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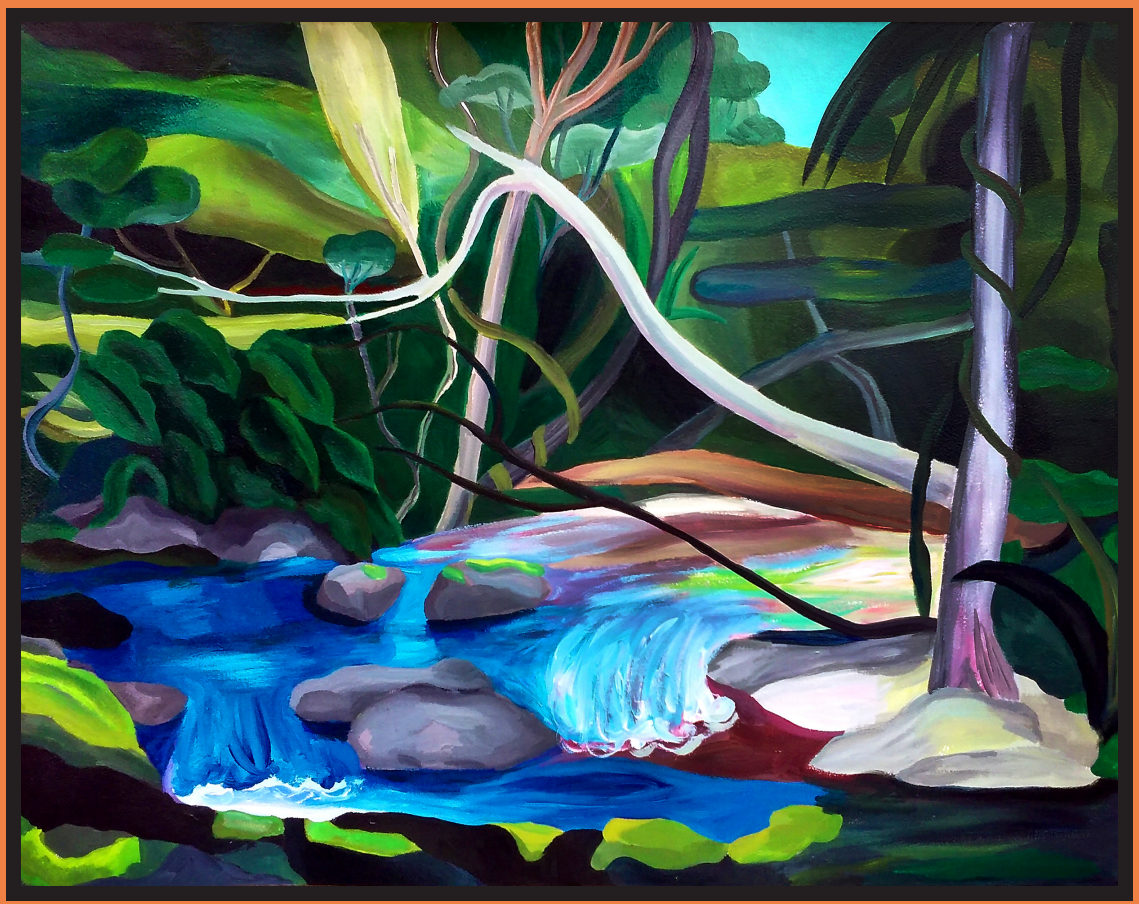

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for the involvement of the MAPK/ERK pathway, whereas the PI3K and JNK inhibitors exhibited only a mild effect on neurite outgrowth. Nonetheless, the number of neurites per cell was significantly greater in the presence of the JNK inhibitor. It is concluded that FK506 is a more efficient neurodifferentiating agent than RA, and it is proposed that the FK506 mechanism of action requires the MAPK/ERK pathway, whereas the JNK inhibition appears to favour neuronal arborization.

239. 204. **PRESERVED EXPRESSION OF THE NEURONAL CHLORIDE TRANSPORTER KCC2 AND ITS PHOSPHORYLATION AT SERINE 940 AFTER PROGESTERONE ADMINISTRATION IN AN EXPERIMENTAL MODEL OF SPINAL CORD-INJURY-INDUCED SPASTICITY**

