Possible factors involved in sexual preference in rodents: Effect of multiple gestations and endocrine conditions during the prenatal period.

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Abstract:
Commonly there is a sex preference difference: usually males select females, while females in estrus choose male sex partners. However, in all species studied a subpopulation shows same sex preference. Prenatal administration of the aromatase inhibitor, letrozole, induces same sex preference in male rats. An effect mediated by decreasing brain estradiol levels, essential to organize the structures that mediate male sexual behavior in adulthood. The administration of letrozole induces in 30-40% of the subjects same sex preference.
Despite the perinatal endocrine modifications change sexual preference, such shift occurs only in a limited proportion, indicating that other factors may be involved in the determination of sex preference. The immune response hypothesis indicates that multiple gestations induce in the mother an immune response to some elements of Y chromosome, altering the brain sexual differentiation process of the male progeny. In line, sons with older brothers have a higher probability to have homosexual orientation.

The main objective of this work was to determine if multiple gestations of the mother could increase the number of same sex preference male rats compared with a prenatal letrozole treatment and evaluate sexual behavior in the litters of multiparous mothers. To fulfil this objective, Wistar pregnant female rats were used. Initially, a group of pregnant primiparous mothers was administered with vehicle (corn oil) or letrozole (0.56µg/kg) (G10-G21). For the second phase, the males of multiparous females (rats with 4 or more gestations) were tested at 3 months of age for sexual preference and sexual behavior using a three-compartment box and a circular arena, respectively.

Results indicate that there was 5% of males with same sex preference in the litters of control primiparous females. Treatment with letrozole to primiparous mothers increased to 40% the males that had same sex preference. In the case of the male rats whose mothers had many gestations, 43% showed spontaneous same sex preference; these males also displayed feminine and masculine sexual behavior.

Novel Roles for Krüppel-Like Factor 13 (KLF13) in Hippocampal Neurons

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Krüppel-like factors (Klfs) comprise a family of seventeen zinc finger transcription factors. They are grouped into three subfamilies based on the sequences of their N-terminal domains, which comprise sites for interaction with coregulators. Klfs play fundamental roles in regulating diverse biological processes such as cell metabolism. proliferation, differentiation, survival and regeneration. Our work has focused on Klf9, a member of subfamily 3, which promotes and maintains the differentiated state of neurons, and is thus implicated in the loss of regenerative capacity of adult mammalian neurons. To understand the molecular mechanisms of Klf9 actions in neurons, we recently identified Klf9 target genes in mouse hippocampal neurons, and discovered that Klf9 functions predominantly as a transcriptional repressor. One of the most strongly regulated genes by Klf9 is Klf13, also a member of subfamily 3; the two genes likely arose through a gene duplication event in the vertebrate lineage. While it is known that Klf13, similar to Klf9, inhibits neurite outgrowth of retinal ganglion cells following injury, virtually nothing is known about Klf13 cellular actions, target genes or how it functions in chromatin in any cell. The goal of the present work was to analyze and compare the functions of Klf13 and Klf9 to test the hypothesis that these two closely related Klfs have some overlapping, but also different functions in mouse hippocampal neurons. To address this hypothesis, we engineered the adult mouse hippocampus-derived cell line HT22 to control Klf9 or Klf13 expression by addition of tetracycline. We also used CRISPR/Cas9 genome editing to generate Klf9 and Klf13 knock out HT22 cell lines. Analysis of cell cycle regulation showed that Klf9 inhibits, while Klf13 promotes cell cycle progression. To investigate the roles of these two Klfs in cell survival we used serum starvation for 24 hr, followed by MTT assay. We found that the endogenous *Klf13* mRNA increased after 24 h of serum deprivation, while *Klf9* mRNA was strongly decreased. Forced expression of Klf13 increased cell survival as evidenced by increased MTT assay signal. By contrast to the opposite actions of Klf9 and Klf13 on cell cycle and survival, we found that both Klf9 and Klf13 blocked neurite-outgrowth induced by treatment with forskolin+IBMX, which increases cAMP; elevated cAMP is a hallmark of regenerative responses in neurons after injury. The results of the present work show that Klf9 and Klf13 have important functions in hippocampal neurons. Some are opposing (e.g., actions on cell cycle and survival), while others are shared (e.g., blockade of neurite outgrowth/neuronal regeneration). We are now conducting complementary studies to investigate the genomic targets for these two Klfs in hippocampal neurons.

