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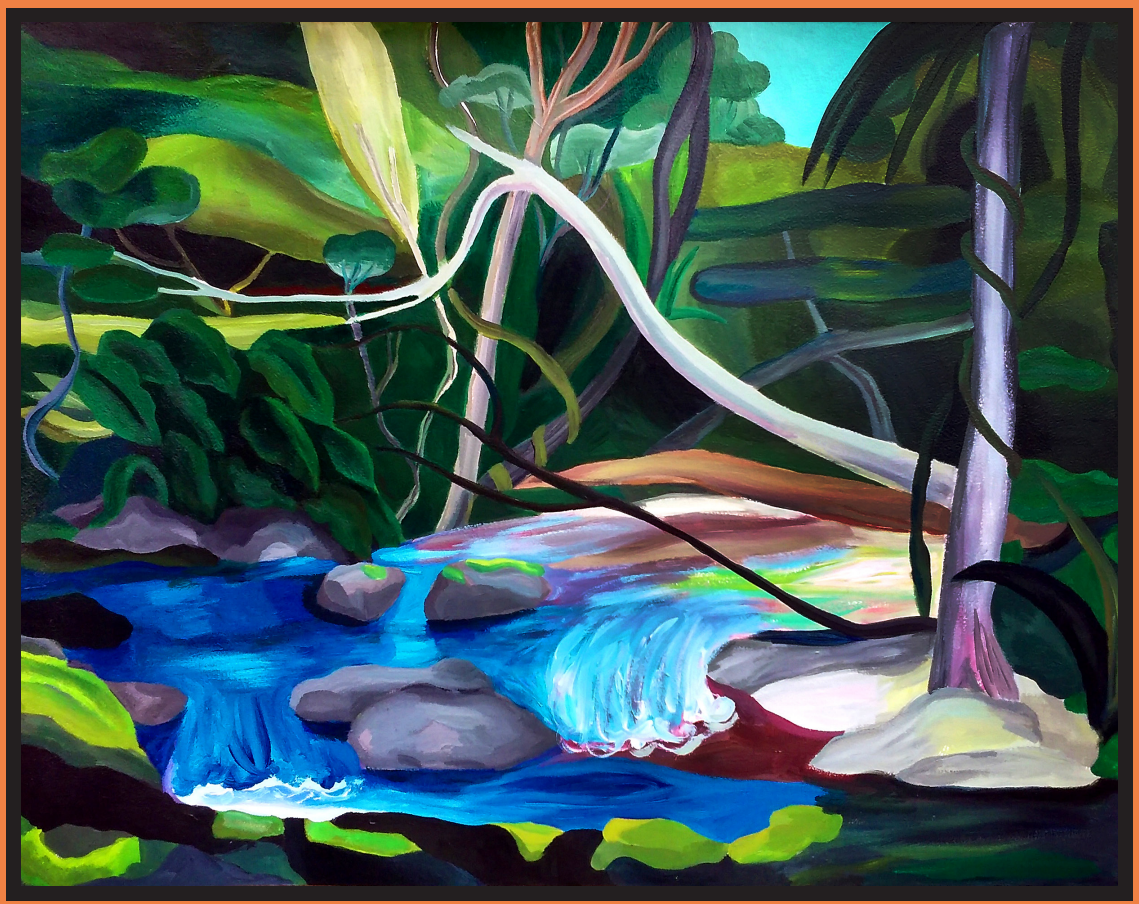

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membrane potential (RMP). Several conditions lead to chronic depolarization by K^+ accumulation (i.e. KCNQ4 impairment), damaging OHC and causing hearing loss. We hypothesized that the KCNQ4 absence, by altering RMP impacts the organization and function 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-