evaluated the stimulating locomotor properties of cocaine and dopamine release in the nucleus accumbens core (NAcc Core). Male Wistar rats (250–350 g) were restrained for two hours, control animals were left undisturbed in their cages. Twenty-one days after this stress episode all animals were assigned to one of the following experiments: I)Locomotor activity in response to i)AMPA microinyections (0, 0.1, 0.3 ug/ul) in NAcc Core ii)the D1 agonist, SKF38393, (0, 0.5; 1.0 mg/kg i.p.) and iii)the association beetwen SKF 0.5 mg/kg and a subumbral dose of AMPA (0.1 ug/ul administered 10 minutes later in NAcc core). II)Microdialysis: dopamine levels were determinated by HPLC in NAc Core in response to three different concentration of AMPA (1.0; 10.0; 100.0 uM) and in the expression of sensitization to cocaine (15 mg/kg ip) during the perfusion of the AMPA antagonist, CNQX (1 nmol), ó vehicle. These results clearly show the participation of AMPA the long-lasting sensitization to cocaine following a single restraint stress session.The stimulation of the D1 makes possible the observation of the stimulant effect produced by subumbral doses of AMPA.These results are discussed in the framework of the stimulating effects that the D1 produce in the surface cellular expression of GluR1 (the AMPA subunit) in the stressed animals.Current experiments are attempting to confirm this hypothesis.

Poster Number (204) Session 11

MODULATION OF GABAC RECEPTORS BY REACTIVE NITROGEN COMPOUNDS

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Modulation of GABAc receptors by reactive nitrogen compounds Javier Gasulla and Daniel J. Calvo INGEBI (CONICET-Universidad de Buenos Aires) Argentina. Nitric oxide ($NO^{\cdot}$) is a difusible gas produced in the central nervous system by neural nitric oxide synthase (nNOS). Different synaptic receptors and ionic channels were demostrated to be modulated by $NO^{\cdot}$ (e.g: NMDA receptor, ryanodine receptor, Ca2+–activated K+ channels, L-type Ca2+ channels, etc) through direct modification of cysteine residues (S-nitrosylation or oxidation to cystine). GABAc receptors have two extracellular and one intracellular cysteines wich are potentially redox sensitive. The aim of the present study is to find out if the activity of GABAc receptors could be regulated by $NO^{\cdot}$. Homomeric 1 GABAc receptors were expressed in Xenopus laevis oocytes and submaximal GABA-evoked (0,3–1µM) chloride currents were electrophysiological recorded using two-electrode voltage clamp technique in the presence or absence of the $NO^{\cdot}$ donors SNOC (S-nitrosocysteine) (100–500µM) and GSNO (S-nitrosoglutathion) (500–1000µM), both of them can liberate free $NO^{\cdot}$ and transnitrosylate protein sulfhydryl groups. In addition we used DEA/NO (diethylamino nonoate) (100–1000µM) that only behaves as a $NO^{\cdot}$ donor. All the compounds tested reversibly potentiated GABA-evoked currents. Preliminary experiments suggested that the effects induced by reactive nitrogen compounds are dose dependent. Our results demonstrate that GABAc receptors can be modulated by reactive nitrogen compounds, with $NO^{\cdot}$ as the most probable candidate to exert this modulation. The mechanisms of action of these agents are currently under study. Supported by FONCyT-CONICET

Neurochemistry and Neuropharmacology
Poster Number (205) Session II

LAMOTRIGINE DOES NOT PROTECT FROM 3-MERCAPTOPROPIONIC ACID INDUCE-SEIZURES

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In previous works we have observed that repetitive administration of the convulsant drug 3-mercaptopropionic acid (MP) enhances brain MDR-1 gene expression and develops refractory phenotype to phenytoin and phenobarbital treatment. In the present work we examine the effect of lamotrigine (LTG) in this experimental model of epilepsy. Lamotrigine is a broad spectrum antiepileptic drug in partial and generalized syndromes.Methods: Wistar rats were divided in 4 groups. Groups A received a single dose i.p. of MP (40-45mg/kg) daily injected during 10days. During the same period, group B, was daily treated with LTG (20mg/kg), 30 minutes previous to MP administration, group C received nimodipine (2mg/kg) 1 hour previous to MP and as control (groupD) rats were injected with saline solution (V). Hippocampal and plasma pharmacokinetics of LTG were evaluated in the different groups after single iv administration of 10 mg/kg by using central microdialysis and traditional blood sampling.Results: Pharmacodynamics studies showed that LTG and Nimo did not protect from MP induces seizures. In coincidence with pharmacodynamic assays, no differences were found in LTG hippocampal and plasma levels comparing all groups. In rats pretreated with V, hippocampal LTG levels were in MP rats (maximal concentration (Cmax):1.36±0.42 µg/ml) compared to C animals (Cmax: 1.80±0.19 µg/ml µg/ml). NIMO pretreatment did not modify central kinetics of LTG in C and MP animals (C rats: Cmax: 1.68±0.50 µg/ml; MP rats: Cmax: 1.58±0.41 µg/ml). Our results indicate that LTG does not protect from MP seizures. Hippocampal LTG levels were similar in MP rats than in controls and in the presence of the Pgp inhibitor NIMO, suggesting that LTG is not a good substrate of P-gp. Therefore, LTG is not an adecuate antiepileptic drug to prevent daily seizures or after repetititive MP administration.

Poster Number (206) Session II

UNCOUPLING OF BENZODIAZEPINE AND GABA BINDING SITES INDUCED BY GABA

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In a previous work we have demonstrated that exposure of rat neocortical cultures to GABA for 5-10 min (t1/2= 3.2 min) initiates a process that results in a reduced interaction between GABA and benzodiazepine binding sites (uncoupling) hours later (t1/2= 12 h), without changes in GABAA receptor number. Uncoupling was accompanied by a decrease in α1, α3, and β1-3 subunit mRNA levels with no change in α2, α4, α5, γ1 and γ2 mRNAs. These alterations in mRNA levels were associated with corresponding changes in subunit protein expression. The decrease in α1 subunit level did not produce, however, a reduction in the proportion of receptors containing α1 as measured by zolpidem binding assays. These results can be explained by the fact that α1 exists in excess and only 20 of the total subunit becomes part of assembled receptors. The strength of allosteric coupling between GABA and benzodiazepine binding sites depends on the α subunit subtype present in the GABAA receptor (α3 α1/2). To determine whether uncoupling produces a reduction in the percentage of receptor composed of α3 subunits, inmunoprecipitation experiments followed by western blot assays were performed. Neocortical cultures were incubated with GABA for 10 min, washed and cells were collected 48 h later. Receptor immunoprecipitation assays were carried out using an antibody against γ2 subunits that are present in most of the receptors. Results from western blot experiments using an antibody anti- α3 showed a decrease in the percentage of receptors containing α3. These results suggest that GABA-induced uncoupling involves a change in the subunit composition, resulting in receptors with a reduced allosteric coupling between GABA and benzodiazepine binding sites.

THE ALPHA-TYPE SUBUNIT LEV-8 GOVERNS THE DESENSITIZATION PROCESS OF C. ELEGANS LEVAMISOLE-SENSITIVE NICOTINIC RECEPTORS

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C. elegans is a free-living nematode and a representative member of a large phylum that includes many parasitic members. Nematode nicotinic acetylcholine receptors (nAChRs) are pentameric ligand-gated ion channels that mediate synaptic transmission throughout the nervous system. The muscle levamisole-sensitive nAChR (L-AChR) is the target of anthelmintic drugs, such as levamisole, which act as potent agonists. Although several subunits have been reported to form the L-AChR, its subunit composition and the role of each subunit remain unknown. LEV-8 is a alpha-type subunit of the L-AChR that when mutated confers partial resistance to the levamisole paralytic effects. To explore the functional role of LEV-8, we performed cell-attached and whole-cell recordings of embryonic muscle cells from wild-type and mutant strains. Recordings from the null mutant strain lev-8(x-15) show ACh- and levamisole-activated channels with a conductance of 39.6±4pS. The kinetics of the channels differs from that of wild-type strains. The mean open times for ACh- and levamisole-activated channels are 3.9- and 1.5-fold more prolonged, respectively, than those from wild-type strains. The frequency of channel openings is markedly reduced with respect to that of wild-type strains. Moreover, in the LEV-8 null mutant strain the frequency decreases significantly with the time of recording, suggesting enhanced desensitization. Macroscopic currents reveal 1.5-fold increase of the desensitization rate and decreased recovery rate from desensitized states in the LEV-8 null mutant strain when compared to the wild type. We conclude that LEV-8 is an accessory subunit that governs the desensitization process of the L-AChR. This study contributes to the elucidation of the stoichiometry of functional nematode muscle L-AChRs.

Poster Number (208) Session II

DIFFERENTIAL NEUROTOXIC EFFECTS INDUCE BY MK-801 IN CORTICAL-LIMBIC STRUCTURES IN FUNCTION OF ACUTE AND CHRONIC TREATMENTS IN RATS

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Non-competitive antagonists of the NMDA glutamate receptor have shown to have neuroprotective, neurotoxic and psychotomimetic properties. However, they all share the common effect of blocking the Ca+ channels linked to these receptors. Reversible and irreversible neurotoxicity induced by these drugs is highly dependent on the dose and treatment. OBJECTIVES: To examine MK-801-induced neurotoxicity in different doses and types of treatment (acute vs chronic) in Wistar rats. METHODS: Thirty-eight adult female rats were divided into 3 groups: control (NaCl 0.9), acute treatment (2.5, 5 and 10 mg/kg) and chronic treatment (2.5, 5 and 10mg/kg). For the chronic treatment, administrations were given every 24 h (e.g. 1 mg/kg for 5 days for the 5mg/kg chronic group). All rats were sacrificed 72 h after the last administration. The Amino-Cupric-Silver technique was used for the detection of neurodegenerative profiles. The study was focused on the olfactory system, hippocampal formation, parahippocampal and retrosplenial cortex. The material was examined by comparative qualitative and densitometric analysis. RESULTS: At equal doses the MK-801 induced neurodegenerative pattern was stronger in acute vs chronic treatments. CONCLUSIONS: The decrease in the pattern of neurodegeneration suggests that neuroadaptative mechanisms, that may involve tolerance, could underlie these differences.

MODULATION OF NITRIC OXIDE SYNTHASE ACTIVITY DUE TO PRENATAL STRESS

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During development animals are especially vulnerable to disturbances on homeostasis. We have previously shown that prenatal stress alters offspring´s behaviour. The objective of the present study was to evaluate the role of nitric oxide in these alterations. Methods: Pregnant Wistar rats were restrained three times a day, 45 minutes each, since 14th day of pregnancy until delivery. Offspring was analyzed for hippocampal nitric oxide synthase (NOS) activity and protein levels and PKC activity. Anxiety-like behaviour and habituation were evaluated in the Open Field and Territory Recognition was also studied. Results: Hippocampal neuronal NOS (nNOS) levels were increased in Prenatally Stressed (PS) animals at post-natal age 7 (PN7), almost twice as much as in Controls. Total NOS activity (pmol/mgtissue/30min) was unchanged, but endothelial NOS (eNOS) activity (obtained in the presence of a selective nNOS inhibitor) was significantly decreased and nNOS enhanced. Activity in the presence of EGTA (inducible NOS, iNOS) was almost undetectable in both groups. We found no differences in total PKC activity in hippocampus at PN7. We observed increased freezing in PS rats and impaired habituation to the Open Field and defects in Territory Recognition in males at PN60. Discussion: It has been described that an increased nNOS activity can affect hippocampal neurogenesis, and may induce neurodegeneration in a variety of animal models. The results reported here could point to a role of nNOS in the behavioural abnormalities described in PS rats.

Poster Number (210) Session II

COCAINE CONTENT MEDIATES THE BEHAVIORAL AND NEUROCHEMICAL EFFECT OF COCA-PASTE BUT NOT ITS NEUROTOXICAL PROPERTY.