Sol Ferreyra[1], Mariana Rey[2], Florencia Labombarda[3,4], Alberto Yorio[5], Héctor Coirini[2], Susana Gonzalez [1,3]
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Spinal cord injury (SCI) decreases the expression/activity of KCC2, a neuronal transporter involved in chloride homeostasis, promoting the development of spasticity. Our previous work demonstrated that progesterone (PG), a neuroactive steroid, improves functional outcomes and prevents injury-induced neuropathic pain. Here, we study whether PG can preserve the expression of KCC2 in the membrane of spinal motoneurons and the phosphorylation of serine 940 (pKCC2), a critical event for its functional activity. Male rats (SD) underwent spinal transection at T13 level and received daily PG (16 mg/kg sc, during 3 days post-injury, n=18) or vehicule (SCI, sc n=18). Uninjured rats were used as control (C, n=18). Transverse sections (20 µm) of the lumbar spinal cord were used for KCC2 immunohistochemistry and images of were acquired with a confocal microscope. Fluorescence intensity was measured at six points on randomly drawn lines at the motoneuron membrane (A1, B1, A2, B2, A3, and B3) and three linear areas in the neuropil near the motor neurons (C1, C2, and C3). KCC2 intensity of each neuron was defined as follows: KCC2 intensity = (A1 + B1 + A2 + B2 + A3 + B3) /6 - (C1 + C2 + C3) / 3. Total KCC2 and pKCC2 were evaluated in membrane fractions by Western blot. Immunofluorescence analysis showed that PG administration preserved the expression of KCC2 at the plasma membrane of spinal neurons ($p<0.01$ vs SCI; ns vs CTL). SCI animals showed a drastic reduction of pKCC2/KCC2 ratio ($p<0.001$ vs CTL), which was significantly increased in PG-treated animals ($p<.0.05$ vs SCI). After 3 days after PG administration, animals did not develop long-term alterations in the frequency-dependent depression of Hoffman (H) reflex a tool to assess spasticity (8 weeks after injury, at 4 and 8Hz, $p<0.001$ vs. SCI), which was impaired in SCI animals ($p<0.001$ vs C). Our findings add strong evidence to support the use of progesterone-based therapies for preventing SCI-induced spasticity.

240. 219. **GABAERGIC SYSTEM AND GNRH EXPRESSION DURING THE REPRODUCTIVE CYCLE IN THE PLAINS VIZCACHA, *Lagostomus maximus***

Cecilia V. Vazquez Dusefante[1], Alejandro R. Schmidt[1,2], Micaela Llanos[1], Ileana Burd[1], Luisa Quiroga[1], Julia Halperin[1,2], Verónica B. Dorfman[1,2,*]
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The plains vizcacha, a rodent that inhabits Argentina, shows peculiar reproductive features such as the reactivation of the hypothalamic-pituitary-ovarian axis during pregnancy with follicular recruitment and pseudo-ovulation at mid-gestation. We showed that the hypothalamic gonadotropin-releasing hormone (GnRH) neurons are modulated by glutamate with different results according to the glutamate receptor subtype. Here we studied the relation of the GABAergic system with the hypothalamic GnRH expression during the reproductive cycle. Non-pregnant ovulating (NPO) and non-ovulating (NPNO) and pregnant (early-, mid- and term-pregnant) vizcachas were used (n=3-5/group). The expression and distribution of GAD65/67 and GABAB in the preoptic area (POA) and the median eminence/arquate nucleus (ME/ARC) was studied by immunohistochemistry, and their relation with GnRH expression by immunofluorescence and confocal analysis. GAD immunoexpression was detected in the neuropil of both POA and ME/ARC regions. The POA showed significant increased expression of GAD in the NPO, early-, and mid-pregnant animals, while the ME/ARC of NPNO and early-pregnant vizcachas showed increased expression than the other groups. In addition, close contacts of GAD immunoreactive terminals were observed surrounding GnRH neurons of the POA. Strikingly, redistribution of GAD was observed in NPO and mid-pregnant animals with conspicuously more expression around the vessels of the primary capillary plexus of the ME where GnRH axonic varicosities arrive. GABAB was determined in neurons of the ME/ARC located among GnRH axonal varicosities with radial distribution related to the third ventricle. However, GABAB expression was almost undetectable in the POA. In the ME/ARC, NPNO, early-, and mid-pregnant animals showed increased GABA-B expression. These results indicate variations of the GABAergic system throughout the reproductive cycle of the female vizcacha with a possible functional impact on GnRH neurons.

241. 235. **MITOCHONDRIAL OXIDATIVE METABOLISM IN MOUSE BRAIN CELL PRIMARY CULTURES**

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[1]Instituto de Bioquímica y Microbiología, UACh, Valdivia, Chile; [2]Center for Interdisciplinary Studies on Nervous System (CISNe), UACh, Valdivia, Chile; [3]Janelia Research Campus HHMI, Ashburn, VA, US.

