The paradox of aerobic glycolysis in the brain

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Some three decades ago it was first observed that neural activity stimulates the fermentation of glucose to lactate despite normal oxygen availability, a local phenomenon termed aerobic glycolysis that is routinely exploited for the purposes of brain mapping by FDG-PET and fMRI. Neurotransmission is energetically expensive and so it is highly counterintuitive that active neurons should prefer fermentation, which produces a mere 6% of the ATP that can be generated during glucose oxidation. Since, it has been reported that the areas of the brain where aerobic glycolysis is strongest are also those most prone to Amyloid Beta peptide deposition and therefore the phenomenon has acquired a clinical interest. While the physiological and pathophysiological meanings of aerobic glycolysis in the brain remain under scrutiny, my group has focused on the underlying mechanisms. We have developed genetically-encoded optical probes and *ad hoc* methods to monitor energy metabolism in real-time with single-cell resolution and have used these technologies *in vitro* an *in vivo* to characterize the metabolic events that accompany neurotransmission. The results suggest a profound division of labor between neurons and glial cells, in which neurons control the production and release of astrocytic lactate by means of intercellular signals acting on different spatial and temporal domains, including glutamate, potassium and ammonium. Astrocytes maintain a dynamic reservoir of cytosolic lactate that is released upon neuronal demand via a novel lactate-permeable ion channel stimulated by depolarization and by lactate itself. Lactate, once considered a waste product of hypoxic cells, is now emerging as a fuel for healthy neurons and as a gliotransmitter.

Astrocyte-neuron metabolite transfer and the central regulation of circulating glucose levels

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The maintenance of glucose homeostasis, a vital necessity for mammals, depends on the concerted interaction of various organ systems including the central nervous system. The mediobasal hypothalamus (MBH) is a key area involved in the regulation of energy metabolism and a component of a brain-liver circuit that controls the endogenous production of glucose. Ample evidence indicates that this circuit contributes to the maintenance of euglycemia. Neurons in the MBH are sensitive to increases in the levels of circulating nutrients and respond to them generating vagal outflow to the liver in order to curtail glucose output. The metabolism of pyruvate to lactate in astrocytes and its subsequent transfer to neurons has been proposed to play an important role in brain energy metabolism. This metabolite transfer is carried out by the astrocyte-neuron lactate shuttle (ANLS) system. Through a combined biochemical, molecular and physiological approach in live rodents, we performed various metabolic interventions to examine the involvement of the ANLS in the hypothalamic *nutrient sensing* of glucogenic amino acids. Our studies support the novel concept that the ANLS is a component of a nutrient sensing mechanism that responds to proline (and pyruvate) to inhibit the production of glucose by the liver. Furthermore, the glucoregulatory action of proline is a previously unrecognized form of hypothalamic amino acid sensing. Lastly, we determined that the consumption of diets enriched in saturated fat leads to a sustained faltering of this regulatory loop favoring the development of glycemic dysregulation.

Circadian desynchronization causes the metabolic syndrome via a disbalance of the autonomic nervous system.

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Recent studies show that frequent violations of conditions set by our biological clock, the suprachiasmatic nucleus (SCN), such as shift work, jet lag, sleep deprivation or simply eating at the wrong time of the day, may have deleterious effects on health. This infringement, also known as circadian desynchronization, is associated with chronic diseases like diabetes, hypertension, cancer and psychiatric disorders. Here we will evaluate evidence that these diseases stem from the need of the SCN for feedback, to fine-tune its output and adjust physiological processes to the requirements of the moment. This feedback can vary from neuronal or hormonal signals from the liver to changes in blood pressure. Desynchronization renders the circadian network dysfunctional, resulting in a breakdown of many functions driven by the SCN disrupting core clock rhythms in the periphery and disorganizing cellular processes that are normally driven by the synchrony between behavior and peripheral signals with neuronal and humoral output of the hypothalamus. Consequently we propose that the loss of synchrony between the different elements of this circadian network as may occur during shiftwork and jet lag is the reason for the occurrence of health problems.