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Coca-Paste (CP) is an illegal abuse drug consumed in several Latin-American countries. In Uruguay, CP consumption appeared in 2002 bringing on serious health and social consequences. CP is a smokable cocaine form. It is an intermediate product obtained during the cocaine alkaloid extraction from coca leaves (Erythroxylon coca). This process ends with the obtainment of cocaine in its salt form as hydrochloride (C-hy), being the white powder to be insufflated. CP addicts present different clinical characteristics from C-hy consumers, suggesting that both drugs could have different actions in the brain. Others substances present in CP (alkaloids, solvents), in addition to the administration route, may account for the differences. To test this hypothesis, we treated male Wistar rats with systemic and acute equimolar doses of cocaine either in the form of CP or C-hy to assess its behavioral (locomotor stimulation using Open Field test) and neurochemical effects (dopamine and metabolites tissue content measured by HPLC-ED). We also investigated the CP neurotoxicity property using culture hippocampal neurons. CP and C-hy induced an increase in the animal locomotor activity showing the same stimulant effect. Moreover, there was a comparable change in dopamine (DA) and metabolites tissue levels in Nucleus Accumbens, response that could be explained by a DA transporter-blockage mechanism. All CP samples assayed induced neurotoxicity and interestingly, CP showed a neurotoxic effect at concentrations at which C-hy did not produce any effect. These data suggest that CP cocaine content mediated the stimulant and neurochemical effect but not its neurotoxic properties. Financial support: PDT-Salud 76/26 (2007-2009).

INCREASE ON CDK5 ACTIVITY IN STRIATAL SYNAPTOSOMES AFTER SENSITIZATION TO AMPHETAMINE IN A NOVEL ENVIRONMENT IN PERIADOLECENTS RATS

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The development of sensitization to the locomotor effects of psychostimulant is strongly influenced by the environmental context in which a stimulant drug is administered. This particularity represents a valuable tool to analyze neurochemical changes specifically associated the development of sensitization. Recent data from our laboratory suggest that the p35/cdk5 complex is involved in the development of behavioral sensitization induced by d-amphetamine (amph) in the periadolecent rat. The present study was designed to analyze whether: a) an acute administration of amph produces sensitization in adolescent rats, b) this effect is modulated by the novelty of the context, and c) changes in activity of Cdk5 are associated with the development of sensitization. Periadolescent rats were given 0 or 4 mg/kg amph in a novel environment or in the homecage. After one day of withdrawal subjects were given vehicle or 2mg/kg amph in the same context where received the first administration of the drug. Locomotor activity and the expression of p35 and Cdk5 activity in synaptosomes of dorsal striatum test were analyzed. Behavioral sensitization was only observed in the novel condition. This sensitization was specifically accompanied with an augmentation of the expression of p35 and the activity of cdk5 in dorsal striatum. These results support the hypothesis which postulates that the p35/cdk5 complex plays a role in the sensitization to the stimulant locomotor effects of amph.

Poster Number (212) Session II

EVALUATION OF LEVODOPA AND PRAMIPEXOLE CO-ADMINISTRATION EFFECTS IN AN ANIMAL MODEL OF PARKINSON'S DISEASE

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Levodopa and dopamine agonists (DA) are currently available treatments for Parkinson's disease. Levodopa is the most effective in alleviating motor disability but frequently induces dyskinesias, which may interfere with motor performance and reduce quality of life. DA have been proposed to have less induction of dyskinesias although they are not as effective as levodopa in the advanced stages of the disease. Our goal is to test if co-administration of levodopa and pramipexole, at doses that do not generate dyskinesias when used in monotherapy, has therapeutic effects without generation of dyskinesias. A levodopa dose-response curve was performed on unilaterally 6-OHDA lesioned rats. Four weeks after the lesion, levodopa was orally administered at doses 6.25; 12.5 and 25 mg/kg during 10 days. Dyskinesias, turning behaviour and use of the contralateral forelimb were tested at day 1, 5 and 10. Tyrosine hydroxylase immunohistochemistry was performed to determine the degree of nigrostriatal dopaminergic system damage. We found that rats treated with levodopa 6.25 mg/kg did not develop dyskinesias whereas rats treated with 12.5 or 25 mg/kg did. The dose of pramipexole to be used in our co-administration experiments will be chosen based on previous results obtained in our laboratory. Once both doses are chosen, drugs will be orally administered together during 10 days and behavioural parameters will be tested. Our hypothesis is that co-administration of levodopa and pramipexole, at doses that fail to produce dyskinesias when used alone, should postpone the onset of dyskinesias and produce a synergistic effect capable of improving the use of the contralateral forelimb used as an index of therapeutic benefit.

COMPARATION BETWEEN ACUTE AND CHRONIC POSTNATAL STRESS IN GLUTAMATERGIC NEURONS IN THE RAT BRAIN

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It is well known that animals exposed to stressful stimuli during their early life develop different neurological disorders when they become adults. In this study, we evaluated the consequences of acute and chronic stress on adult brain on Glutamate transporter (GluT) in vitro, evaluating the uptake of [3H]-Glu by synaptosomes-enriched fractions isolated from rat cerebral frontal cortex (FC) and hippocampus (HIC) by time-course and kinetic studies. In acute stress, the rats were separated from their mothers and divided in two groups: control and stress. While control rats were moved to a separated cage, stress rats were exposed to cold stress (4°C) during 1 h. In repeated stress the rats were separated from their mothers and exposed to cold stress (4°C) for 1 h at postnatal day (PD) 7 during 20 days. These animals were allowed to a 30 days recovery period until adulthood. At the end of the stress period, animals were killed by decapitation. FC and HIC were dissected to study GluT and trunk blood samples were collected to determinate corticosterone levels. Acute stress results show an HIC increase in both affinity (Km) and maximum velocity (Vmax), while in the FC only the affinity was increased. Repeated chronic stress shows changes only in Vmax: rise in FC and decrease in HIC. The time-course on FC in acute stress shows an uptake decrease while in chronic stress the uptake was similar in both groups. HIC did not show significant differences either chronic or acute stress. The levels of corticosterone decreased in chronic stress. These results suggest that the exposure to early stressful adverse life events affects hypothalamic-pituitary-adrenal (HPA) axis and alter the glutamatergic neurons. Supported by UBACYT B019 and CONICET, PIP 5869

ETHANOL CHRONICALLY ALTERS DERIVATED PURINE NUCLEOTIDE HYDROLYSIS AND NUCLEOTIDASE GENE EXPRESSION IN ZEBRAFISH BRAIN

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Ethanol is a drug widely consumed and exerts many actions in CNS, modifying several signal transduction pathways. Zebrafish has been used on biochemical and behavioral studies about alcoholism and dependence. However, there is no evidence effect of chronic ethanol exposure in the purinergic system, in which extracellular nucleotides act as signaling molecules, being inactivated by ecto-nucleotidases. The aim of this study was to evaluate adenine and guanine nucleotide hydrolysis and gene expression of NTPDases (1, 2 and 3) and 5'-nucleotidase after long-term ethanol exposure. Animals were exposed to ethanol in concentration 0.5 during 7, 14 and 28 days (n=7). The activities (mean; standard deviation) of control group were for ATP (536.44;52.22), ADP (182.05;29.96), AMP (36.76;9.06), GTP (158.80;29.67) GDP (35.93;6.23) and GMP (27.26;3.36). There were no significant changes on ATP and GTP hydrolysis after all treatments. However, a decrease on ADP (46 and 34) and GDP (48 and 36) hydrolysis was verified after 7 and 14 days, respectively. After 7 and 14 days exposures, it was observed a significant decrease on AMP (48 and 36) hydrolysis, and GMP hydrolysis was inhibited only after 7 days (46). Ethanol increased NTPDase1, NTPDase2_mq and NTPDase3 transcript levels after 28 days of exposure. In contrast, NTPDase2_mv and NTPDase3 transcript levels decreased after 7 and 14 days, respectively. However, NTPDase2_mg and 5'- nucleotidase gene expression were not altered. Altogether, the ecto-nucleotidase cascade alterations could be a target of chronic toxicity promoted by ethanol, modulating adenine and guanine nucleotides levels, as well nucleosides adenosine and guanosine for their specific receptors.

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DIFFERENTIAL EXPRESSION OF NURR1 IN THE VENTRAL TEGMENTAL AREA OF LOW AND HIGH NICOTINE-RESPONDER RATS

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The transcription factor Nurr1, a member of the NGFI-B family of nuclear orphan receptors, is highly expressed in rodent midbrain dopamine neurons and is essential for their phenotypic development and maintenance. There are several lines of evidence indicating that nicotine produces behavioral effects via actions on the mesolimbic dopamine system. However, it is still unknown whether Nurr1 participates in nicotine-induced behavioral changes. Locomotor horizontal activity in rats is a behavioral index of nicotine effect on the brain. We evaluated the locomotor response to an acute nicotine injection, obtaining two groups: high and low responder rats. In these animals, we measured Nurr1 protein expression in the ventral tegmental area (VTA). In addition, we trained the animals in a conditioned place preference (CPP) test, in order to evaluate nicotine rewarding properties in these two behavioral groups. Our results showed that in the VTA of high nicotine responders, Nurr1 expression is increased compared to low responders. These two behavioral groups displayed no significant differences in the CPP test. These preliminary findings indicate that an increased expression of Nurr1 in the VTA accompany nicotine-induced locomotor activity. However, low and high responder rats performed equally when rewarding properties of nicotine were assessed by CPP. Acknowledgements This work was support by grant MSI N° P06/008-F (MEA, Chile) and FONCYT-CONICET (ROB).

BRAIN AT1 ANGIOTENSIN II RECEPTORS INVOLVEMENT IN THE NEUROCHEMICAL LONG TERM EFFECTS INDUCED BY AMPHETAMINE

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The enhanced response to psychostimulants, termed behavioral sensitization, relies on time-dependent neuroplastic changes in the brain circuitry involved in motivational behavior. These changes are associated with the long-lasting hyper-reactivity of the mesolimbic dopaminergic pathway. It has been shown that a single exposure to amphetamine is sufficient to induce long-term behavioral, neurochemical and neuroendocrine sensitization in rats. The present study tested the hypothesis that Ang II AT1 receptors are involved in the neuroadaptative changes induced by a single exposure to amphetamine and that such changes are related to the development of behavioral and neurochemical sensitization. We studied the expression of neurochemical sensitization in Wistar male rats (250-280g) pretreated with an AT1 blocker, candesartan or vehicle (3 mg/kg p.o) for five days and after that injected once with amphetamine 5mg/kg i.p. The experiments were performed three weeks after amphetamine administration and the DA release from the nucleus accumbens core induced by amphetamine challenge was tested using in vivo microdialysis. In other group of animals the behavioral sensitization to D1 and D2 dopaminergic agonists was tested. In addition, in animals exposed to amphetamine it was determined the expression of AT1 receptors in relevant brain areas using immunohystochemistry. It was also tested the effect of AT1 blockade on the acute behavioral and neurochemical response to amphetamine. Our results suggests that AT1 blockade in some way affected the activity of the dopamine transporter or vesicular transporter that later resulted in a decrease of dopamine release in candesartan-amphetamine pretreated animals. We also found that amphetamine exposure induce persistent changes in Ang II AT1 receptors in ventral and dorsal striatum and amygdala

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GLUTAMATE-DEPENDENT HIPPOCAMPAL SYNAPTIC REMODELLING DECREASES CELL ADHESION MOLECULES EXPRESSION: CORRELATION WITH AN EXPERIMENTAL MODEL OF DEPRESSION

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Dendritic atrophy of hippocampal CA3 neurons found in experimental depression is probably related to excessive glutamate (GLU) release. Based on our previous results showing decreased hippocampal synaptophysin (SYN) and PSD-95 expression in animals exposed to the learned helplessness (LH) paradigm, an experimental model of depression, we studied the ultrastructural morphology of synapses and cell adhesion molecule expression in LH animals. In primary hippocampal neurons we analyzed the impact of GLU hyperstimulation on synapse morphology and synaptic protein expression. EM studies showed increased synaptic cleft width at the CA3 synapses of LH animals. While in control rats synaptic vesicles per synapse (SV/S) ratio was homogenous, in LH group SV/S ratio presented extreme low or high values. Postsynaptic density (PSD) morphology was altered in LH rats, while PSD length decreased; PSD width increased rendering similar values in total area. LH rats also showed decreased immunostaining for NCAM and PSA-NCAM, cell adhesion molecules implicated in plasticity and expressed by GLU neurons. In vitro, hippocampal primary neurons exposed to GLU presented reduced MAP-2, NCAM and PSA-NCAM immunostaining. Whereas PSD-95 and SYN puncta number diminished, individual puncta size was not modified for PSD-95 and was increased for SYN. Our results indicate that excessive neuronal exposure to GLU induces synaptic changes in vitro that resemble those observed in LH animals. These results support the hypothesis that glutamatergic hyperactivity in LH rats could reduce cell adhesion molecule expression leading to decreased synaptic connectivity in hippocampal CA3. Grants PICT34397, UBACYT B422