Glucose is the main source of energy for mammalian cells. Once glucose is transported to the cell, it is oxidized through glycolysis and Krebs cycle. Regarding brain energy metabolism, it is known that this organ is one of the most energetically expensive, showing a great neuronal dependence on obtaining energy through mitochondrial oxidative metabolism. Culture conditions play an important role in primary cultures from animal experimental models. However, chemical (composition of the medium, buffering system, pH) or physical (O_2 tension, temperature or extracellular matrix) variables are rarely studied, and they may not closely mimic the *in vivo* environment. Hence, the aim of this work is to study the adaptative mitochondrial oxidative metabolism in brain cell primary cultures. Using a fluorescent sensor genetically encoded for NADH and NAD^+, we determined the mitochondrial oxidative metabolism in neurons and astrocytes from cortical brain, as well as in astrocyte-enriched primary cultures. We observed an “anaerobic” glycolytic metabolism in the early stages of neuronal primary cultures, and an adaptive response tending to increase mitochondrial oxidative metabolism in later stages (19 independent experiments; n=4; *p<0,0121, **p<0,0032, ****p<0,0001; ns>0,9999). On the other hand, both astrocyte-enriched cultures and astrocytes co-cultured with neurons showed an “anaerobic” glycolytic metabolism (11 independent experiments; n=5, *p<0,0119; ns>0,9999), as the *in vivo* evidence shows. Future studies should be considered to analyze whether this metabolic adaptation is consistent with *in vitro* synaptic maturation, among other issues. All data in this study were normalized and treated with one-way ANOVA followed by a Bonferroni post-test.

242. 301. **CHRONIC DEPOLARIZATION OF OHC IMPAIRS THE MATURATION PROCESS OF THE MOC SYSTEM**

Ezequiel Rías[1,2], Ingrid Ouwerkerk[1,2], Guillermo Spitzmaul[1,2], Leonardo Dionisio[1,2].
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The efferent pathway mediated by the medial olivocochlear (MOC) system regulates the excitability of outer hair cells (OHC). In response to sound overstimulation, the MOC system activates nicotinic acetylcholine receptor α9α10, which in turn, activates BK and SK2 channels, helping KCNQ4 to remove K^+, and to restore resting

membrane potential (RMP). Several conditions lead to chronic depolarization by K^+ accumulation (i.e. KCNQ4 impairment), damaging OHC and causing hearing loss. We hypothesized that the KCNQ4 absence, by altering RMP impacts the organization and function of the MOC system affecting the setting of the hearing process.
Using confocal imaging, we evaluated the location of MOC terminals on OHC in *Kcnq4*$^{+/+}$ and *Kcnq4*$^{-/-}$ animals at different stages: immature (2 postnatal weeks (W)), and fully developed (3, 4, and 10W). At mature ages, MOC terminals are exclusively located in the OHC basal domain in WT animals. At 2W, both genotypes possess 32% of synaptic contacts in the lateral domain. Subsequently, all terminals relocated to the basal domain in WT animals. However, in KO ones, 9.5%, 15% and 1.5% of the terminals remained in the lateral domain at 3, 4 and 10W, respectively. Moreover, we detected a decrease in both, the number of synaptic contacts per OHC and their volume, in 4 and 10W KO animals remaining unaltered in WT ones. On the other hand, we analyzed by qPCR the expression of the postsynaptic efferent components located in the MOC synapse. In 4W *Kcnq4*$^{-/-}$ animals, the mRNA expression of α10 subunit decreased 3.5-fold with no changes in α9 subunit; and BK and SK2 decreased 8-fold. However, at 10W, α10 expression returned to WT levels while BK increases 6-fold. These findings show that chronic depolarization affect the efferent innervation development and the expression of its components in OHC, impacting the MOC system function. This contributes to hearing impairment by compromising the precise tuning role exerted by the MOC system on OHC transduction.

243. 354. **THERAPEUTIC EFFECT OF METFORMIN IN EXPERIMENTAL OPTIC NEURITIS**

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In a previous work we have developed an experimental model of primary optic neuritis (NEO) in rats through the microinjection of lipopolysaccharide (LPS) directly into the optic nerve (ON), which reproduces the central hallmarks of primary human NEO. Currently, there are no effective therapies for the treatment of NEO. Beneficial effects of metformin have been demonstrated in several inflammatory diseases of the central nervous system. The objective of this work was to evaluate the effect of the treatment with metformin on the axoglial alterations of the ON and the retina induced by experimental NEO. To do this, adult male Wistar rats were injected with 1 µl of LPS (4.5 µg/µl) in one NO, whereas the contralateral ON was injected with vehicle (sterile saline). A group of animals was treated with metformin (i.p.) (100 mg/kg) at 24 h before and at 2, 4 and 6 days after the injection of LPS or vehicle (preventive treatment). Another group of animals received metformin (100 mg/kg) at days 4 and 6 post-LPS/vehicle (delayed treatment). At 21 days post-LPS/vehicle, the following parameters were analysed: i) visual pathway function (visual evoked potentials (VEPs)), ii) consensual pupillary reflex (CPR), iii) microglia/macrophage reactivity, iv) astrocytic reactivity, v) number of axons, vi) demyelination, and vi) number of retinal ganglion cells (RGCs). LPS induced a significant and persistent decrease in VEPs and RPC amplitude, increased Iba-1 immunoreactivity and ON astrocytosis, demyelination and loss of ON axons, as well as loss of RGCs ($P<0.01$ vs. vehicle). Pre-treatment with metformin significantly prevented the alterations these parameters ($P<0.01$ vs. LPS). Delayed treatment with metformin significantly reversed the decrease in VEPs and RPC amplitudes caused by LPS injection ($P<0.01$ vs. vehicle). In summary, these results suggest that metformin could be considered a new treatment for experimental NEO and a potential therapeutic strategy to treat NEO in humans.