Optogenetic activation of nucleus accumbens' axon fibers transiently stops consumption of sucrose

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The over consumption of sucrose and other highly rewarding foods is one of the main causes for the current epidemic of obesity. One important component of a network involved in the liking, wanting and control of sucrose feeding is the anterior nucleus accumbens shell (aNAc shell). In particular, in rats, it has been shown that electrical stimulation of aNAc shell fibers transiently stops their intake of sucrose. However, details of this activation, as well as its effect on areas to which the aNAc is connected on feeding, reward and satiety require further exploration. To investigate these aspects we used transgenic mice that expressed a light-gated ion channel (ChR2) in glutamatergic fibers in the aNAc shell while recording from aNAc neurons and in two areas to which it is connected; the medial Prefrontal Cortex (mPFC) and the lateral hypothalamus (LH). This was done while the animals freely licked for sucrose. We found that in the ChR2 mice, but not their wild type littermates, that a 1 s photostimulation of the glutamatergic aNAc's fibers immediately stopped sucrose feeding, and that with increasing frequency (4-20 Hz) and intensity (1.5-15 mW) the resumption of feeding was delayed. Behavioral studies revealed that activation of glutamatergic afferents were independent of nutritional value and rewarding in the sense of wanting), since sucrose-naïve ChR2 mice rapidly learned to avidly lick an empty sipper to self-photostimulate. The enhancement of the wanting aspect of reward was also evidenced when ChR2 mice freely licking for sucrose were stimulated intermittently at 20 Hz in three 5 minute blocks and showed, during the three unstimulated blocks, a significantly greater increase in sucrose consumption than the WT animals, even to the point of satiety. Optical stimulation of glutamatergic aNAc fibers evoked both activation (the majority) and inhibitory single unit responses that covaried with the optical stimulation in the aNAc, LH and mPFC. Analysis of the latencies between the laser activation and the earliest significant change in the firing rate showed that the aNAc exhibited two peaks, a smaller early one at 11 ms, reflecting the direct activation, and a delayed but larger one at 33 ms that likely reflects responses returning from the LH and mPFC. In summary, we have characterized components a network involved in the wanting and learning aspects of feeding that do not depend on nutritional value or satiety. In summary, our data demonstrate that optical activation of excitatory afferents of the aNAc shell is rewarding (and it can attribute incentive salience to licking an empty sipper), but paradoxically it can also transiently stops sucrose feeding, independently of nutritional value, and without affecting satiety or the total amount of sucrose consumed, thus our data uncover a strong limitation for the use of electrical stimulation of NAc's glutamatergic fiber for the treatment of obesity.

Reducción de la actividad dopaminérgica cortical inducida por beta-amiloide está relaciona con deficiencias en la plasticidad sináptica y la cognición en un modelo murino de enfermedad de Alzheimer

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La enfermedad de Alzheimer (AD) es una enfermedad neurodegenerativa que se manifiesta por alteraciones en la comunicación sináptica y la pérdida de la memoria. Sin embargo,los mecanismos sinápticos que subyacen a la deficiencia cognitiva no están del todo comprendidos. Por lo tanto, nuestro objetivo fue estudiar la relación entre varios neurotransmisores y la disfunción cognitiva en modelos de AD. Se utilizó un modelo transgénico de AD (3xTg-AD) y la administración de oligómeros de beta-amiloide exógenos en ratones silvestres. Se encontró que la acumulación de la beta-amiloide disminuye los niveles de dopamina cortical y deteriora la facilitación sináptica a largo plazo después de la estimulación eléctrica de alta frecuencia, lo que dio lugar a alteración de la memoria de reconocimiento. Sorprendentemente, el aumento de los niveles de dopamina corticales mejoran la facilitación sináptica y la memoria. Nuestros resultados sugieren que la disminución de dopamina inducida por beta-amiloide es un mecanismo que subyace a las primeras alteraciones sinápticas y de memoria observados en modelos de la enfermedad.

Cortical dopamine activity reduction induced by beta amyloid is related with cognitive and synaptic plasticity deficits in Alzheimer's disease mouse model

Alzheimer's disease (AD) is a neurodegenerative disease manifested by alterations in synaptic communication and memory loss. However, the synaptic mechanisms underlying cognitive impairment are not entirely understood. Thus, we aimed to study the relationship between several neurotransmitters and cognitive dysfunction in AD models. We used a transgenic mouse model of AD (3xTg-AD) and the administration of exogenous Amyloid-β oligomers into WT mice. We found that the accumulation of beta-amyloid decreases dopamine levels and impaired *in vivo* long-term potentiation (LTP) after high frequency electrical stimulation, which led to impaired recognition memory. Surprisingly, increasing cortical dopamine levels rescued both HFS-induced LTP and memory. Our results suggest that Aβ-induced dopamine depletion is a core mechanism underlying the early synaptopathy and memory alterations observed in AD models.