Poster Number (218) Session III

INVOLVEMENT OF ACCUMBAL DOPAMINE D1 AND GLUTAMATE NMDA RECEPTORS IN THE EXPRESSION OF ETHANOL-INDUCED BEHAVIORAL SENSITIZATION

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Repeated ethanol (EtOH) administration in mice may induce behavioral sensitization, defined as a progressive potentiation of stimulant effects. There is a variability among species and strains in the development of sensitization. This process is associated with neuroadaptations in the brain reward systems, including the nucleus accumbens (NAcc). The goal of the present study was to analyze the accumbal dopamine D1 and glutamate NMDA receptors participation in the locomotion behavioral response to D1 or NMDA agonists in mice with different levels of sensitization to EtOH. In two experiments, mice received repeated administration of 2.2 g/kg EtOH or saline during 21 days. According to their locomotor response on the last day of treatment, EtOH-treated mice were classified into two groups: sensitized or non-sensitized. After 5-10 days of surgical procedure to implement intra-NAcc cannulae, mice were challenged each other day with intra-NAcc administrations, having their locomotor activity recorded for 1h. In experiment 1, mice received saline, SFK-38393 (D1 agonist) in 0.1µg/side, 0.5µg/side or 1.0µg/side doses (in 0,2µl) intra-NAcc. The dose of 0.1µg/side SKF-38393 induced significant stimulant effects in sensitized mice during the first fifteen minutes. These results suggest that mice sensitized to EtOH present functionally hyperresponsive D1 receptors in the NAcc. In experiment 2, another group of mice received saline, NMDA (NMDA agonist) in 0.01µg/side, 0.02µg/side e 0.04µg/side doses (in 0,2µl) intra-NAcc. The dose of 0.04µg/side NMDA induced stimulant effects only in saline and sensitized animals. The non-sensitized group did not show stimulant response indicating they have hyporresponsive NMDA receptors in the Nacc.

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UTILITY OF A C6-GLIOMA SYSTEM FOR EXPLORATORY RISK ASSESSMENT OF ENVIRONMENTALLY RELEVANT INSECTICIDES

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Real environments and food products may carry low levels of multiple hazardous compounds having diverse modes of action. For instance, according to recent single-compound toxicological information from rats and environmental data, organophosphate (OP) and pyrethroid (PYR) insecticide residues pollute indoor and outdoor settings but in levels that imply no health risk for humans. Here we present an exploratory, in vitro model, aimed to identify environmentally relevant insecticides exposure situations that require CRA-like research efforts in in vivo models of greater human relevance. We will show time (4-24-48 h)- and dose (0.1-250 uM; DMSO-vehicle control)-effect data for two OP and four PYR compounds. We use a C6-glioma culture system and a battery of effect measures to examine the individual action of these insecticides. Moreover, two fetal bovine serum (FBS) conditions are assayed (FBS 2-10). Using 24h-exposed, C6 cultures in D-MEM supplemented with 2 FBS, followed by MTT assays for citotoxicity in 96-well plates, a high correlation between BMD15 estimates for cell viability and rat oral LD50s was apparent for three PYRs (deltamethrinbifenthrinteflu thrin). The BMDS for chlorpyrifos (OP) showed a divergence from this relative potencies trend. Acephate (OP) produced no evident C6-cell viability decrease in any exposure condition. We are presently testing if Hoechst-33258 cytological observations and AchE assays in the C6 system may help interpreting above findings. These pilot studies will be used to appropriately design in vivo, environmentally relevant OP-PYR mixture studies aimed to test additivity using a battery of biochemical and neurobehavioral endpoints of neurotoxicity in the rat.

STUDY OF THE RELATIONSHIP BETWEEN LESION SEVERITY AND BEHAVIORAL RESPONSE TO DOPAMINERGIC TREATMENT IN AN ANIMAL MODEL OF PARKINSON'S DISEASE.

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Parkinson's disease is characterized by degeneration of dopaminergic neurons of the nigrostriatal pathway. The main symptoms are bradykinesia, rigidity, resting tremor and postural instability. We studied the relationship between the effects of levodopa and the D2 agonist pramipexole on behavioral deficits and lesion severity. Male Wistar rats received three unilateral 6-hydroxydopamine (6-OHDA) injections in the striatum. Rats were randomly assigned to a three week treatment either with water, levodopa or pramipexole. The cylinder test was performed to study the improvement of the akinesia of the affected contralateral forelimb under treatment. After being sacrificed, immunohistochemistry for tyrosine hydroxylase was performed on the substantia nigra, and the percentage of remaining cells compared to the control hemisphere was determined. Treatment with levodopa or pramipexole improved the akinesia of the contralateral forelimb in the cylinder test to normal levels in some animals. The three unilateral 6-OHDA injections in the striatum produced the degeneration of the nigrostriatal pathway resulting in remaining neuronal populations of 20-60 compared to the control hemisphere. We found that there was a significant correlation between the degree of TH positive cells loss and the use of the contralateral forelimb only in the pramipexole treated animals. D2-agonist mediated responses are known to be facilitated by concomitant D1 stimulation by either endogenous dopamine or a D1-agonist. Our findings support this hypothesis as the D2 receptor agonist pramipexole was unable to induce reversion responses in rats with low percentages of remaining cells, while with levodopa this was not the case.

DOES MTOR PLAY A ROLE IN THE GENERATION OF LEVODOPA-INDUCED DYSKINESIAS

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Dyskinesias are one of the major limiting side effects encountered in the treatment of Parkinson's disease. Increasing data suggest that the development of levodopa induced dyskinesias (LID) involves profound and persistent molecular changes in the striatum. However the intimate mechanisms that underlie LID are poorly understood. Strong evidence also suggests alterations in the induction phase of corticostriatal long term potentiation (LTP) and depotentiation in LID. It is known that LTP involves processes requiring protein synthesis. In view of this, it is tempting to speculate that molecular factors known to be involved in plastic changes such as LTP would also play a role in the development of LID. Mammalian target of rapamycin (mTOR) is a serine-threonine protein kinase that modulates cell growth, proliferation and synaptic plasticity via the regulation of protein synthesis. To understand some of the molecular factors and mechanisms involved in the development of LID we inhibited mTOR during sensitization to levodopa. To that effect, 22-gauge stainless steel cannulae were implanted hemilaterally in the striatum of 6-OHDA lesioned rats. Rats received 0.5 µl of vehicle or rapamycin (30, 60 and 120 nM) 15 min before levodopa (25 mg/kg), once every 48 h for a total of three times (sensitization). Two days after that, both groups received 25mg/kg levodopa. Contralateral rotations, dyskinesias and the use of the contralateral forelimb were tested. We found no significant differences in dyskinesia score between vehicle and rapamycin treated animals. This preliminary data suggests that mTOR is probably not involved in the molecular changes that lead to the development of LID in an animal model of parkinsonism.

Poster Number (222) Session III

THE EFFECTS OF REPEATED EARLY MATERNAL SEPARATION AND COLD STRESS ON BRAIN DEVELOPMENT

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During postnatal development, the central nervous system (CNS) is highly sensitive to the effects of drugs, stressors and environment. Early life events have profound consequences in growth and development. The aim of this study was to investigate the consequences of repeated early maternal separation and cold stress exposition on GABAergic function and determinate whether the combination between cold and desensitization to maternal separation was an age-specific event on adult brain. Rats pups were separated from their mother and exposed to cold stress (4°C) for 1 h at postnatal day (PD) 5, 7 and 13 during 20 days. These animals were allowed to a 30 days recovery period until adulthood. The rats were killed by decapitation and trunk blood samples were collected to measure corticosterone levels. Frontal cortex (FC) and hippocampus (HIC) were dissected in order to study GABA uptake. Our results shows that the time course of repeated stress decreased GABA uptake only on FC at PD5, while at PD7 diminished significantly either on FC or HIC. Also, at PD13, we found a significant GABA uptake decrease on HIC. Chronic stress did not alter the basal levels of corticosterone at the different ages studied. These preliminary results support the notion that the development of the FC is affected by stressors during early life. The findings are in agreement with the hypothesis of compensatory changes development in response to repeated stress. Although we need to carry out more tests, we propose FC as key in the development of adaptative mechanisms. Supported by UBACYT B019 and CONICET, PIP 5869

Neurochemistry and Neuropharmacology
Poster Number (223) Session III

CENTRAL NORADRENALINE DECREASES THE AMBULATION IN OPEN FIELD TEST IN CHICKS: MODULATION BY A α-ADRENOCEPTOR ANTAGONIST.

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Noradrenaline (NA) released centrally has a dual modulation on the noradrenergic system and causes a wide range of effects by the activation of multiple adrenoreceptors subtypes. Each type of adrenoceptors has own pharmacological characteristics, and consequently their activation could have different effects until opposite effects. Adrenaline and NA released during an acute stressful event activate different subtypes from α- and α-adrenoreceptors, at cerebral level. In previous studies from our group, we observed that NA at low doses (between 0.0025 µg/µl and 0.05 µg/µl) and at high doses (0.5 and 1 µg/µl), administered icv immediately before the Open Field test, revealed a dose-dependent effect on the latency to ambulation, in 6-day-old chicks, suggesting that this inhibitory effect of NA on the locomotion, in stressed birds, could be mediated to different adrenoreceptors subtypes. The aim of current work was to observe whether the differences in the locomotor activity, in an Open field test, induced by several doses of NA involve the participation of α-adrenoreceptors. The experiments were carried out with a dose of fentolamina, a noradrenergic antagonist, of 0.250 µmol/kg administered intraperitoneally. Fifteen min later, different doses of NA were injected icv immediately before the Open field test. The results showed that the fentolamina, co-administered with NA, only at higher concentration (0.25, 0.50, 1.00 µg/ul) inhibited the ambulation and these effects on locomotor activity appears to be mediated by α-adrenoceptors.

Poster Number (224) Session III

ENRICHED ENVIRONMENT PREVENTS THE DIMINUTION OF PSD-95 AND A CELL ADHESION MOLECULE AND PRODUCES A PLASTIC EFFECT THROUGH THE INCREASE OF MAP2 AND NEUREXIN IN ANIMALS EXPOSED TO AN EXPERIMENTAL MODEL OF DEPRESSION

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In a previous work we demonstrated that 21 days of enriched environment (EE) produced the reversion of the depressive-like behavior and of the diminution of both the light subunit of neurofilament and the postsynaptic density 95 (PSD-95) in rats exposed to an experimental model of depression, the learned helplessness (LH). In order to elucidate which mechanisms are involved in the reversion of these proteins, we analyzed the immunoreactive area of neuroligin (NLG), which interacts with PSD-95, and neurexin (NRX). Both NLG and NRX are cell adhesion molecules involved in the synaptogenesis. NLG anchors PSD-95 and produced its activation, therefore leading to a presynaptic activation by binding to NRX. The measurement of NLG and NRX after 10 and 21 days of enrichment showed that EE increased NRX immunoreactivity and that it prevented the diminution of NLG observed in LH animals housed in standard cages. A similar result than that was found in PSD-95 immunoreactivity. Besides, MAP2, a marker of dendritic differentiation, was increased in stressed animals housed in the EE (LHEE group). All these results suggest that the EE produces differential effects on the proteins studied and that induces plastic actions in animals exposed to the LH paradigm. Supporting grants: ANPCyT PICT-2005-31953, UBA M073.