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Bursting in the *substantia nigra reticulata* in the absence of dopaminergic modulation

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The *substantia nigra reticulata* (SNr), is considered to be one of the main output nuclei of the basal ganglia. As such, firing patterns in the SNr carry information that results from information processing in the basal ganglia as a whole. Bursting in SNr gabaergic neurons have been linked to anomalous activity in the basal ganglia, especially in pathologies like Parkinson's disease. To study the emergence of burst firing in SNr neurons, we performed patch clamp recordings from slices in three groups of experiments: (i) slices from normal animals (control), (ii) with acute blockade of D1- and D2-like dopamine receptors with their selective antagonists SCH23390 and sulpiride, respectively (DAx for short), and (iii) slices from animals lesioned with 6-OHDA (Parkinsonian). In doing so, we stumbled upon an interesting problem: the detection of bursting patterns from spike trains. One reason for the difficulty is that bursting, regarded here as a period of significantly high firing rate within a spike train, is highly dependent on the distribution interspike intervals, or equivalently, its instantaneous firing rates. Bursting may mean very low instantaneous firing rates for one train, and very high rates for another. We addressed this issue developing a flexible, scale-free approach, detecting bursting by means of restricted visibility graphs, taking the interspike intervals within a train into account, but only relative to the distribution of intervals for that train. In brief, to characterize the structure of the sequences of interspike intervals and study its relationship with the appearance of bursts and regular firing, we implement a modification of the parametric natural visibility graph algorithm (PNVG, Snarskii and Bezsudnov, 2016) in which the visibility angles are restricted to a range. As expected, we found bursting in spike trains from neurons from the 6-OHDA. Remarkably, we also found that acute blockade of dopamine receptors was enough to produce bursting and irregular firing in SNr neurons, suggesting that the encoding capability of SNr neurons is been severely altered when the dopaminergic modulation is absent.

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Thalamo-striatal contribution tothe start/executions of an action sequence

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The performance of an action relies on the initiation and execution of appropriate movement sequences. Recently it has been documented that specific patters of activity inthe basal ganglia, specifically in the striatum, are necessary for the initiation and executionof actions. It is known that the two main inputs driving the striatal activity are the cortico-striatal and thalamo-striatal projections. In this study investigated theinteraction between the thalamus and basal ganglia aiming to answer: Which is thethalamic contribution to the initiation and execution of an action sequence? To address this question, weperformed three experiments while animals initiated/executed an action sequence: 1) we recorded the activity of different thalamic nuclei, 2) we identified thalamic nuclei projecting to the sensorimotor versus associative striatal compartments, 3) weinhibited the thalamo→striatal terminal in the sensorimotor versus theassociative compartments of the striatum.

To trained animals to initiateand execute action sequences we train animals to performedself-paced presses of alever (fix ratio 8). To record the activityof the thalamus we performed electrophysiological recordings using electrodes arrays(4x4) implanting them into the thalamus [Parafascicular(PF) and Ventral Posterior Thalamic nuclei (VTs)]. To inhibit the thalamic projections to the striatum we use the VGLUT2-Cre mice, which express the Crerecombinase driven by the promoter VGluT2 (vesicular glutamate transporter), givingspecificity to express opsins into the thalamic neurons. Then by expressing the opsinArcheorhodopsin we specifically inhibit their axons in the striatum (depending on the positioning of a fiber optics) *in vivo* while animalsinitiate/perform an action sequence.

As results we observe that both the projections of the PF nucleus and the VTs are required to properly initiate and execute an action sequence, specifically the activity of the VTs provides feedback by modulating (delimiting) the length of the sequence of actions. We suggest that the thalamo-striatal projection is providing preparatory andon-line modulation to the striatal activity necessary for the appropriate performance ofaction sequences.

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VALUATION OF THE POTENTIAL OF COMBINATIONS WITH MEMANTINE (M); M + ACETYL L-CARNITINE (ALCAR), M + CURCUMIN (C) IN AN EXPERIMENTAL MODEL OF COGNITIVE DEFICIT.