The Mitochondrial DNA Hypothesis of Alzheimer's Disease:Research on molecular mechanisms of neurodegeneration.

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Current diagnostic guidelines for AD use a combination of clinical phenotype criteria together with the presence of biomarker evidence. However, AD exhibits a long asymptomatic phase and preclinical diagnosis of AD with the use of only biomarker evidence is still in the process of validation, because currently known cerebrospinal fluid biomarkers (CSF) of AD are also altered in vascular dementia, stroke and in normal aging. The aim of our research is to identify disease specific pathophysiological biomarkers of AD that precede the appearance of clinical symptoms.

Extensive evidence indicates that mitochondrial function is altered in AD. Oxidative stress and energy deficiency are fundamental characteristics of the disease, but whether they are an early event or a result of the disease process is unclear.Using quantitative PCR techniques, we measured circulating cell free mitochondrial DNA (mtDNA) in CSF from subjects classified according to their concentrations of Aβ1-42, t-tau and p-tau in CSF and by the presence or absence of dementia. We found that asymptomatic patients at risk of AD, and symptomatic AD patients, but not patients diagnosed with fronto-temporal lobar degeneration or with Creutzfeldt-Jakob disease, exhibit a significant decrease in circulating cell free mtDNA in the CSF. In addition, pre-symptomatic subjects carrying pathogenic PSEN1 gene mutations that cause familial AD show low mtDNA content in CSF before the appearance of AD related biomarkers in CSF.

Neurons are highly dependent on aerobic energy provided by mitochondria, and a decline in the amount of mtDNA of the magnitude found in CSF is likely to cause neurodegeneration consequent to cellular energy deprivation. Our present findings indicate that low content of mtDNA in CSF may be a novel biomarker for the early detection of preclinical AD and support the hypothesis that mtDNA depletion is a fundamental pathophysiological mechanism of dementia of the AD type. The observation that depletion of mtDNA precedes the appearance of clinical symptoms in both familial and sporadic AD subjects indicates that, independently of the etiology, regulation of mtDNA copy number is a common mechanism onto which different pathways causing AD converge.Support: MINECO, Spain (SAF2014-56644-R) and CIBERNED (PI2013/08-3).

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Changes in AMPA receptors and associated proteins are related to synaptic and learning impairment in early stages of Alzheimer's Disease

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β-amyloid (Aβ), a peptide generated from the amyloid precursor protein (APP), is widely believed to underlie the pathophysiology of Alzheimer's disease (AD). Emerging evidences suggest that soluble Aβ oligomers (oAβ) adversely affect synaptic function, leading to cognitive failure associated with AD. The Aβ-induced synaptic dysfunction has been attributed to the synaptic removal of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors (AMPAR). However, the molecular mechanisms underlying the loss of AMPAR induced by Aß at synapses are largely unknown. We have examined the effect of oAβ on phosphorylated GluR1 at serine 845 (Ser845), a residue that plays an essential role in the trafficking of AMPARs towards extrasynaptic sites and the subsequent delivery to synapses during synaptic plasticity events. We found that oAβ reduce basal levels of Ser845 phosphorylation and surface expression of AMPARs affecting AMPAR subunit composition. oAβ-induced GluR1 dephosphorylation and reduced receptor surface levels are mediated by an increase in calcium influx and activation of calcineurin. Moreover, oAβ block the extrasynaptic delivery of AMPARs induced by chemical synaptic potentiation (cLTP). In addition, reduced levels of total and phosphorylated GluR1 are associated with initial spatial memory deficits in a transgenic mouse model of Alzheimer's disease. Moreover, oAβ is affecting A-kinase anchoring protein 79/150 (AKAP79/150) levels by a mechanism related with calcium influx. We have shown that oAβ and NMDA-mediated cLTP induces a degradation in AKAP150 protein levels that is independent on calcineurin (CaN). The reduction in AKAP150 parallels oAβ and cLTD-mediated GluA1 AMPARs endocytosis and dephosphorylation of GluA1 Ser-845. A causative relationship between the decrease in AKAP150 levels and the endocytosis of AMPARs is also supported since silencing AKAP150 produced the expected dephosphorylation of GluA1 Ser-845 and the endocytosis of GluA1 AMPARs whereas overexpression of AKAP150, restoring AKAP150 levels, blocked cLTD-mediated AMPARs endocytosis and dephosphorylation of GluA1. Since AKAP79/150 is a synaptic protein that has been proposed to function as a signaling scaffold that regulates AMPAR phosphorylation, channel activity, and endosomal trafficking associated to synaptic plasticity, the oAβ-mediated changes in AKAP 79/150 levels could be related to a deregulation of synaptic AMPA receptors in early stages of AD.