SOCIAL ISOLATION ENHANCES ETHANOL-MEDIATED LOCOMOTOR STIMULATION IN PREWEANLING RATS

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Preweanling rats are highly sensitive to the locomotor stimulation induced by relatively high ethanol doses. In adult mice this ethanol (EtOH) effect is modulated by stress. The goals of the present study were to analyze a) whether EtOH-mediated stimulation is enhanced under acute stress in preweanling rats, and b) the role of corticosterone (cort) related to this ethanol effect. Stress was induced by means of a social isolation treatment known to enhance basal cort levels. In Exp1, four hours before ethanol administration (0 or 2.5 g/kg) preweanling rats were isolated or remained in their homecage. In Exp 2 ethanol-mediated locomotor activation was assessed in adrenalectomized pups (appropiate sham controls were included in the design). In Exp3 pups were given 0, 3 or 6 mgkg cort before ethanol administration.. The dependent variable in all the experimients was locomotor activity (measured 5-10 and 35-40 minutes after ethanol administration). Social stress strongly enhanced ethanol-mediated locomotor stimulation but had no effect on locomotor acivity patterns in water-treated controls. (Exp 1). Adrenalectomized pups did not differ from controls in terms of locomotor activity induced by ethanol (Exp 2), and exogenous cort did not to enhance ethanol-mediated activation (Exp 3). These results demostrate that stress modulates ethanol locomotor effects in early stages of development. Additionally, the interaction between stress and ethanol upon locomotor stimulation is independent from cort activity.

Poster Number (226) Session III

SYSTEMIC ADMINISTRATION OF INSULIN AND EPINEPHRINE MODULATE THE GABAA RECRUITMENT IN CHICKS WITH DIFFERENT EMOTIONAL REACTIVITY

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Many studies have shown that neurotransmitters systems, excitatory and inhibitory as the GABAergic system, are responsible to evaluate different stressful events. Postsynaptic density, cellular surface expression and synaptic traffic of GABAAR can be modulated by extracellular signals such as insulin and epinephrine. Our previous findings, in day-old-chicks, show different behavioral, pharmacological and neurochemical responses to novelty between individuals among the same population. Thus, this different emotional reactivity was used to categorize birds with different degrees of fear and/or anxiety and they were termed as high latency (HL), moderate latency (ML) or low latency (LL). Moreover, systemic administration of insulin and different doses of epinephrine increase GABAAR in synaptosomes from control (not stressed) chicks and stressed ones, respectively. In this work, a Partial Water Immersion induced an increase of GABAAR in all subpopulations categorized. However, control chicks, from ML and HL subpopulations, showed different susceptibility to an insulin injection (2.5 IU/mg). However, the insulin effect was not additive to the stress-induced increase suggesting that both effects occur through similar mechanisms. Co-administration of insulin and epinephrine (0.25 mg/kg) increased the receptor density in HL group compared to insulin alone. No significant increase in 0.5 mg/kg of epinephrine was observed, suggesting that epinephrine action depends on, and adds to the increase induced by insulin alone possibly by increasing the synaptic strength in subpopulations with higher fearfulness.

IMPACT OF LOUD NOISE ON RAT ASSOCIATIVE MEMORY. HIPPOCAMPAL NEURONAL ALTERATION AND OXIDATIVE STATUS IMBALANCE

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Acoustic contamination is produced in the environment by the presence of noise which can affect several systems through oxidative stress generation. Since hippocampus has been involved in associative memory, the aim of the present work was to test if the exposure to loud noise can affect hippocampal-related memory. In addition, hippocampal histology and oxidative status were tested in exposed rats. Male Wistar rats of 15 days were exposed to white noise (100dB, 2h/day) and separated into two groups, acute (AE, 2h/day) and chronic exposure (CE, 2h/day for 15 d). Passive avoidance test (PA) was used to evaluate the associative memory in 30-days-old rats. The levels of ROS and the activities of superoxide dismutase (SOD) and catalase (CAT) were measured at 30 days. Moreover, histological assessment was also performed. Results showed an impairment in PA test in exposed CE animals, with a decreased latency to enter the dark compartment, 24 hs after the electric footshock (rate T2/T1: AE, NS; CE, p0.05). The basal ROS levels were decreased (AE, p0.001; CE, p0.001), while antioxidant enzymes activities were increased after noise exposure (CAT: AE, p0.001; CE, p0.05; SOD: AE, p0.05; CE, NS). Histological changes were found, with neuronal death, nuclear hyperchromasia and citoplasmatic shrinkage, both in CA1 and dentate gyrus regions. These results suggest that AE and CE to loud noise are capable of inducing associative memory impairments in developing rats, what is mainly related to hippocampal histological damage. The increase in CAT and SOD activities could be triggered as a compensatory response to noise-induced damage, leading to a decrease in basal ROS levels.

Poster Number (228) Session III

MELANIN CONCENTRATING HORMONE MICROINJECTED INTO DE DORSAL RAPHE NUCLEUS IN RATS ELICITS A DEPRESSIVE-LIKE BEHAVIOR IN THE FORCED SWIM TEST

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Melanin-concentrating hormone (MCH), a cyclic 19-aminoacid peptide, is produced by neurons in the lateral hypothalamus and zona incerta projecting broadly throughout the brain. There are MCHergic fibers in the dorsal raphe nucleus (DRN) and regions of the limbic system suggesting a role for MCH in the regulation of emotional states. The biological effects of MCH are mediated through two receptors, MCH1-R (rodents and humans) and MCH2-R (humans). Recently, it has been shown that MCH1-R antagonists elicit an antidepressive effect in animal models. However, the mechanisms by which MCH or MCH1-R antagonism participate in the regulation of mood states are still unknown. Sprague Dawley male rats were implanted with a guide cannula into the DRN and five days after the stereotaxic surgery, MCH or anti-MCH antibody (immunoneutralization) were locally microinjected. The behavioral effects on the forced swim test (FST) were immediately after evaluated. MCH evoked a depressive-like behavior indicated by a significant increase in the immobility time and a concomitant decrease in climbing behavior. In contrast, MCH immunoneutralization elicited an antidepressant effect, decreasing immobility and increasing swimming time. The behavioral effects observed in the FST were independent to locomotor activity evaluated in the Open Field test. Moreover, animals pre-treated with fluoxetine (20 mg/kg) showed a significant blockade of the depressive-like response provoked by the microinjection of MCH into the DRN. The present results strongly suggest that MCHergic projections towards the DRN are involved in the control of depressive-related behaviors through the regulation of the serotoninergic transmission. Financial support: PDT-Salud 76

BEHAVIORAL AND NEUROCHEMICAL VARIATIONS DURING NICOTINE WITHDRAWAL IN MICE. PREVENTION WITH BACLOFEN.

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Nicotine (NIC) is critical in the maintenance of tobacco use and is the major active component of tobacco. The aim of the present study was to analyze the neurochemical variations in various brain regions of mice during NIC withdrawal syndrome and its prevention with baclofen (BAC, GABAB receptor agonist). Swiss-Webster albino mice received NIC (2.5 mg/kg, sc) 4 times daily, for 7 days. On day 8, dependent mice received the nicotine antagonist mecamylamine (MEC, 2 mg/kg, ip) 1 h after the last dose of NIC. A second group of dependent mice received BAC (2 mg/kg, ip) before MEC-precipitated abstinence. Somatic signs were measured for 30 min. The levels of dopamine (DA), serotonin (5-HT) and its metabolites were determined by HPLC in the striatum, cortex and hippocampus. NIC withdrawal produced a significant increase in wet-dog-shakes (P0.05) and paw tremors (P0.01) at 10 min. BAC prevented the incidence of these withdrawal signs. The global withdrawal score was also attenuated by BAC (P0.001). DA and DOPAC cortical levels decreased (P0.05; P0.001, respectively) in the abstinent group, while BAC reestablished these levels 10 min after NIC withdrawal. Furthermore, DA and 5-HT striatal levels decreased (P0.01; P0.01, respectively) during NIC withdrawal and BAC reestablished the decrease caused by the withdrawal. These results indicate that BAC prevents NIC withdrawal syndrome. This could be related to changes in dopaminergic and serotonergic activity measured 10 min after NIC withdrawal.

Poster Number (230) Session 1

PRESSURE PATTERNS PRODUCED BY ADULT AND TESTOSTERONE TREATED JUVENILE CANARIES.

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Singing behaviour in songbirds shows strong parallels with human vocal learning. As in humans, development of a learned vocalization first requires exposure to an acoustic model of species typical song and, subsequently, a sensory-motor practice period after which the vocalization is produced in a stereotyped manner. This requires mastering motor instructions driving the vocal organ and the respiratory system. Recently, it was shown that in the case of canaries (Serinus canaria), the diverse syllables constituting the song are generated with air sac pressure patterns with characteristic shapes, remarkably, those belonging to a very specific mathematical family. Here we treated juvenile canaries with testosterone at the onset of the sensory-motor practice period. This hormone exposure induced a rapid development of song production. After 14 days of treatment, juveniles produced stereotyped song, whose syllabic rates and song structure were similar to those produced by adults. We also recorded sub syringeal air sac pressure during song to study respiratory motor gestures. Testosterone treated juveniles sang with similar air sac pressure patterns as those produced by adults while untreated control birds of the same age did not. Detailed temporal structure and pressure modulation patterns emerged rapidly with testosterone treatment.

Motor Systems
Poster Number (231) Session 1

SOURCE-TRACT COUPLING IN BIRDSONG PRODUCTION

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Birdsong is a complex phenomenon, generated by a nonlinear vocal device capable of displaying complex solutions even under simple physiological motor commands. Among the peripheral physical mechanisms responsible for the generation of complex sounds in songbirds, the understanding of the dynamics emerging from the interaction between the sound source and the upper vocal tract remains most elusive. In this work we study a highly dissipative limit of a simple sound source model interacting with a tract, mathematically described in terms of a delay differential equation. We explore the system numerically and, by means of reducing the problem to a phase equation, we are capable of studying its periodic solutions. Close in parameter space to the point where the resonances of the tract match the frequencies of the uncoupled source solutions, we find coexistence of periodic limit cycles. This hysteresis phenomenon allows us to interpret recently reported features found in the vocalization of some songbirds, in particular, ``frequency jumps\.

Poster Number (232) Session 11

NEURAL SUBSTRATES OF MOTOR LEARNING IN UNPREDICTABLE ENVIRONMENTS

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Our bodies change and so does our environment. The fact that we manage to perform accurate movements despite this variable scenario posits a major challenge to the field of motor control. Adaptation of reaching movements to constant perturbations of sensory feedback points to the cerebellum and motor cortex as key structures mediating this type of learning. Yet, most perturbations encountered in our daily life are variable and, thus, not predictable (e.g. walking on an icy sidewalk). Psychophysical data suggests that, in front of uncertainty, humans adapt to perturbations by compensating for the error of the previous, not the current, movement. My Ph. D project aims to examine whether this behavior that differs from what is observed in certain environments reflects a different type of processing within cortico-thalamo-cerebellar networks and to evaluate the impact of long-term training in a variable environment on the generalization of learning. Our proposal will be approached experimentally by using transcranial magnetic stimulation to characterize the role and temporal contribution of motor regions to the acquisition and retention of reaching adaptation. In addition, magnetic resonance imaging will be used to evaluate the impact of long-term training in unpredictable environments on structural plasticity of the motor network.

Motor Systems

Poster Number (233) Session II

INDUCIBLE DELETION OF DOPAMINE D2 RECEPTORS IN ADULT MICE TRIGGERS A PARKINSONIAN-LIKE MOTOR SYNDROME

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Mouse gene knockout technology has been one of the major breakthroughs of the last 20 years for in vivo gene functional studies. Although many insights have been gained from numerous reports, we also learned the limitations of this technology such as the occurrence of compensatory adaptations to the absence of the gene product that leads to alternative developmental programs. For example, mice carrying null alleles for the dopamine D2 receptor (D2R) develop compensations that produce a hypolocomotor state that is much less severe than that induced by the acute pharmacological blockade of D2Rs in wild-type mice. To study the participation of D2Rs in normally developed adult mice, we created inducible Drd2 null mutant mice by crossing Drd2flox/flox mice with transgenic mice ubiquitously expressing cre recombinase fused to a mutated ligand binding domain of the estrogen receptor (Cre-ERTM). Tamoxifen binding to cytosolic Cre-ERTM translocates into the nucleus promoting excision of the critical coding exon 2 of Drd2. Two-month old compound Drd2flox/flox.Cre-ERTM (indDrd2KO) mice were injected with 50 mg/kg tamoxifen for 10 days. Three weeks later the number of D2Rs in indDrd2KO mice was 80 lower as determined by [3H]nemonapride binding. IndDrd2KO mice displayed a Parkinsonian-like phenotype characterized by resting tremor, inability to negotiate on a rotarod, lack of movement on a suspension bar and a 75 drop in locomotor activity due to fewer movement initiations. IndDrd2KO mice showed decreased responses haloperidol and amphetamine. Thus, loss of D2Rs in adult mice produces motor deficits that are much more severe than those observed in classical Drd2 knockout mice revealing the real importance of D2R function.