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Introduction:Dementia is a syndrome of persistent intellectual deterioration, manifested through alterations in memory as a cardinal symptom, which conditions social, work and family dysfunction. Age is a major risk factor for dementia, as it occurs in people over 60 years of age. In Mexico there are more than 10 million adults 60 years of age or older. Biochemical and molecular events have been associated with the development of dementia such as decreased acetylcholine (ACh), deposition of beta-amyloid aggregates (A-β) and hyperphosphorylated Tau, decreased nitric oxide synthesis (NO), Intracellular calcium increase, oxidative stress, and glutamate-induced excitotoxicity. The treatment of choice is the use of N-methyl-D-aspartate (NMDA) receptor antagonists such as memantine and the use of anticholinesterases (iAChE) such as donezepil, galantamine and rivastigmine. Dementia being a progressive and irreversible pathology is necessary for the development of new treatments that counteract the progressive effects of dementia; For which we propose the administration of curcumin and acetyl L-carnitine, curcumin has anti-inflammatory and anti-inflammatory capacities, in addition to reducing deposits A-β and ALCAR has been shown to decrease behavioral deterioration and boost the performance of tasks with memory.**Objective:** To determine and compare the effect of the administration of Memantine (M) (M + Curcumin (C) or M + Acetyl L-carnitine (ALCAR) combinations) on cognitive impairment induced by the Mixed Dementia model, as well as on Some biological markers of inflammation and neuroprotection in rodents exposed to the different treatments combined. **Methods:**were evaluated two cognitive tests (T-Maze and Object Recognition), as well as glutathione (GSH) and glutathione peroxidase (GPx) and Acetyl Cholinesterase (AChE). Values were analyzed with two-way ANOVA followed by Dunnet. The differences were considered significant with $p \leq 0.05$. **Results:** In the cognitive tests we observed that the administration of M signifcantly improves the cognitive response of the mice. In the biochemical tests: GSH had no significant difference with respect to the control, so in GPx no significant changes were observed with respect to the scopolamine groups. **Conclusion:** Memantine promotes the increase in the cognitive ability of mice exposed to scopolamine. Curcumin and ALCAR blocked the prooxidant effect of scopolamine. The GPx activity suggests that the ALCAR has an antioxidant effect independent of the increase in the GSH turnover rate. Our results suggest a possible control of mitochondrial functionality through Nrf2.

Evolution of the Alzheimer's-associated neuroinflammatory process in Down Syndrome

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Background: Alzheimer's Disease (AD) anti-inflammatory therapies have failed when administered at AD clinical stages. However, cognitively normal individuals under long term anti-inflammatory treatment have a reduced risk of developing Alzheimer's Disease (AD). This highlights the existence of two different neuroinflammatory process in AD.

Down syndrome (DS) individuals are at increased risk of developing early onset Alzheimer's Disease (AD). Given the triplication of chromosome 21, people with DS show an age-dependent intraneuronal accumulation of Amyloid Beta (AB) (Busciglio, 2002) which develops into a full-blown AD-neuropathology and, in most cases, dementia. We have earlier reported that early intraneuronal accumulation of AB unleashes an early disease aggravating pro-inflammatory process in transgenic rodent models of AD-like pathology (Ferretti et al., 2012, Hanzel, 2014). Moreover, we have reported an upregulation of inflammatory factors in plasma from DS-AD asymptomatic and DS-AD individuals (Iulita et al., 2016). In light of this, we hypothesized that early AB accumulation in DS individuals will promote an early pro-inflammatory process in AD-asymptomatic DS individuals.

Methods: Postmortem frozen frontal cortex tissue of DS infants, DS-AD adults and their age matched controlswere analyzed for pro-inflammatory gene expression by a qPCR array (QIAGEN). Individual qPCR analysis was performed in the adult population. Furthermore, pro-inflammatory protein expression was analyzed in the conditioned media of DS and non-DS fetal cortical cells.

Results: Our initial results in DS-infants suggest an upregulation of pro-inflammatory factors IL-1B, IL-33, IL-6, IL-12a, IL12b, MCP-1, caspase-1 and 5. A downregulation of IFN-B and CARD18 was also observed. While DS-adults also show an upregulation of some of these molecules, the fold change was more substantial in DS-infants. CCL2 and IL-6 protein expression was elevated in the conditioned media of DS-fetal cells as compared to non-DS cell cultures.