Unraveling the brain activity for action switching may be the key to understand the role of basal ganglia on the generation of motor problems

Key to understanding the malfunctioning of the brain when it is subject of neurodegenerative states is to identify the dynamic interactions between the different neuronal sub-circuits in healthy animals and compare it to models replicating the symptoms of the neurodegenerative diseases.

In our lab we are interested in understanding the processes behind the inability to appropriately switch between actions. We consider that an action has several components, for example in Parkinson disease it has been documented that patients are capable of moving but only under specific conditions (rid a bike but are unable to initiate walking). Another example are the symptoms of what happens in obsessive-compulsive disorders (OCD), individuals perform repetitive behaviors without affecting the fidelity of the movement but it seems the ability to stop or switch to other actions is diminish. Therefore performing an action has several components, initiation, performance, switching between movements and termination. In order to understand how the subcircuits of the brain controls these different phases of the generation of actions we focus on two basic questions: ¿which subcircuits are controlling the generation of actions? and ¿how each of these subcircuits contributes to the appropriated generation of actions?, both in the healthy and neuropatological state.

To address these questions we study the cortex-basal ganglia-thalamic loops (Cx-BG-Th) while animals initiate, perform and switch between sequences of actions, it has been hypothesized that the Cx-BG-Th loops allows the proper selection of actions and that their malfunctioning impedes appropriately initiate, perform, switch or terminate actions. In particular we focus on evaluating the contribution of the different sources of excitation to the striatum (biggest input of the BG) as well as on dissecting the specific contribution of the two general subcircuits of the basal ganglia: the striatonigral and the striatopallidal pathways in vivo.

As preliminary results I will present how the different striatal subcircuits contribute to the generation of actions sequences and whether the cortex or the thalamus is leading the activity of the striatum during the generation of actions. In the long term our expectative is to characterize the contribution of the Cx-BG-Th loops to the ability of smoothly switch between actions sequences both in the healthy condition and compare it to the contribution of the same sub-circuits in model of malfunctioning of the brain.

"Characterization of the neuronal pathology in mitochondrial disease"

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Dysfunctions in the ability of mitochondria to generate energy lead to mitochondrial disease, a group of severe and often fatal pathologies characterized by muscular and central nervous system affectation. Among these, Leigh syndrome (LS) is one of the most common childhood mitochondrial disease, presentinghypotonia, failure to thrive, progressive mental and motor dysfunction, and respiratory insufficiency leading to early death. LS patients present characteristic brain lesions predominantly in basal ganglia and brain stem. However, the cause of the selective susceptibility of theseneuronal populations has not been elucidated. Using a mouse model of LS that lacks the mitochondrial complex I subunit *Ndufs4* (Ndufs4KO mice), we have assessed the contribution of defined neuronal populations to the pathology and characterized the cellular and molecular pathways involved in neuronal death induced by mitochondrial dysfunction. Our results have shown that vestibular neurons are particularly susceptible to mitochondrial dysfunction, and that their death leads to the fatal phenotype observed in Ndufs4KO mice. Furthermore, we have identified several potential therapeutic interventions, paving the way for future treatments for mitochondrial disease.