Poster Number (234) Session III

A CEREBELLUM-PARIETAL NETWORK REFLECTS INTERINDIVIDUAL DIFFERENCES IN THE RATE OF MOTOR SKILL LEARNING

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Functional organization of the brain is highly plastic. Structural and functional changes can be detected at a macroanatomical level through the use of non-invasive magnetic resonance imaging . Functional MRI provides an indirect measure of cerebral activity based on the level of blood oxygenation. This project is aimed at detecting changes in brain structure induced by motor skill training using a longitudinal approach. For this purpose, we obtained structural and functional images from a group of 9 healthy young participants before and after one week of training on a visuomotor adaptation task. Visuomotor coordination was disrupted by altering the spatial correspondence between the location of the target and the direction of movement of the hand, reflected on the screen by the cursor. On average, visuomotor adaptation was achieved within 4 days. Removal of the perturbation on day 7 was accompanied by aftereffects, reflecting the formation of a motor memory for the perturbation. The results indicate that long term visuomotor adaptation is associated with greater activity in the contralateral left parietal lobe and in the ipsilateral posterior cerebellum, consistent with the hand somatotopy. These regions belong to the motor network and have been related to sensorimotor remapping and forward learning, respectively. Interestingly, further analysis revealed that the parietal activation and part of the cerebelar activation are explained by interindividual differences in the speed of learning, with faster learners showing increased activity in these regions than slower learners. Given that there were no differences in mean performance across scanning sessions, the changes in activation can only be explained by motor learning

Motor Systems
Poster Number (235) Session III

ABSTRACT STIMULI INDUCE MIRROR ACTIVITY IN M1

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In humans, activity of the motor system can be elicited by passive observation of actions or static pictures with implied action. Here, we explored the possibility that the motor system can be activated predictably, by abstract stimuli bearing no physical similarity with an action. Participants view dynamic videos of a hand moving either the index or the pinky finger, while the electromyographical activity of their right first dorsal interosseus (FDI) was recorded. Subjects first learned the association between a colored cue and an index finger movement, and between a different colored cue and a pinky finger movement (visuovisual association). After training, cortical excitability for the FDI was measured by delivering single pulses of TMS over the left primary motor during the presentation of the cue or at the maximal finger aperture of finger movements. Subsequently, subjects learned to associate each cue with the actual finger movement (visuomotor association). After training, they underwent a second TMS session identical to the previous one. As expected, cortical excitability recorded during the observation of index finger movements was higher than during observation of pinky finger movements for both learning conditions. Cortical excitability was similar for both cues when recorded after visuovisual association, but was significantly larger for the cue associated with index movement than for the cue associated with pinky movements after visuomotor association, suggesting that action embodiment is crucial. Our study is the first to show that motor simulation can be induced by observation of abstract stimuli bearing no physical resemblance with an action.

Sensorial Systems
Poster Number (236) Session 1

ESPECTRAL DEPRIVATION NEUROPLASTIC CHANGES AT RETINAL LEVEL

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Coding of spectral information by the photoreceptors is at least ambiguous. Spectral information must be recoded in the retina and others postretinal centres in order to achieve a functional meaning. Light processing requires the comparison of stimulation patterns of at least two spectral channels in order to lead to percepts such as hue, saturation and brightness of colors. Morphometric and densitometric analyses were performed at the level of the first retinal synapse, in the outer plexiform layer and at the second order synapses at the inner plexiform layer. Animals were divided into four groups, all of them with a 12h light and 12h dark circadian cycle. For rearing under spectral deprivation, light was generated using high power leds. One group was exposed to a white cold light, another to red light (592nm), other to green light (520nm) and the last one to blue light (460nm). After 6, 9 and 12 day the chicks were deeply anesthetized and perfused through the left ventricle. Eyes were dissected out, postfixed and retinas were cut and immunolabeled mainly to detect calbindin, calretinin and SV2 as well as others markers. Our preliminary results showed that retinas from animals reared with red, green or blue light have smaller synaptic pedicle than animals reared in white light. We also found differences in the cone outer segment lengths, related with the sensitivity of the cells. The IPL pattern of expression of some proteins reveals that spectral deprivation affects not only the first synaptic level. In summary, we have shown developmental plasticity in the color vision system of the chick retina. UBACyT 0014

Sensorial Systems
Poster Number (237) Session I

FUNCTIONAL CONSEQUENCES OF ADAPTIVE EVOLUTION OF THE MAMMALIAN A9A10 NICOTINIC RECEPTOR

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The a9a10 nicotinic acetylcholine receptor (nAChR) mediates efferent inhibition of cochlear hair cells in mammals and birds. This inhibition results from the activation of a calcium-dependent K+ current thought to depend on calcium entry through the activated nAChR. Sequence analysis of the CHRNA10 genes of different species revealed signs of adaptive evolution in the mammalian lineage (Franchini and Elgoyhen, 2006). Therefore, one could propose that the mammalian a9a10 receptor (i.e., from R. norvegicus) would have functional properties different from those of the avian receptor (i.e., from G. gallus) as a result of specific, non-synonymous substitutions within the CHRNA10 gene. To test this hypothesis, we analyzed the properties of the recombinant chicken a9a10 receptor, using the two-electrode voltage-clamp technique in Xenopus laevis oocytes expressing these subunits. The sensitivity to ACh of the G. gallus receptor was lower than that of the R. norvegicus receptor (EC50=21.7±1.2 microM and 13.8±1.7 microM, respectively). The G. gallus a9a10 receptor shows a desensitization profile similar to that of the heteromeric a9a10 R. norvegicus nAChR. Interestingly, the oocyte's endogenous calcium dependent chloride current strongly activated by the opening of the rat a9a10 nAChR was not significantly activated by the G. gallus a9a10 nAChR, suggesting that the calcium permeability of the avian receptor is substantially lower than that of the mammalian receptor. These results indicate that the mammalian a9a10 receptor has acquired new functional properties which are different from those of non-mammalian species. Supported by NIH, HHMI, UBA and ANPCyT.

Sensorial Systems
Poster Number (238) Session II

LEARNING TUNES SPATIO-TEMPORAL PATTERNS IN EARLY OLFACTORY CODING

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The olfactory system is commonly based on a large number of generalist receptors whose combinatorial activation guarantees an almost infinite number of percepts. However, an individual animal does never encounter such wide range of stimuli. Instead, it has to optimize its sensory system to gain discrimination of the odors that are present in the reduced environment in which it exists. We use honey bees and their capacity for olfactory learning to address how experience shapes stimuli processing in the antennal lobe. Honey bee foragers learn about floral odors that are rewarded and also learn to ignore flowers that have no predictive value. They must establish if any new encountered flower is similar to a previous rewarded one or to a non-rewarded one, turning foraging decision into a fine tuned generalization-discrimination task. We performed behavioral experiments and calcium imaging of odor driven activity in the antennal lobe to study if learning modifies the perceptual boundaries used to classify a floral perfume within a rewarded or a non-rewarded flower category. We designed odor blends that mimic the variability within and between two real cultivars of snapdragon flowers. All blends could be differentiated based on the relative concentration of the components, which was more similar within cultivar than between them. Bees were trained to either generalize or differentiate between both cultivars. Odor representation was measured in projection neurons of the antennal lobe. Antennal lobe activity was modified by learning in a way that odor representations of rewarded and non rewarded flowers are more different. These data suggest that learning tunes the AL such that relevant odors become more discriminable.

FROM PSYCHOPHYSICS TO NEURAL ACTIVITY: AN INFERENCE ABOUT THE MOTION PATHWAY IN VISUAL PERCEPTION

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Recently, we showed that the spatial layout of a stimulus affects our ability to locate a motion defined boundary. However, this effect does not appear or is very weak when the task is to discriminate a transparent stimulus (Martín, Barraza, & Colombo, 2009). Both segmentation tasks would be performed by V1 and/or V2 cells (Marcar et al., 2000). In addition, it has been shown that the case of segmentation of adjacent surfaces would be mediated by a feedback from MT to these lower areas (Hupe et al., 2001). Because the effect of the spatial layout would reflect an integrative mechanism occurring in MT such was proposed by Verghese & Stone, (1997), then we may hypothesize that the difference between the two kinds of segmentation reported in our previous work could be due to the fact that transparency is not mediated by this feedback. In the case of two adjoining surfaces with different speeds, an integration process may improve the speed estimation of each surface by keeping the information of the two different speeds but, in the case of transparency, an integration in the scale of MT would blend the local signals and thus, losing the information given by the speed difference. An alternative hypothesis is that the results are just reflecting differences in the psychophysical tasks. In order to disentangle these two alternatives we devised an experiment in which we test the effect of stimulus layout on speed threshold as a function of target size. Results show that increasing the angular distance among patches reduces the speed threshold only for targets sizes larger than 0.4 deg, which suggests that transparent stimuli are not affected by the spatial integration occurring after V1/V2.

Poster Number (240) Session III

SENSORY COLLISIONS IN THE MONKEY BRAIN

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The primate brain integrates information to produce coherent cognition. This leads to different manifestations of interference when two stimuli are presented in a short temporal window: fusing them in a common percept, the exclusion of one of the two stimuli from consciousness or temporal delays in certain elements of the processing stream. Here we studied the collision of visual and auditory stimuli in the monkey brain measuring fMRI signals, injecting a contrast agent (monocrystalline iron oxide nanoparticle [MION]). MION based fMRI increases the resolution by a factor of about 5 relative to the BOLD technique, but the response function of the MION signal is considerably slower. We first show that an analysis of the phase signal of the MION response can be used to obtain time-resolved fMRI, with a resolution of few hundred milliseconds. We then use this technique to understand temporal ordering of sensory responses. The analysis of interactions between visual and auditory stimuli showed that: 1) Temporal ordering of the responses in primary and associative sensory cortices follows tightly stimulus presentation even during simultaneous presentation; 2) There is a broad large-scale cross-modality inhibition in sensory responses. 3) Few areas show a positive interaction (an auditory response which is boosted by visual stimuli or vice-versa). These areas are largely localized in the left-hemisphere. While only speculative, this may suggest that language asymmetries observed in the human brain may thus result from an architecture which integrates multi-modal information mostly localized to the left-hemisphere.

Sensorial Systems
Poster Number (241) Session III

CURRENT-DEPENDENT NOISE SOURCES IN ADAPTING AUDITORY NEURONS

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Neurons are noisy. Upon repeated presentations of a given stimulus, the output spike trains show a certain degree of trial-to-trial variability. Even primary sensory receptors, that do not receive synaptic inputs from other neurons, show variability. One fundamental question in neuroscience is to understand the source of such erratic behavior. As a first step, here we determine how the amount of noise in the output spike train depends on the input signal, in grasshopper auditory receptors. Although these neurons respond with high precision to natural conspecific songs, pure tones elicit strikingly noisy responses. Therefore, the stochastic biophysical processes involved in the cell response are more clearly revealed by pure tone stimuli. In addition, auditory receptor neurons exhibit strong spike-frequency adaptation, induced by spike-evoked adaptation currents. These currents evolve slowly in time. When stimulated with a steady, single tone, therefore, receptor neurons receive an effective input current that decreases slowly over time. Here we study a simple model neuron including adaptation effects that successfully describes the rate response of sensory auditory neurons of the locust. A relationship between the mean and the variance of the time-dependent ISI distribution allows us to characterize the noise sources in the experimental system. In particular, we find that the amount of noise depends on the transduced sound intensity in single tone experiments. Moreover, the noise level is shown to be modulated by the total amount of current entering the cell, both the current mediated by mechano-receptors involved in the transduction process and the current associated to the adaptation process.