244. 377. **SPHINGOSINE-1-PHOSPHATE SIGNALING IS ESSENTIAL FOR PRESERVING MORPHOLOGY AND FOCAL ADHESIONS OF RETINA PIGMENT EPITHELIAL CELLS**

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Cell-cell interactions between retinal pigment epithelium (RPE) cells provide the retina with a physical and metabolic barrier, the disruption of which characterizes many inflammatory and proliferative retinopathies. However, the underlying causes of this disruption are still ill-defined. We showed that the bioactive sphingolipids sphingosine-1-phosphate (S1P) and ceramide-1-phosphate (C1P) promote migration and inflammation in RPE cells. Using the human RPE cell line ARPE-19, we now analyzed whether S1P regulates cell morphology and RPE monolayer integrity. Inhibiting S1P synthesis with PF543, a sphingosine kinase 1 (SphK1) inhibitor, markedly decreased ARPE-19 cell migration in confluent cultures, without affecting cell survival. Using 50% confluent cultures, to better observe morphological changes, we determined that PF543 treatment promoted a remarkable cell retraction; highly elongated cells, absent in controls, augmented to 34±2% ($p>0.01$), their cell length/width ratio increasing to 5.3, from 1.6 in controls. S1P addition, 1 h after PF543 treatment, restored cell morphology, reducing elongated cells to 8±1.4% ($p>0.01$), suggesting that S1P inside-out signaling is required for preserving cell morphology. In contrast, C1P addition did not restore cell morphology in PF543-treated cells. When we preincubated cells with PF543 and JTE-013, a S1P2 receptor (S1P2) antagonist, before S1P addition, JTE-013 partially blocked S1P restoration of cell morphology. To analyze the mechanisms involved in cell adhesion, we determined distribution of paxillin, a scaffold protein in focal adhesions. While controls showed spot-like paxillin clusters in the cell periphery, these clusters disappeared in PF543-treated cells and were restored after S1P addition. These results suggest that inhibiting S1P synthesis leads to morphological changes and focal adhesion remodeling, and activation of the S1P/S1P2 axis is required for preserving cell morphology and establishing focal adhesions.

245. 409. **INFLUENCE OF ISOLATION ON MOTOR PERFORMANCE IN FEMALE (NFR/wr) MICE, A CONDITION WITH GENETIC SUSCEPTIBILITY TO MOTONEURON DEGENERATION**

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Amyotrophic lateral sclerosis (ALS) is a fatal motoneuron disease characterized by progressive motor impairment leading to severe disability. ALS shows higher incidence in men and women are older at onset. The Wobbler (wr/wr) mouse is a recognized model of ALS. The autosomal mutation in the wr gene encodes for the vesicular protein sorting (Vps) 54 transport protein and causes motoneuron disease in homozygous condition. Heterozygous mice (NFR/wr) show a healthy phenotype. We postulate that genetic susceptibility to motoneuron degeneration is influenced by stressful situations. We studied the progression of motor performance on the accelerating rotarod in female NFR/NFR or NFR/wr mice at 2 ages (4- and 12-month-old) during 8 weeks. After training, animals were evaluated in the rotarod weekly during 2 weeks. Then, mice were separate in 2 groups during 6 weeks: 1) family or 2) socially isolated. Before sacrifice, isolated mice were subjected to acute stress during 2 hs. All animals were sacrificed during diestrus. We found that family-4-month-old NFR/wr mice showed a better performance than family-NFR/NFR ($p<0.01$) while family 12-month-old, NFR/NFR and NFR/wr, showed a similar performance. With regards to isolation, 2-way ANOVA followed by Tukey post-hoc test showed that NFR/wr ran shorter distance under isolation than family NFR/wr ($p<0.05$) at both ages. Body weight of 4-month-old NFR/NFR mice increased after 8 weeks of evaluation while both ages of NFR/wr showed sim-