Enhancingmaturation, survivalandaxonalgrowthofembryonicstemcell-derivedneurons

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Neuronal differentiation of embryonic stem cells (ESC) to dopamine (DaN) and motor neurons (MN) have been reported. After neuronal differentiation, neurotrophic factors promote maturation and survival. However, the role of neurotrophins in neuronal commitment is elusive. We develop edlines of mouse ESC that retain pluri potency and constitutively release Glial-derived neurotrophic factor (GDNF). Secretion of GDNF to the medium during differentiation of ESC to DaN was significantly high erin GDNF-ESC than in controls. We observed that GDNF-ESC differentiated more efficiently than controls to DaN with mes encephalic identity. Upon challenge with the neurotoxin 6-hydroxy-dopamine, GDNF was protective for these neurons that are lost in Parkinson´s disease. To investigate a broader role of GDNF in neuronal differentiation, MN were produced from mouse ESC. In GDNF-over expressing cells, a significant increase in proliferative MN precursors positive for Olig2, relative to controls, was found. At terminal differentiation, almost all differentiated neurons express phenotypic markers of MN in GDNF cultures, with lower proportions in control cells. These MN express Green Fluorescent Protein under the control of the Hb9 promoter, allow ingus to identify the mand perform electrophysiological whole cell recordings. MN derivedfrom GDNF-expressing cells exhibited a higher number of evokedaction potentials and more mature phenotypes, as reflected by the presence of calcium potentials, rebound action potentials, as well as spontaneous action potentials and synapticcurrents. Excitotoxicity induced by kainatein MN was significantly higher in control cells compared to GDNF-ESC.On the other hand, we have described that Semaphorin 3C (Sema3C) can attract and enhance the growth of axons of mouse ESC-derived DaN, both in vitro and in vivo. We have recently tested if conjugation of recombinant Sema 3C with a biocompatible hydrogel releases the protein to the medium and if such release can enhance axonal growth of human ESC-derived DaN in micro fluidic chambers. The results show a significant increase of dopaminergic axonal growt hafter exposure to Sema3C hydrogel, compared to the effect of the hydrogel combined to a control protein. Altogether, these data show that GDNF promotes proliferation and neuronal differentiation from pluripotent cells, also enhancing maturation and conferring neuroprotection. Regarding axonal growth, the use of hydrogels as a vehicle for Sema3C administration to direct axons of DaNgrafts in vivo should be explored.

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Reversal of synapse degeneration by restoring Wnt signalling in the adult hippocampus: a therapeutic role in Alzheimer's disease?

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Synapse degeneration is an early and invariant feature of neurodegenerative diseasesand correlates with cognitive declinein Alzheimer's disease (AD). However, the molecular mechanisms that trigger synaptic vulnerability remain poorly understood.Given that synaptic failure has occurred when AD is diagnosed, it is crucial to understand the mechanisms that control the regrowth of synapses after substantial degeneration.The endogenous Wnt antagonist Dickkopf-1 (Dkk1) is present in AD brains and in AD mouse models andis upregulated by Amyloid-ß (Aß).Importantly, blockade of Dkk1 with neutralizing antibodies suppresses the degenerative effect to Aß on synapses. In a mouse model that inducibly expresses Dkk1 in the adult hippocampus, Dkk1 triggers synapse disassembly andimpairsbasal synaptic transmission. These synaptic deficits are present in the absence of cell death. Importantly, theta burst-induced long-term potentiation (LTP) is completely abolished in the CA1 region of iDkk1 mice and these mice exhibit deficits in long-term memory. Thus, deficient Wnt signalling triggers synaptic dysfunction. Reactivation of the Wnt signalling pathway by cessation of Dkk1 expression, after synapse degeneration, results in the complete recovery of synapses and LTP in the hippocampus of iDkk1 mice.We propose thatdeficiency in Wnt signalling is a key contributor to synaptic degeneration at early stages of AD. Our studies demonstrate a novel role for Wnt signalling in regulating synapse integrity. They also reveal a remarkable regenerative capacity of synapses in the adult hippocampus and highlight the therapeutic potential of Wnt pathway modulation for treating neurodegenerative diseases like AD.

High abundance and diversity of deletions in the mitochondrial genome in different stages of life in the mouse brain

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The mitochondrial genome is a double stranded DNA molecule of which there may be up to thousands copies per cell and required for mitochondrial functions. Mutations of various types may occur de novo in somatic cells or be transmitted through germ line by maternal inheritance. Among these alterations, deletions are the most frequent and have been linked in humans to debilitanting and often fatal neuromuscular diseases. These alterations have been also associated to normal aging in humans, primates and rodents; controversies exist, however, regarding the stage of life in which they appear and accumulate coexisting in heteroplasmy with wild-type genomes or causing cell disfunction or disease. In this work we demostrate a high abundance and diversity of deletions in the mitochondrial genome in the brain of healthy mice in different life stages, from embryos to aged individuals. Most of these deletions involve the loss of a single nucleotide but the deletion of kilobases in a single event was also detected; in both extremes, their presence was also detected at the RNA level. Deletions were found with frequencies that increase or decrease throughout life. Our studies thus reveal a complex mitochondrial mutational dynamics in a dynamic equilibrium which is part of normal development, growth, and aging.
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"Neuronal Networks with plausible biophysical properties"