Poster Number (242) Session III

THE SPECTRAL CHARACTERISTICS OF SOUNDS INFLUENCE THE DISTANCE PERCEPTION TO THE ACOUSTIC SOURCE

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Over the past 100 years great efforts have been made to learn the strategies used by our nervous system to estimate the spatial location of acoustic sources within the three levels of auditory space: the horizontal plane (azimuth), the vertical plane, and the distance. The acoustic cues our nervous system uses to estimate the source position in the horizontal and vertical planes are well known and have been treated in numerous works. However, little is known about the strategies used by our nervous system to estimate the distance from the sound source. Most studies of auditory perception of distance are focused on spectral changes in auditory stimulus induced by its relationship with the environment. However, we have no information about potential cues that may contain audio stimuli regardless of their interaction with the environment. In this work we present curves of distance perception in human subjects using auditory stimuli with different spectral characteristics. In the first set of experiments we show that subjects under spectrally complex auditory stimuli (white noise) perceive better the changes in the distance from the source compared to pure tones stimuli treatments. In the second set of experiments we used pure tones of different frequencies (high, medium and low). In this case, subjects perceive better the changes in the distance from the source when stimulated with a tone of 1600 Hz than when using stimuli of 700 and 4000 Hz. Therefore, we show that the spectral characteristics of sounds can significantly influence the perception of the distance from the sound source.

PROPERTIES OF THE OLIVOCOCHLEAR-OUTER HAIR CELL SYNAPSE IN THE MOUSE COCHLEA

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In the Organ of Corti, the sensory epithelia of the of the mammalian auditory system, inner hair cells (IHCs) transduce sound stimuli into electrical signals that are conveyed to the central nervous system (CNS), while outer hair cells (OHCs), by virtue of their electromotility, participate in the amplification of sound. OHCs function is modulated by efferent cholinergic olivocochlear (OC) fibers projecting from the CNS. In the present work we studied the properties of the OC synapse onto OHCs. Briefly, synaptic activity was recorded in voltage-clamped OHCs from an excised apical turn of the mouse cochlea (10-12 postnatal days) during stimulation of OC fibers with a bipolar electrode placed in the modiolar region. Activation of efferent terminals by single shocks evoked inhibitory postsynaptic currents (IPSCs) with very low rate of success (quantal content: 0.14 ± 0.03, n=30 cells). Paired-pulse protocols showed that this synapse facilitates with maximum efficacy at pulse intervals of 10 ms (facilitation index = 2.1±0.4; n=8). Accordingly, trains of stimuli at different frequencies (10-100 Hz) produced increasing levels of transmitter release. This phenomenon, together with summation of synaptic currents, resulted in an increase of OHC responses proportional to the stimulus frequency (Imax/single-shock IPSC= 5.4±1.0; 8.5±3.7; 12.3±0,8; 15.6± 1,0 for 25, 50, 60 and 80 Hz, respectively, n=2-4). These results show that this synapse can facilitate at intervals that correspond to the physiological frequencies at which OC fibers fire. This property could be relevant in coding different degrees of activation of OC fibers in response to variable sound intensities.

Poster Number (244) Session 1

THE LEVEL OF INTRINSIC ELECTRICAL ACTIVITY REGULATES NEURONAL MATURATION IN THE ADULT HIPPOCAMPUS

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Functional integration of newborn granule cells into hippocampal circuits is orchestrated by environmental signals and intrinsic programs. Not much is known about how a decrease in neuronal activity affects the development and plasticity of dendrites, axons and synaptic connections in newborn granule cells. To answer this question we designed a strategy to decrease intrinsic activity of developing neurons of the adult dentate gyrus and analyze their morphological and functional properties. We constructed a retrovirus encoding a potassium inward rectifier channel (Kir2.1) and green fluorescent protein (GFP). A non-conductive channel bearing a point mutation (Kir2.1mut) was used as negative control. The virus was delivered stereotaxically into the dentate gyrus of 6–7 week-old female mice. Mice were sacrificed 2, 3 or 5 weeks post injection (wpi) and labeled cells were analyzed by electrophysiology and confocal imaging. Kir+ neurons expressed higher levels of the immature neuronal markers doublecortin and calretinin and reduced levels of the mature marker Calbindin when compared to control cells. Kir neurons also displayed a reduced dendritic length consistent with a protracted development. In addition, electrophysiology revealed a reduced membrane capacitance, which reflects a smaller area of the plasma membrane. Afferent connectivity was studied by miniature excitatory postsynaptic currents (minis) at 5 wpi. Mini frequency was diminished in Kir cells, in agreement with the reduced number of excitatory synapses found by confocal microscopy. Our observations support the notion that electrical activity is essential for a correct timing of integration and maturation of newborn granule cells of the adult dentate gyrus.

Synaptic Trasmissions And Excitability
Poster Number (245) Session I

NEUROMODULATING EFFECT OF PREGABALIN ON NEUROTRANSMITTER RELEASE AT THE MOUSE CALYX OF HELD

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Pregabalin (PGB) is an anticonvulsant and analgesic medication. The mechanism of action of PGB has been only partially characterized; it is generally accepted that PGB subtly reduces calcium-dependent overflow of neurotransmitters in several tissues. The α2-δ type 1 auxiliary subunit of voltage-gated calcium channels is the primary high-affinity binding site for PGB. However, the cellular and molecular basis of its inhibitory action on neurotransmitter release is unknown. Here, we studied the effect of PGB on the Calyx of Held-Medial Nucleus of the Trapezoid Body (MNTB) synapse in brainstem slices using whole cell patch clamp. Excitatory postsynaptic currents (EPSCs) and presynaptic calcium currents were recorded. The amplitude of EPSCs was reduced by a 30 (500 µM, 15 min). During high frequency stimulation PGB has no effect on short term depression but a faster rate of recovery from synaptic depression at 100 Hz was observed with PGB. We found a decrease in the frequency of minis in +PGB vs. -PGB conditions and an enhancement of pair pulse facilitation. These data suggest a presynaptic effect of PGB. On the other hand, P/Q-type calcium channels mediated currents decreased in the presence of PGB evoked by either action potential trains or long duration square pulses (I-V protocol). Calcium current activation curves, showed no differences. However, two pulses inactivation protocol shows a larger rescue of the inactivation mediated by PGB. These results suggest that PGB: 1) blocks presynaptic P/Q-type mediated calcium currents that would reduce synaptic transmission, and 2) accelerates the recovery of P/Q channels from inactivated states that would allow for shorter recovery times after high frequency synaptic stimulation

PRESYNAPTIC RESTING MEMBRANE POTENTIAL CONTROLS SYNAPTIC STRENGTH AND TIMING AT THE IHC RIBBON SYNAPSE

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In the mammalian cochlea, inner hair cell (IHC) are responsible for the detection and transduction of sound signals into electrical potentials. This information is then transmitted to the brain through its afferent synapse. In order to code for fast and transient acoustic signals, this synapse requires high efficiency and temporal precision. Simultaneous whole cell patch clamp recordings where performed from IHCs and contacting afferent dendrites in excised organs of Corti from neonatal rats. The afferent synaptic response was studied while manipulating IHC membrane potential and calcium influx. We have previously characterized the voltage dependence of release. In response to long (1 s) IHC depolarizations, the afferent fiber response showed synaptic depression. When IHCs were depolarized from a holding potential of -89 mV to -29 mV for only 2 ms, a high failure rate for release was found. Successful responses were small in amplitude and showed long synaptic delays (3-4 ms). If a conditioning step to an intermediate potential (~-50 mV) was applied to the IHC before the test pulse, a significant increase in the probability of release was observed. Additionally, the delay of the response was shorter (~1.5 ms). Similar results were found when conditioning was induced with a paired pulse protocol. These results suggest that release at the IHC ribbon synapse can be modulated by the presynaptic membrane potential resembling facilitation in the CNS. IHC physiological resting potential (~-60 mV) allows for transmitter release in the absence of any sound stimulation and, as we show here, may produce a steady facilitated regime on the synapse. This might be a mechanism by which precision of exocytosis at this synapse is improved.

PREGABALIN EFFECT ON TRANSMITTER RELEASE AT THE MOUSE NEUROMUSCULAR JUNCTION

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Pregabalin (PGB) is an anticonvulsant and analgesic medication which was initially synthesized as a GABA analogous but strikingly had no effect on its receptors. The primary high-affinity binding site for PGB is the α2-δ auxiliary subunit of voltage-gated calcium channels but the cellular and molecular details of its action are completely unknown. The main objective of this work is to understand the effect of PGB at the mouse neuromuscular junction and to characterize its modulation on vesicular release and recycling. Experiments were performed on the levator auris muscle of Swiss mice and fluorescence microscopy of FM2-10 labeled synaptic vesicles were used to reach our aim. We studied the effect of PGB at two different concentrations on the distaining of a full neuromuscular terminal FM2-10 loaded. Results showed that PGB 1mM treatment held up the kinetic decay significantly. The fluorescence distaining was fitted to a biexponential function that models first-order release processes when two different time constants are involved. These time constants are associated to different vesicle pools of different size. Both time constants augmented with the presence of the drug and the size of the fast pool increased versus the control at 1mM concentration. PGB 100 µM had no effect on the distaining decay suggesting dose response behaviour. To study whether PGB is altering both P/Q and L channels, we performed experiments with the L channel blocker nitrendipine. In addition, electrophysiological experiments will be done to contrast the results obtained with imaging technique. All this evidence suggests that PGB acts presynaptically reducing neurotransmitter release.

Synaptic Trasmissions And Excitability
Poster Number (248) Session 11

PHYSIOLOGICAL RELEVANCE OF IMMEDIATELY RELEASABLE POOL RECOVERY, AND ITS CA2+ MODULATION

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Inside ready releasable pool, there is in chromaffin cells a small group of vesicles named immediately releasable pool (IRP), which can be release by short pulses due to the proximity between vesicles and P/Q Ca2+ channels. This work analyzes the effect of cytosolic Ca2+ on IRP refilling, and how stimulation frequency affects the maintenance of IRP exocytosis. IRP size was estimated by patch clamp cell capacitance measurements at various free Ca2+ concentrations in patch pipette. Surprisingly, pipette Ca2+ concentrations between 0 to 300nM show no significant change in IRP size (32±1fF, n=83). We next studied the effect of Ca2+ on IRP recovery after the application of a 50 ms depolarization to deplete completely the pool. The addition of 200 nM free Ca2+ to the patch pipette increased the initial recovery velocity in 37 respect to no calcium added (at 2 s, 0.35±0.05 vs 0.57±0.06, p0.02). These results suggest that while IRP is saturated in basal conditions, the refilling after depletion depends on cytosolic [Ca2+]. By IRP definition, a single action potential (AP) should release just some vesicles from IRP. An AP like depolarization (APld) induced a capacitance jump of 8.9±0.7fF (35 of IRP), which was significantly decreased to 3±1fF (p0.02) by a P/Q calcium channel blocker, as expected. Because the physiological AP firing rate varies from 0.5 to 10 Hz, we wonder if the refilling velocity of IRP was enough to sustain secretion at this frequency range. By application of paired APld separated by variable time intervals, we found that for intervals between 200ms (5Hz) and 10s (0.1Hz) exocytosis recovers with an exponential time constant of 0.8±0.1s, but a facilitation process was found for time intervals 200 ms.

EXPANDING CORTICAL DYNAMIC RANGE BY COORDINATING INPUT SPECIFIC EXCITATION WITH GLOBAL INHIBITION

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The cortex is sensitive to weak stimuli and responds to stronger inputs without saturating, but the mechanisms that enable this wide range of operation are not fully understood. We have addressed this issue in rat hippocampal slices where we monitored the progressive recruitment of CA1 pyramidal cells in response to stimuli of increasing strength delivered to the Shaffer collaterals, their main excitatory afferent input. We found that recruitment of cortical neurons is staggered over a wide range of intensities because neurons activated by strong stimuli necessitate several-fold larger excitation to spike than neurons recruited by weaker inputs. Whereas the staggering results from an increase in widespread, basket cell-generated inhibition, the order of neuronal recruitment is set by local differences in afferent excitation. This mechanism drastically expands the dynamic range of distinct cortical populations without requiring changes in neuronal gain. Furthermore, it enables the recruitment of individual neurons at either the low or high end of the stimulus range, depending on the combination of active excitatory inputs.