Conclusions: These results suggest the existence of two different neuroinflammatory processes in the continuum of the AD neuropathology in DS.

mTOR pathway inhibition by metformin plus caloric restriction has beneficial anti-epileptic effects.

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Área 3: Neuropatología

Caloric restriction (CR) has anti-convulsive and anti-epileptogenic effects in different animal models. These actions are at least partially due to an inhibition of the mechanistic target of rapamycin (mTOR) signaling pathway. The adenosine monophosphate-activated protein kinase (AMPK) is an important upstream participant of the mTOR cascade, which inhibits it function when energy levels are low. Since hyperactive mTOR participates in the pathophysiology of epilepsy, its inhibition results in beneficial anti-epileptic effects. One way to achieve this is to activate AMPK with metformin. Thus, we studied the effect of metformin -either alone or combined with CR- on the electrical kindling model of epilepsy.
CR plus metformin showed many protective anti-convulsive actions upon both focal and generalized convulsive seizures. Thus, CR plus metformin would likely be very beneficial by reducing all measures of epileptic activity in patients. Patients that are overweight, obese or that have metabolic syndrome in addition to an epileptic disease are an ideal population in which to initiate clinical trials. CR plus metformin are especially good since both have a lot better side-effect profile and are much more cost-effective than the other molecules that inhibit the mTOR cascade, such as sirolimus (rapamycin) and derived drugs.

Effect of acidic pH and growth factor withdrawal on human hippocampal neural precursor cells (hHippNPCs) commitment to neuronal phenotype: implications in neurodegenerative diseases.

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* The study was performed in this Institution. Area of the Study: 4. Development and Aging.

NPCs are pluripotent cells of the nervous system, with autorenewal capability. They give rise to the three principal phenotypes in CNS: neurons, glia and oligodendrocytes. Neurotrophic factors had crucial roles in proliferation, differentiation and survival of NPCs. Neurodegenerative diseases are characterized by a reduction in growth factors levels and neurogenesis and an impairment in protein recycling by autophagy or proteasome, that results in protein aggregation. To elucidate the impact of stress on neural differentiation, recycling systems and tau phosphorylation, we cultured embryonic hHippNPCs in the presence or absence of 5 ng/ml FGF-2 for 2 to 7 days or treat them for 25 minutes at pH 5.7 and subsequently culture them in the presence or absence of FGF-2 for 2 to 7 days. By Western blot and immunocytochemistry the expression of NPCs, proliferation, glial, neuronal and synaptic markers and total, phosphorylated and oligomeric tau was assessed. We also evaluate cell viability, autophagy and proteasome activation and electrophysiological properties. We found significant decrease in Nestin, Sox-2, Lin28, PCNA and GFAP expression at 7 days in cells cultured in absence of FGF-2 and in cells exposed to pH 5.7 in the presence or absence of FGF-2. Synaptic markers: PSD95, Arc and neuronal differentiation markers: DCX, NF and NeuN, were increased. Tau expression was increased in cells cultured in the absence of growth factors for 2 and 7 days or in acidic conditions for 7 days. Tau oligomers were increased at 2 days without growth factors or pH5.7 in the presence of FGF-2. Tau phosphorylation, autophagy and proteasome markers were also increased in both stress treatments for 7 days. At 2 days in acidic conditions with or without FGF-2, ROS where significantly increased and transcription factor Nrf-2 activated. hHippNPCs cultured in the absence of FGF-2 or in acidic conditions showed outward potassium currents and small inward sodium currents when differentiate for 28 days. We conclude that both growth factor withdrawal and acidic environment induce neuronal differentiation of hHippNPCs, promote tau expression, phosphorylation and aggregation and induce activation of major recycling systems as a response to cellular stress that activates signal transduction and regulates gene expression. Both growth factor withdrawal and acidic environment in our experiments constitute stress conditions that resemble what happens in neurodegenerative diseases where growth factors are scarce and acidosis could exist.