Dr. Mario Treviño Villegas

Computations in cortical circuits require action potentials from excitatory and inhibitory neurons. Evidence from *in vitro* and *in vivo* experiments accumulated over the last two decades has allowed us to characterize, with relative detail, the response properties of a variety of cortical neurons. Derived from these studies, we now know that both the intrinsic properties of cells and their synaptic interactions are highly heterogeneous. In my laboratory, we are interested in understanding how this diversity in mechanisms is integrated at the level of neuronal microcircuits. We address this question both experimentally and theoretically. In this talk, I will show you some examples of how we've been creating and testing families of virtual neuronal networks with diverse cellular and synaptic mechanisms, and with a variety of connectivity rules. I´ll also discuss a recent finding which suggests that inhibitory interneurons might actively participate in producing asynchronous states in cortical networks. This state requires a proper mixture of shared excitation and inhibition leading to network activity with relative asynchrony between neighboring cells. Such contribution (from interneurons) would be extremely important because it would tend to reduce the spike correlation between neighboring pyramidal cells, thus possibly increasing the information-processing capacity of neural networks. The predictions derived from this and other theoretical models will help us to generate informed hypotheses before conducting experiments.

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Neural population dynamics in the primate motor cortex during interval timing.

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We studied the response properties of neurons in the primate medial premotor cortex during isochronous tapping to an auditory or visual metronome. Monkeys performed a three sequential elements task with five different target-intervals. Neurons were classified as sensory or motor based on a time-warping transformation,which determined whether the cell activity was statistically better aligned to sensory or motorevents. Interestingly, we found a large proportion of cells classified as sensory or motor. Two distinctive clusters of sensory cells were observed, namely, one cell population with short response-onset latencies to the previous stimulus both, and another that were probably predicting the occurrence of the next stimuli. These cells were calledclassic- and predictive-sensory neurons, respectively. Classic-sensory neurons showed a clear bias towards the visual modality, were mostly unimodal, and were more responsive to the first stimulus, with a decrease in activity for followingelements of the metronome sequence. In contrast, predictive-sensory neurons responded to both modalities and showed similar response profiles across serial-order elements. Motor cells were mostly bimodal and showed a consecutive activity-onset across discrete neural ensembles, generating a rapid succession of neural events between the two taps defining a produced interval. The cyclical configuration in activation profiles engaged more motor cells as the serial-order elements progressed across the task, and the rate of cell recruitment over time decreased as a function of the target-intervals. Our findings support the idea that motor cells were responsible for the rhythmic progression of taps in the task, gaining more importance as the trial advanced, while,simultaneously, the classic-sensory cells lost their functional impact.

Astrocyte-mediated signaling in the activation of peripheral inflammatory responses to CNS damage

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Area: 1. Glia

Astrocytes contribute a great deal to concerted responses to stimuli in the brain that include several ways of communication among various cell types. Of special note, is the integration of inflammatory responses to neuronal death, trauma or infection. While it has been long known that these cells are key to inflammatory responses in the brain, focus has been chiefly put on their role in cytokine production, edema control and axonal growth. On the other hand, the quest for humoral transmitters that convey inflammatory signals from the central nervous system to peripheral immunological organs is still an active topic of research. In this work we have found that astrocytes play a crucial role in the integration of signaling that originates from inflammatory cues in the brain, which are further transmitted on peripheral tissues, such as liver and spleen, through the secretion of extracellular vesicles. The release of these vesicles depends on the proper synthesis of ceramides, which is up-regulated by inflammatory molecules like interleukin-1 beta in astrocytes. Extracellular vesicles shed from astrocytes readily cross the intact blood-brain barrier and regulate the peripheral acute phase response elicited by inflammation in the central nervous system. Once in the periphery, molecules trapped in the astrocyte-derived vesicles trigger priming and activation of leukocytes that are then recruited to the site of inflammation in the brain parenchyma. The contribution of astrocytes to systemic responses of inflammation following brain injury has not been thoroughly examined and these findings add to a better understanding of intercellular communication pathways controlled by brain cells.

Of lipids and adult neurogenesis: The role of astroglial phospholipid phosphatases

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Neurogenesis is the process during which new functional neurons are formed from progenitor cells. In the adult brain, this process is mainly restricted to the ventricular-subventricular zone (V-SVZ) of the lateral ventricles and dentate gyrus' subgranular zone (SGZ) of the hippocampus. Recent single-cell RNAseq transcriptomic analyses have associated sphingolipid metabolism and/or signaling to the maintenance of neural stem cells quiescence, making these processes a key point in the regulation of neurogenesis in these niches.