RELIABLE ACTIVATION OF IMMATURE NEURONS IN THE ADULT HIPPOCAMPUS

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Neurons born in the adult dentate gyrus develop, mature, and connect over a long interval that last from six to eight weeks. It has been proposed that, while developing, young neurons play a relevant role in hippocampal signal processing owing to their distinctive electrical properties. However, it has remained unknown whether immature neurons can be recruited into a network before synaptic and functional maturity have been achieved. To address this question, we used retroviral expression of GFP to identify developing granule cells of the adult mouse hippocampus. We investigated on young and mature dentate granule cells the balance between afferent excitation and inhibition, intrinsic excitability, and recruitment into the hippocampal circuitry using patch clamp recordings in acute slices. We found that young neurons are highly efficient in transducing ionic currents into membrane depolarization due to their high input resistance, which decreases substantially in mature neurons as the inward rectifier potassium (Kir) conductance increases. Moreover, excitatory inputs onto young neurons are significantly weaker than those of mature cells. In addition, preliminary data shows that inhibitory afferents to young neurons exhibit smaller strength than that of mature dentate granule cells. We next evaluated spiking probability evoked by stimulation of excitatory afferents in the presence of GABA receptor antagonists. Under these conditions we found that young and mature neurons exhibited similar firing behavior, indicating that the differences in excitatory drive of young and mature neurons are compensated by changes in membrane excitability rendering an equalized firing activity. The role of the inhibitory circuitry on the recruitment of young neurons in the dentate gyrus is currently being investigated. Our observations demonstrate that the adult hippocampus continuously generates a population of highly excitable young neurons capable of information processing.

Synaptic Trasmissions And Excitability
Poster Number (251) Session III

DELAYED SYNAPTOGENESIS BY THE β-AMYLOID PEPTIDE IN THE ADULT BRAIN

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Clinical hallmarks of Alzheimer´s disease (AD) have been related to extracellular deposits of β-amyloid peptide (Aβ) in the cerebral cortex and hippocampus as amyloid plaques. Aβ peptide is the cleavage product by beta and gamma secretase of a bigger transmembrane protein known as the amyloid precursor protein (APP). Although AD was described more than 100 years ago, its pathogenic mechanism remains unclear. In humans and animal models of AD, cognitive decline becomes evident much earlier than amyloid plaque formation. There is also evidence of dendritic spine abnormalities in a variety of mental retardation syndromes. In this work we propose that Aβ affects synapse formation, and this mechanism is responsible for the early cognitive alterations seen in AD. We use adult neurogenesis to study the effects of Aβ on de novo synaptogenesis by retrovirally traducing APP and/or reporter proteins in newborn neurons of the adult hippocampus in two different models: 1- Transgenic mice Tg2576 express the Swedish mutation of APP, which produces elevated levels of Aβ across the brain. In order to observe the degree of excitatory inputs that newborn neurons reach in this context we are studying dendritic spine density in young and old animals. Preliminary results show no differences in spine density at any of the studied groups. 2-APP overexpresion in neurons of wild type mice for studying the cell-autonomous effects of Aβ. In this model we are currently performing electrophysiological recordings to monitor the function and integration of these neurons at different developmental stages. Preliminary results show a putative delay in the development and integration of neurons infected with an amylidogenic construction.

Poster Number (252) Session III

ADENOSINE MODULATES THE FAST RELEASE VESICLE POOL AT MOUSE NEUROMUSCULAR JUNCTION

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At mouse neuromuscular junction (NMJ) there are two functionally distinct synaptic vesicle pools according to FM dyes loading/ unloading patterns: a fast destaining vesicle pool which is rapidly recycled during high frequency stimulation and is modulated through L channel, and a slow destaining vesicle pool which is recycled during prolonged stimulation and keeps on refilling after end of stimulation. It has been reported that presynaptic receptors play a role in adjusting the pattern of neuromuscular transmission. Modulation of Ca2+ currents at mammalian NMJ occurs through hydrolysis of ATP to adenosine, followed by the activation of adenosine inhibitory (A1 and A3) and excitatory (A2A and A2B) receptors. However, whether adenosine may regulate vesicle recycling is a question which has not been addressed until now. We used fluorescence microscopy of FM2-10-labeled synaptic vesicles and electrophysiological recordings to examine whether adenosine has a role on vesicle recycling. We found that the quantal content significantly decreased by 40 in presence of adenosine and increased by 25 in presence of DPCPX (A1 antagonist) at high (50 Hz) frequency stimulation, suggesting an inhibitory effect of either exogenously applied or endogenous adenosine. We studied the effect of adenosine and DPCPX on the amount of FM2-10 loaded during a stimulation protocol that preferentially load the fast destaining pool (5 s at 50 Hz). In both cases, we found that loading was lower than control experiments. However, dye unloading during a second round of stimulation was faster when the dye was loaded in presence of DPCPX but not in presence of adenosine. These results showed that: 1) exogenously applied and endogenous adenosine has an inhibitory effect on transmitter release and reduces the size of the recycling pool, 2) the antagonist of the adenosine inhibitory receptor, DPCPX, increases the neurotransmitter release recycling vesicles towards a fast release pool and 3) in presence or absence of adenosine, there are activity-dependent differences in endocytosic mechanisms. Adenosine, as L channel, modulates vesicle recycling.

Synaptic Trasmissions And Excitability
Poster Number (253) Session III

COCAINE ACUTE "BINGE" ADMINISTRATION ABNORMALLY ENHANCE THALAMIC GABERGIC SYNAPTIC TRANSMISSION IN MICE.

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Attentional and sensorial processing deficits in cocaine addicts are relevant to cocaine abuse treatment. Thalamocortical system is involved in sensory processing, however, little is known about possible mechanisms mediating cocaine effects on the thalamocortical circuitry. Thalamic ventrobasal nucleus (VB) is known to be densely innervated by GABAergic terminals from reticular neurons. Here we studied whether cocaine acute "binge" (3x15mg injections 1 h apart) would enhance GABAergic feed-back transmission from reticular to VB neurons. In vitro, voltage clamp recordings of VB thalamic neurons in the presence of TTX, AP5, CNQX showed higher levels of GABA-A-mediated synaptic transmission lasting over 24 hours after last injection of cocaine. Indeed, mIPSCs recorded from VB neurons presented an increment in amplitudes and higher frequencies compared to saline, partially reverted after 24 hr. Also immunohistochemical experiments were performed on brain slices containing primary somatosensory cortex (S1) and thalamic nuclei using antibodies for GAD 65/67 in saline and cocaine groups. No significant differences were found on immunostaining levels. Bath application of the D2/D3-agonist Ropinirole enhanced GABA-A minis amplitudes while reducing their inter-event intervals. Thus, these results suggest a possible role of D2/D3 receptors in VB's GABA-A minis enhancement induced by cocaine. Supported by: ANPCyT PICT 2007-01009 and PIDRI-PRH 2007 (to Dr. Urbano), Wellcome Trust, 068941/Z/02/Z; grant#6220; UBACYT X223; ANPCyT PICT2006-199 (to Dr. Uchitel), NIH NS13742 (to Dr. Llinás) and PICT 31953 (ANPCyT), PIP 5870 (CONICET) and UBACYT M073 (to Dr. Wikinski).

Synaptic Trasmissions And Excitability

Poster Number (254) Session III

MODULATION OF ACH RELEASE AT THE EFFERENT-IHC SYNAPSE BY PRESYNAPTIC GABAB RECEPTORS

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Before the onset of hearing, inner hair cells (IHCs) of the mammalian cochlea are transiently innervated by medial olivocohlear (MOC) efferent fibers. This synapse is cholinergic, inhibitory and mediated by the α9α10 nicotinic receptor. Although ACh is the main transmitter released at this synapse, there is evidence showing that GABA is present at MOC synaptic terminals. However, no GABAergic currents have been recorded so far in IHCs. Moreover, the possibility that synaptically released GABA could be modulating the cholinergic input at MOC-synapses by acting on presynaptic GABAB receptors has not been investigated yet. In the present work, we evaluated the effect of two modulators of GABAB receptors on the quantal content of transmitter release at the MOC-IHC synapse. Postsynaptic currents, evoked by electrically stimulating the efferent fibers, were recorded in voltage-clamped (-90 mV) IHCs from acutely isolated mouse organs of Corti. Quantal content was significantly increased by the antagonist CGP35348 at 1uM (55 ± 19 p 0.05) and significantly decreased by 1uM of the agonist Baclofen (68 ± 8 p 0.001). Our results suggest GABA might be exerting a negative feedback control on the release of ACh through presynaptic GABAB receptors.

Motor Systems
Poster Number (255) Session III

EVIDENCE OF DINAMIC IN THE VOCAL TRACT OF SUBOSCINE BIRDS

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The vocal system of the birds consists of two blocks: the vocal organ, called syrinx, where the sound is generated; and the group of cavities located from the syrinx exit to the peak (vocal tract), responsible for the spectral filtering of the sound.

In the last years, important progress has been made in the understanding of the syrinx dynamics, while little is known about the importance of a tunable vocal tract coupled to the bird's vocal organ. This lack of attention could be due in part to the fact that many species are characterized by the tonality of their songs, with minimal, if any, spectral richness. However, precise matching of the vocal tract resonances to syringeal frequencies has been recently reported for some species of songbirds, characterized by spectrally poor songs. Here we investigated the role of the vocal tract in the spectrally rich calls of a non-oscine bird, reconstructed the dynamics of its vocal tract, and synthesized complete vocalizations from air sac pressure measurements.

Poster Number (256) Session III

ELECTROPHYSIOLOGY OF RAT VIBRISSAL SYSTEM: ANALYSIS OF MULTIFIBER SIGNALS, TEXTURE DISCRIMINATION, DIGITAL PROCESSING TECHNIQUES AND NEURAL CODE

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When rats acquire sensory information by actively moving their vibrissae, a neural code is manifested at different levels of the sensory system. Behavioral studies in tactile discrimination agree in that the rats can distinguish surfaces of different roughness by whisking their vibrissae. It has been demonstrated, recently, that a texture code in peripheral afferent nerve activity of the vibrissal system would exist [1] and that the firing rate would be the encoding mechanism that underlies the texture discrimination in primary somatosensory cortex [2]. In these investigations we characterized some aspects of texture sensing in anesthetized rats during active touch. The multifiber discharge from a deep vibrissal nerve during the sweeps different materials (wood, metal, acrylic, sandpaper) with similar degrees of roughness and different grain size were analyzed. Vibrissal movement was induced with two-branch facial nerve stimulation. We consider the change pressure against the vibrissa as a way to improve the tactile information acquisition. The signals were compared with a reference signal (control), vibrissa sweeping the air. We have also explored the existence of new temporal patterns based on 'events' related to texture neural code. Two new methods for afferent activity analysis were proposed: a Time-Frequency analysis and Inter-event Time analysis. RMS values and power pectrum density (PSD) have also been used in the analyses. We also proposed a method based on information theory to quantifying the neural code. As roughness increased, the RMS values also increased in almost all cases, thus suggesting a direct relation. In addition, a better discrimination performance in the retraction phase was observed. PSD analysis showed differences in the frequency components of maximum energy (Fmax) among sweeping situations. The Time-frequency analysis

allowed to compare Fmax throughout the time. Differences in protraction and retraction phase were found. Likewise, varying the pressure could represent a behavioral strategy that improves the information acquisition for texture discrimination. Finally, we have demonstrated and quantified for the first time the existence of temporal patterns related to the roughness information by analyzing the multifiber activity (average activity) in one vibrissa innervation.

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Index by session

INDEX BY SESSION

Session 1

Cognition, Behavior And Memory

on frustration, anxiety and physical pain responses in rats.

P18.- Dagnino, Bruno - From local to global: identifying strategic shifts of attention and goals in a rapidly changing setup

P19.- Daneri, M. Florencia - Effect of lesions of the medial pallium on the use of visual cues in spatial learning in amphibians

P20.- De Giovanni, Laura Noemi - The NMDA antagonist MK-801 blocks stress-induced reinstatement in the conditioned place preference model

P21.- de la Fuente, Verónica - Molecular mechanisms in the switch between reconsolidation and extinction of fear memory

P22.- Depino, Amaicha Mara - Behavioral alterations in mice lacking SPARC

P23.- Dorman, Guido - Spatial novelty interferes with long-term memory persistence during a late critical time window

P24.- Elias Costa, Martin - On making the wrong choice: Why the unconscious could prevent you from winning the Peron Cup.