Autophagy fails to prevent glucose deprivation/glucose reintroduction-induced neuronal death due to calpain-mediated lysosomal dysfunction in cortical neurons

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Autophagy is triggered during nutrient and energy deprivation in a variety of cells as a homeostatic response to metabolic stress. In the CNS deficient autophagy has been implicated in neurodegenerative diseases and ischemic brain injury. However, its role in hypoglycemic damage is poorly understood and the dynamics of autophagy during the hypoglycemic and the glucose reperfusion periods has not been fully described. In the present study we analyzed the changes in the content of the autophagy proteins BECN1, LC3-II and p62/SQSTM1 by Western blot, and autophagosome formation was followed through time-lapse experiments, during glucose deprivation (GD) and glucose reintroduction (GR) in cortical cultures. According to the results, autophagosome formation rapidly increased during GD, and was followed by an active autophagic flux early after glucose replenishment. However, cells progressively died during GR and autophagy inhibition reduced neuronal death. Neurons undergoing apoptosis during GR did not form autophagosomes, while those surviving up to late GR showed autophagosomes. Calpain activity strongly increased during GR and remained elevated during progressive neuronal death. Its activation led to the cleavage of LAMP2 resulting in lysosome membrane permeabilization (LMP) and release of cathepsin B to the cytosol. Calpain inhibition prevented LMP and increased the number of neurons containing lysosomes and autophagosomes increasing cell viability. Taken together, the present results suggest that calpain-mediated lysosome dysfunction during GR turns an adaptive autophagy response to energy stress into a defective autophagy pathway, which contributes to neuronal death. In these conditions, autophagy inhibition results in the improvement of cell survival.

Resveratrol reduces edema through sur1 expression regulation in cerebral ischemia

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Introduction. Cerebral vascular endothelial cells (CVEC) regulate the flow of ions and molecules between bloodstream and brain tissue, maintaining homeostasis in the parenchyma. During cerebral ischemia, CVEC function is impaired, causing lossof microvessels structural integrity with the subsequently cerebral edema formation. In the initial phase of edema establishment, the SUR1-NCCa ion channel increases its *de novo* expression favoring the massive internalization of Na^+ and water into the cell. Expression of the *Abcc8* gene encoding SUR1 depends on the transcriptional factor Sp1. Since binding activity of this transcriptional factor is sensitive to oxidative stress, antioxidants such as resveratrol, might blocked target Sp1 genes and have a protective effect on cerebral ischemia. **Objective.** We evaluated whether resveratrol prevents edema formation through regulation of SUR1-NaCC *de novo* expression in cerebral ischemia. **Material and methods**. Wistar rats were subjected to occlusion of the middle cerebral artery (MCAO) for 2 h followed by 24 h of reperfusion. Resveratrol was given (1 mg/kg, in 50 % ethanol; *i. v.*) at the onset of reperfusion. Protective effect was evaluated measuring infarct area by TTC stain, neurological state by a behavioral test and the survival rate. Edema was evaluated using brain water content measured andmicrovascular permeability by blue Evans extravasation. Binding activity of Sp was measured by EMSA assays and expression of SUR1 by qPCR and immunoblotting. **Results.**Bindingactivity of the transcriptional factors Sp was increased significantly by MCAO. After 15 minutes of reperfusion was observed the highest increase in the binding (22.13-fold). Consequently, Abcc8 mRNA (5.8-fold) and SUR1 protein (26.0-fold) levels were increased after 24 h of reperfusion. These changes were associated with cerebral edema formation, increase on water content (4.1%) and microvascular permeability (13.42%). Similarly, the infarct area increased, representing 40.8% of the brain area which was associated to the subsequent deterioration of the neurological state (52.3%) and reduction of survival rate(61.9%). Administration of resveratrol had a protective effect: reduced the water content to 2.9% and permeability of microvessels to 5.20%. Likewise, resveratrol reduced the infarct area to 29.3%, improved neurologic status to 2.9% and survival to 90.4%. These results coincides with the effect of resveratrol on binding activity of the transcriptional factors Sp, as well as Abcc8 mRNA levels and the SUR1 protein which return to baseline levels. In addition, similar effect on SUR1 expression was observed with the administration of other antioxidants at equimolar concentrations.**Conclusions**. By inhibiting SUR1 expression, resveratrol reduces edema formation on cerebral ischemia. Thisprotective effect could be due to its antioxidant capacity since other antioxidant compounds have the same effect. Our findings represent an advance in the description of the molecular mechanisms of action of resveratrol on cerebral ischemia protection that exhorts its subsequent application in clinical studies.