The phospholipid phosphatase-3 (PLPP3) is an integral membrane enzyme with the ability of regulating the concentration and signaling activities of several bioactive lipids, including sphingosine-1-phosphate (S1P). In the adult brain, PLPP3 and some S1P G protein-coupled receptors (GPCRs) are highly expressed in neurogenic areas. This suggested that PLPP3 could participate in regulating the concentration and biological activity of this lipid in both neurogenic niches.

In this work we show that PLPP3 expresses in astroglial cells including radial and non-radial neural stem cells (NSCs) in the V-SVZ and SGZ. Using the Cre/*loxP* system to conditionally inactivate *Plpp3* in the neural lineage, we analyzed the consequences of the lack of PLPP3 deficiency on denate gyrus' progenitor proliferation and differentiation both *in vivo* and *in vitro.* Our *in vitro* studies revealed that in the absence of PLPP3, hippocampal progenitors form fewer and smaller neurospheres than control cells. Furthermore, the number of neural progenitors incorporating BrdU was diminished and a higher proportion of neurons differentiated in mutant neurospheres with respect to their corresponding controls. In agreement with our *in vitro* findings, the number of BrdU labelled cells (after a 2 hrs pulse) in the SGZ of PLPP3 deficient mice was reduced when compared to control brains. Additionally, the amount of neuroblasts in the mutant hippocampi was reduced, and mutant neuroblasts displayed disrupted morphology, showing abnormal arrangement of their dendritic three and ectopia.

Ablation of *Plpp3* also produced a strong down-regulation of the type 1 receptor of S1P ($S1P_1$) in hippocampus, SVZ and derived neurospheres.

Our data indicate that PLPP3 has an important role in regulating neural progenitor cell proliferation and neuroblast differentiation in the adult murine hippocampus, probably through regulating $S1P_1$ receptor signaling.

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Glial Glutamate Transporters: Key Players in Excitatory Transmission

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Glutamate is the major excitatory neurotransmitter in teh vertebarate brain and it elictis its action through specific membrane receptors and transporters expressed both in neurons and glia cells. Despite of the fact that the neurocentric vision of brain function argues against a glial invovement in synaptic tranactions, in the last years a plethora of data has demostrated an active role of these cells in information proccessing in the Central Nervous System. In the case os glutamatergic and GABAergic transmission, glia cells play a compulsury role in terms of the ryclincng of the transmitters via the *so called* **GABA/Glutamate/Glutamine shuttle**. Furthermore, a metabolic couplig between neuros and astrocytes has also been described. Using the model of cultured Bergmann glia cells, a detailed and exquiste functional and physical interaction of glial transporters (glutamate, glutamine and glucose), will be presented. These functional interactions are important not only to secure a proper pool of releasable neurotransmitter, but also are involved in a continued and dynamic change in glial gene expression patterns triggered by neuronal activity through tanscriptional and translational events.

The Role of Progesterone in Glioblastoma Growth

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Glioblastomas (astrocytomas grade IV) are the most frequent and aggressive brain tumors in humans. They are derived from lower grade astrocytomas or cancer stem cells, and are more prevalent in men than in women (3:2). It has been reported that progesterone, a sex steroid hormone, participates in the growth of several tumors, including those originated in the brain. Progesterone exerts many of its effects through the interaction with its intracellular receptor (PR) which is a ligand-activated transcription factor. PR expression directly correlates with the evolution of astrocytomas grade, suggesting that PR-positive tumors exhibit a high oncogenic potential. Both *in vitro* and *in vivo* experiments have demonstrated that progesterone, mainly by the interaction with PR, promotes cell proliferation, migration and invasion of human glioblastoma cells. These effects are mediated by changes in the expression of several genes involved in the control of cell cycle and metastasis. Interestingly, the PR antagonist, RU486, reduces the proliferation of glioblastoma cells induced by the activation of protein kinase C. These results suggest that PR should be a target for diminishing glioblastomas progression.

Learning during early ontogeny: Involvement of the opioid system in modulating ethanol-mediated reinforcing aspects.