P25.- Etchemendy, Pablo Esteban - Thinking about chess: An ethological approach to decision-making

P26.- Falibene, Agustina - Serotonin and feeding behaviour in a nectivorous ant

P27.- Farías Sarquís, Yamila - Mild Cognitive Impairment and Normal Aging. Quantitative differences in the cognitive and behavioral profiles

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P86.- Depetris Chauvin, Ana - The electrical silencing of pacemaker neurons cause reversible disruption of circadian locomotor activity in Drosophila melanogaster

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P103.- Alaimo, Agustina - Relevance of OPA-1 in the manganese induced mitochondrial apoptotic pathway

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P105.- Aparicio, Evangelina - Notch Pathway and the Effect of Apotransferrin on Remyelination

P106.- Avilés-Reyes, Rolando Xavier - Reactive gliosis after brain ischemia is reduced in animals previously exposed to an experimental model of sleep apnea by intermittent hypoxia

P107.- Battista, Ariadna - Extracellular ADP regulates lesion-induced cell proliferation and death in the zebrafish retina

P108.- Beauquis, Juan - Altered hippocampal neurogenesis in a transgenic mouse model of Alzheimer's Disease (AD). changes induced by long term exposure to an enriched environment (EE).

P109.- Belingheri, Ana Verónica - Rapid Endocytosis in Mouse Chromaffin Cells

P110.- Bello Gay, Estefanía - Mice lacking presynaptic dopamine D2 autoreceptors display hyperactivity and increased motivation for food reward

P111.- Bernabó, Guillermo - CG6115, a gene involved in progressive neurodegeneration

P112.- Bernis, Maria Eugenia - Axogenic effect of WNT-3a factor in cultured hippocampal neurons.

P113.- Boffi, Juan Carlos - Mutational analysis of the agonist binding site of the á9á10 Nicotinic Cholinergic Receptor.

P114.- Cromberg, Lucas Eneas - Chemotactic effects of Urokinase-type Plasminogen Activator (uPA) on postmitotic neurons and growth cones in the developing central nervous system

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P164.- Bavassi, Luz - Nontrivial features of sensorimotor synchronization predicted by a mathematical model for finger tapping

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P192.- Caceres, Lucila Guadalupe - Neuroprotective effect of 17 â-Estradiol on learning and memory processes affected by neonatal X-Radiation

P193.- Calero, Cecilia I - Functional studies on the mechanisms underlying redox modulation of GABAc receptors.

P194.- Carpentieri, Agata R - Melatonin prevents apoptosis triggered by oxidative stress in retinal ganglion cell culture.

P195.- Cid, Mariana Paula - Participation of the GABAergic system on the glutamate release of synaptosomes from animals with Experimental Autoimmune Encephalomyelitis (EAE)

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P198.- Cuesta, Santiago - Antioxidant status in rat´s brain areas after exposure to sodium metavanadate

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P29.- Federman, Noel - Studying the role of transcription factor acetylation during memory consolidation

P30.- Feld, Mariana - Behavioral and molecular characterization of a triple transgenic mouse model of Alzheimer's disease.

P31.- Ferreira, Tatiana - Dorsal striatum lesion disrupts conditioned somatomotor but

P32.- Ferrer, Roque - Previous experience with defensive behaviours in threatening environments might modulate active behaviours in the Forced Swimming Test.

P33.- Freidin, Esteban - Consummatory induction through postingestive consequences but not S-S association between subsequent foods

P34.- Frenkel, Lia - Neuroanatomic distribution of angiotensin II-like neuropeptide within the central nervous system of the crab Chasmagnathus. Physiological changes triggered by water deprivation.

P35.- Fustiñana, María Sol - A pavlovian-conditioning in the crab

P36.- Garagoli, Fernando - Disrupting memory persistence

P37.- Giachero, Marcelo - The phase of Labilization/Reconsolidation updates new aversive information to a previously consolidated fear memory.

P38.- Goldin, Andrea - Mate Marote: Interacting with childrens minds

P39.- Gonzalez, Patricia - Molecular mechanisms involved in the

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P40.- González, María Carolina - Persistent memories induce immediate early genes expression in the cortex

P41.- Graziano, Martín - Revisiting the unlimited capacity and pre-attentive view of iconic memory: cognitive and neurophysiologic estudies

P42.- Graziano, Martín - Parsing a perceptual decision in a sequence of moments of thought

P43.- Hepp, Yanil - Localized NMDA receptor ablation as tool for memory dissection in Chasmagnathus granulatus

P44.- Iurman, Mariana G. - Instrumental responses of the common toad (Bufo arenarum) according to different external saline solutions

P45.- Justel, Nadia - Sexual Hormones and Frustration

P46.- Kamienkowski, Juan Esteban - Brain Mechanisms of Information Integration in a Visual Scene

P47.- Katche, Cynthia - A delayed wave of c-Fos expression in the dorsal hippocampus is involved specifically in persistence of long-term memory storage

P48.- Klappenbach, Martín - Dopamine would be necessary for aversive learning in a crab

P49.- Krawczyk, María - Nicotinic cholinergic mechanisms on memory reconsolidation of an inhibitory avoidance response in mice.

P50.- Kufa, Maria del Pilar - Assessment and Follow-up of the infant cognitive and neurodevelopment of babies who born in high and middle risk.

P51.- Landmann, Claire - A fronto-parietal network mediates the predictive activation of the mirror system in response to an abstract cue

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P55.- Martínez, M. Cecilia - Do memories compete for proteins

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P122.- Franco, D.Lorena - ENA/VASP downregulation triggers cell death by impairing axonal maintenance in hippocampal neurons

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P124.- Galvani, Geronimo - Nitric Oxide Synthase in the brain of wild bees

P125.- Goitia, Belén - Modulation by iron of the expression of transcription factors involved in the peripheral nervous system myelinogenesis

P126.- Gonzalez, Laura E - Amyotrophic Lateral Sclerosis auto-antibodies and absence of P/Q-type calcium channels

P127.- González Inchauspe, Carlota - Differential consequence of gain-of-function FHM1 Mutation on neurons in knock-in mice depending on the duration of the action potential.

P128.- Gorojod, Roxana Mayra - The lysosomal pathway: a new strategy in manganese-induced cell death

P129.- Heredia, Florencia - Aâ-toxicity in neurons requires APP-dependent signaling through Gâã subunit of Go protein

P130.- Hinckelmann, María Victoria - Early endogenous modifications during the neuroprotection of Parkinson's disease induced by Enriched Environment

P131.- Lorenzo, Alfredo - Interaction of Ab and APP analysed by using different cell types.

P132.- Luchelli, Luciana - NPSAX: a novel structure for mRNA regulation at synapse

P133.- Martínez, Jimena - -synuclein translocation to mitochondria enhances free radical formation

P134.- Martínez Vivot, Rocío - De-differentiation of Schwann cells and iron uptake. A closer look.

P135.- Maschi, Dario - A novel translational regulation pathway that involves Smaug1 and Nanos1 regulates synapse biogenesis and function in mammals.

P136.- Mathieu, Patricia - Role of immune signals on the survival, differentiation and proliferation of transplanted aNSC

P137.- Miranda, Gisela - Ceramide-1-phosphate: a new mediator of proliferation and differentiation of retina photoreceptor neurons

P138.- Monaco, Sandra - Melatonin Prevents apoptosis of Photoreceptors during development in vitro

P139.- Piantanida, Ana Paula - Isolation and characterization of adult neural stem cells from the SVZ for cell-based therapy for Parkinson´s disease

P140.- Piantanida, Ana Paula - Characterization of adult neural stem cells from the SVZ after different cultivation times: differentiating role of TGF-beta

P141.- Rapacioli, M - Immunohistochemical characterization of cortical developmental stages in the chick optic tectum

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P168.- Rossi Pool, Román - Hebbian Plasticity and Homeostasis in a Model of Hipercolumn of the Visual Cortex

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P178.- Dionisio, Leonardo - The neuronal GABAergic system in human lymphocytes

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P180.- Gordillo, Mauricio - Adrenergic agents modify ovarian P450

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P248.- Marengo, Fernando D. - Physiological Relevance of immediately releasable pool recovery, and its Ca2+ Modulation

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P250.- Mongiat, Lucas A. - Reliable Activation of Immature Neurons in the Adult Hippocampus

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P57.- Mc Cabe, Sofia - Behavioral pharmacology of octopamine in a Neotropical stingless bee, Melipona scutellaris

P58.- Molinas, Julieta - Visually mediated decisions of the escape direction in the crab Chasmagnathus

P59.- Mongi Bragato, Bethania - Preproenkephalin knockout mice did not show sensitization to the behavioral effects of cocaine.

P60.- Monti, Carolina - Changes in hippocampal arc protein expression and synaptic plasticity by the presentation of contextual cues linked to drug experience

P61.- Moreira, Karin - Haloperidol prevents memory deficit induced by sleep deprivation in rats

P62.- Mota, Natalia - Graph analysis of psychotic dream reports: quantitative differences between schizophrenia and mania

P63.- Navajas, Joaquín - Implicit preferences and gaze in the course of a decision

P64.- Pardi, Belén - Increased susceptibility to deleterious effects of stress exposure during neurodevelopment.

P65.- Pautassi, Ricardo M - Operant self-administration of alcohol and sucrose in adolescent rats

P66.- Pérez-Cuesta, Luis María - Reconsolidation and extinction of memory in the crab: mutual exclusion or co-existence

P67.- Pedetta, Silvia - Serotonin and appetitive memory

P68.- Rodríguez, María Laura C. - Clonazepam improves memory when administered contingent upon reconsolidation in humans

P69.- Rodriguez, Jennifer - Development of a 3D tracking device based on two Nintendo Wii controllers

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P72.- Shalóm, Diego E. - Hand movements in a natural task as a window to cognition

P73.- Slipczuk, Leandro - BDNF activates mTOR to regulate GluR1 expression required for memory formation

P74.- Snitcofsky, Marina - Two Open Field exposure facilitates performance in an Inhibitory Avoidance task

P75.- Suárez, Luis Daniel - In search of the mechanisms that differentially determine long-term memory storage and expression

P76.- Tabullo, Angel Javier - P600 effects in an artificial grammar learning task: modulation by frequency of trained syntactic structure

P77.- Velazquez, Fernanda - Superior encoding of information with moral content

P78.- Verónica, Coccoz - Memory improvement by stress during reconsolidation in humans.

P79.- Vigliecca, Nora Silvana - Is the folstein's mini mental test an aphasia test

P80.- Vigliecca, Nora Silvana - Concurrent and concept validity-study of the Brief Aphasia Evaluation (BAE) in patients with lateralized encephalic lesions

P81.- Villarreal, Mirta - The neural substract of gesture recognition within and without a natural visual context

P82.- Wainselboim, Alejandro Javier - Inferential learning of new

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P143.- Rodríguez Celín, A - Cortico-angiogenesis dynamics in the developing chick optic tectum corticogenesis

P144.- Rozés Salvador, Victoria - Interaction of Aâ and APP analysed by using different cell types.

P145.- Sanchez, Emilse Silvina - Pregnancy and opioid addiction treatment: Buprenorphine affects myelination in the developing brain

P146.- Sanchez, Susana Inés - Potential role of Angiotensin II AT2 receptors in purkinje cells migration.

P147.- Sanchez, Emilse S. - Pregnancy and opioid addiction treatment: BUPRENORPHINE affects myelination in the developing brain

P148.- Sapienza, Carla Elisa - Melatonin induces apoptosis in C6 glioma cells. Therapeutic Implications.

P149.- Saraceno, G. Ezequiel - Neuroprotective effects of 17 beta Estradiol on CA1 hippocampal area of perinatal asphyctic rats

P150.- Saraceno, G. Ezequiel - M6a Glycoprotein is involved in neuronal plasticity after perinatal Asphyxia

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P154.- Tau, Julia - Trophic stimulation of embryonic cells from rat corpus striatum

P155.- Trinchero, Mariela F. - An activity-dependent anatomical gradient for neuronal development in the adult hippocampus

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P159.- Wenker, Shirley - Erythropoietin differential action on mature and immature SH-SY5Y cell cultures

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P185.- Ramallo, Martin - The role of arginine vasotocin in reproduction and social Behavior in the cichlid fish Cichlasoma dimerus

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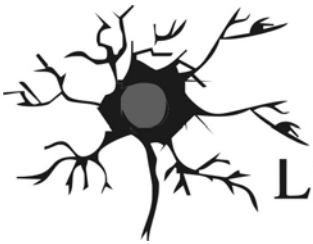

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Impreso en agosto de 2009
en los talleres gráficos de Pronto GRÁFICA
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