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Ethanol self-administration and seeking behaviors are modulated by the action of the opioid system, during early ontogeny. Prenatal blockade of the opioid system, before ethanol administration, inhibited the expected increase in ethanol-related appetitive and consummatory behaviors in neonate and infant rats. During infancy, subjects also rapidly learn to self-administer ethanol under an operant conditioned paradigm; opioid system is involved in ethanol reinforcing mechanisms. We found, employing a pharmacological approach that mu, delta and kappa opioid receptors have to be active to promote positive ethanol reinforcement in infants. We will show evidences that a high ethanol affinity occurs during early ontogeny and that this preference implies a fully functional opioid system. In addition, we investigated the effect of prenatal ethanol exposure and infantile alcohol intake, in Methionine-enkephalin (Met-enk) contents in the ventral tegmental area [VTA], nucleus accumbens [NAcc], prefrontal cortex [PFC], substantia nigra [SN], caudate-putamen [CP], amygdala, hypothalamus and hippocampus. Infantile Met-enk content in PFC and NAcc was increased as a consequence of prenatal exposure to ethanol. Conversely, Met-enk levels in the VTA were reduced by prenatal ethanol manipulation. Prenatal ethanol also increased peptide levels in the medial-posterior CP, hippocampus and hypothalamus. These findings show that prenatal ethanol exposure induces changes in behavioral parameters that could be mediated by Met-enk levels in regions of the mesocorticolimbic and nigrostriatal systems, hypothalamus and hippocampus. These results support the role of mesocorticolimbic enkephalins in ethanol reinforcement in infancy, as has been reported in adults. This work was supported by grants from ANPCyT (PICT 2011-0130); CONICET and SECyT-UNC {PA} and CONACyT 34359-N, Mexico {MM}.

Area: Drug Abuse

Neurobiology of solvent misuse

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The intentional inhalation of volatile solvents for their psychoactive effects is a common practice with adverse health consequences, especially among children and adolescents. Despite this, the research concerning the neurobiology of inhalant misuse lags behind that of mostabused drugs. Toluene is the main component of several products used as inhalants and also the best-studied solvent. It has rewarding effects and a mixed pharmacological profile that includes central nervous system depressant actions and hallucinations. These effects are closely associated with molecular proteins (voltage and ligand-gated ion channels), which can be blocked (e.g., NMDA receptors, 5-HT_{2A} receptors, sodium and calcium channels)or positivelymodulated (e.g. $GABA_A$, glycine and $5HT_3$receptors)not only by toluene, but also by other solvents. Repeated exposure to toluene causes cognitive deficits, significant changes in several neurotransmitter systems, organic damage, and epigenetic alterations in key brain structures associated to reward and memory processes. Tolerance to anxiolytic and anticonvulsant effects, as well as sensitization to locomotor activity can occur in chronically exposed animals. The developing brain during gestation and adolescence is particularly vulnerable to the deleterious toluene's effects. This presentation will reviewthe significant progress that has been made in understanding the neurobiological basis for solvent misuse, but also the challenges that remain in recognizing the long-lasting effects of this particular group of drugs.

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Cortical development alterations induced by endocannabinoid signaling manipulation

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Considering the neurodevelopmental role of the endocannabinoid system we sought to investigate the neurobiological substrate underlying structural and functional alterations caused by embryonic Δ^9-tetrahydrocannabinol (THC) exposure. We focused in CB_1 receptors as this G protein-coupled receptor mediates the majority of cannabinoids actions in the nervous system.

We administered THC to pregnant mice during a restricted gestational time window and analysed the consequences in the offspring by diverse histological and behavioural means. We employed CB_1-null mice as a control and a Cre-mediated, neuronal lineage-specific CB_1-re-expression strategy, in order to determine the identity of THC-targeted neurons.

Embryonic THC exposure interfered with subcerebral projection neuron generation, altered corticospinal connectivity and caused long-lasting alterations in the skilled motor performance of the offspring. THC-induced neuronal traits were reminiscent to those elicited by CB_1 receptor genetic ablation and CB_1-null mice were resistant to THC-induced alterations. Selective embryonic re-expression of CB_1 in dorsal telencephalic glutamatergic neurons rescued the deficits in corticospinal motor neuron development of CB_1-deficient mice and restored their susceptibility to THC-induced motor alterations. In addition, temporally-restricted embryonic THC administration induced an increase in seizure susceptibility which, in this case, mediated by its ability to interfere with the neurodevelopmental role of CB_1 receptor on both excitatory and inhibitory neuronal populations. New findings regarding the sexual dimorphism in the vulnerability to cannabinoid exposure will be presented.

Our results show that some functional consequences of embryonic cannabinoid exposure that persist in the adulthood are solely mediated by the interference with the neurodevelopmental role of the CB_1 receptor. The use of selective genetic rescue of CB_1 receptors proves as a valuable strategy for identifying the precise neuronal populations responsible of prenatal cannabis consequences.

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