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and heated 115°C for 40 min. Extractions were performed by adding 5% (w/v) ethanol, vortexed, sonicated and agitated. The mixture was centrifuged and the supernatant was evaporated under stream of N_2. THC, cannabidiol (CBD) and cannabinol (CBN) were quantified by HPLC. CC syn from adult (4-6 months) and aged (24-26 months) rats were isolated by differential centrifugation and purified in ficoll gradients. MAGL activity was assessed by incubating syn with either THC enriched CE (10^{-3}-50 µM THC) or 1 µM pure THC, and [^{3}H]-MAG, simultaneously. It was observed that CE containing 1 µM THC decreased MAGL activity in aged (p=0.0166) but not in adult syn (p>0.05). However, 1 µM pure THC failed to modulate 2-AG hydrolysis (p>0.05). This findings, could suggest that THC enriched CE could attenuate the deregulation of 2-AG metabolism observed in aging, and that this effect could only be generated when syn are exposed to the PC in the presence of the entire CE.

391. (122) **MOLECULAR ALTERATIONS CAUSED BY CHRONIC COCHLEAR DEPOLARIZATION IN A MOUSE MODEL OF HEARING LOSS**

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The voltage-gated potassium (K+) channel KCNQ4 is the main responsible for the extrusion of the K+ that enters the cochlear sensory cells upon sound stimulation. Besides, outer hair cells (OHC) excitability is under control of the efferent neurons of the Medial Olivocochlear (MOC) system. In response to overstimulation, MOC cholinergic neurons activate the calcium-induced K+ channels BK and SK2, which extrude K+ out of the cell repolarizing the membrane. Intracellular accumulation of K+ leads to a chronic depolarization that may damage hair cells causing hearing loss (HL). KCNQ4 activity impairment is the main cause of DFNA2, a non-syndromic progressive HL. Using a mouse model lacking Kcnq4 (*Kcnq4-/-*), we reported that OHC death begins at the basal turn progressing to the apex in 3-6-week-old (W) animals. We hypothesized that the KCNQ4 absence causes MOC chronic overstimulation leading to activation of death pathways. Using immunofluorescence (IF), we evaluated the MOC terminals and observed a lower synaptic density and mislocalization of the efferent terminals contacting OHC in 4W *Kcnq4-/-* mice. In addition, we analyzed by qPCR the gene expression of the efferent components located in the MOC terminals. We detected a ~3.5-fold decrease in the mRNA expression of the nicotinic receptor α10 subunit with no changes in the α9 subunit, and a ~8-fold decrease in the mRNA expression of BK and SK2 in 4W *Kcnq4-/-* animals. Finally, we studied the possible pathways involved in OHC death. By IF, we found an increase of cleaved-caspase 3 expression in the OHC at the basal turn and gene expression analysis by qPCR revealed that the pro-apoptotic *Bax* transcript was upregulated while anti-apoptotic *Bcl2* was downregulated in *Kcnq4-/-* mice. These results demonstrate an alteration of the efferent transmission in OHC that could contribute to the activation of the apoptotic pathway driving to OHC death.

392. (123) **EPIGENETIC MECHANISMS UNDERLYING ASTROGLIAL HETEROGENEITY IN REACTIVE ASTROGLIOSIS: TARGETING CHROMATIN REMODELERS AS A POSSIBLE THERAPY TO REDUCE DAMAGE AFTER BRAIN INJURY**

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Astrocytes respond to brain injury through a phenomenon called reactive astrogliosis in which a pro-inflammatory and pathological subpopulation of astrocyte has been described, capable of promoting neuroinflammation and neuronal death. Astrocyte pathological conversion with a pro-inflammatory gain of function involves dramatic and stable transcriptomic changes, probably following activation of transcription factor NF-kB. NF-kB interacts with chromatin remodelling enzymes and recruits them to regulatory regions of target genes promoting epigenetic changes in other cell types.
We aim to address the epigenetic mechanisms that are associated with NF-kB activation in reactive astrocytes that might lead to the establishment of an astrocyte pathological identity.
Using immunofluorescence microscopy and PCR analysis in primary cultures of mouse cortical astrocytes with different microglia abundance and exposed to pro-inflammatory stimulus LPS (Lipopolysaccharide), we observed that LPS significantly promoted: 1) Sequential NF-kB activation in microglia>>astrocytes together with morphological and transcriptional changes, 2) A variable intensity of initial NF-kB activation in astrocytes depending on microglial abundance and the release of microglial soluble factors and 3) A microglial-dependent increase in gene activating histone marks H3K9K14ac and H3K27ac and a decrease in the repressive mark H3K9me3. *In vivo* brain ischemia recapitulated the increase in H3K27ac specifically in reactive astrocytes from ischemic penumbra and inhibition of histone deacetylases exacerbated astrogliosis and brain damage.
Our results showing changes in histone mark abundance are highly indicative of chromatin remodeling events in a subpopulation of pro-inflammatory reactive astrocytes. Such epigenetic mechanisms may represent plausible therapeutic targets to reduce astrocyte pro-inflammatory phenotype, neuroinflammation and neuronal loss after brain injury.
Grants: UBACYT, FONCYT, ISN-CAEN, APBIOTECH

393. (125) **SPLENECTOMY: SHEDDING LIGHT ON THE SPLEEN-BRAIN INFLAMMATORY COUPLING IN A MODEL OF TEMPORAL LOBE EPILEPSY**

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A high percentage of patients with temporal lobe epilepsy (TLE), one of the most frequent neurological diseases, refer an initial precipitating event (IPE), such as complex febrile seizures during childhood, followed by a silent latency period (LP), until the onset of the chronic seizures phase. Using the lithium-pilocarpine rat model of TLE we previously showed that neurodegeneration, reactive gliosis and macrophages brain infiltration occur during the LP and that early interventions limiting immune activation during the LP increase epileptic threshold during the chronic phase (Rossi et al., 2013; 2017). The model consists of the administration of lithium-pilocarpine (127 mg/kg /30 mg/kg, 20h apart) to male Wistar rats. Animals develop Status Epilepticus (SE) that mimics human IPE and SE is limited to 20 min by 20 mg/kg i.p. diazepam. In this work, we have found morphological evidence of early spleen white pulp activation 1 day post SE (DPSE), while increased CD3+ and CD4+ lymphocytes in the choroid plexus, without changes in the gut-associated lymphoid tissue (GALT), followed by a decreased abundance of naïve lymphocytes in blood and spleen smears were found at 2-3DPSE.
In order to evaluate the relevance of the spleen-brain inflammatory coupling in the LP that follows pilocarpine-induced SE, we performed splenectomy (n=6) to 210-220 g male Wistar rats anesthetized with ketamine-xylazine (90 mg/kg/10 mg/kg) 1 week before the lithium-pilocarpine treatment. Sham animals were used as controls. Our loss of function studies showed that splenectomy decreased astrogliosis, neuroinflammation and deep cervical lymph nodes size at 7DPSE. We conclude that peripheral immune system is responding to specific brain-derived clues triggered by the SE and the spleen is involved in the modulation of neuroinflammation that follows SE.
Supported by PICT 2017-2203; UBACYT; and FONCYT fellowship (PS).

394. (152) **UNDERSTANDING THE SPATIO-TEMPORAL DISTRIBUTION OF REACTIVE ASTROCYTES AFTER FOCAL BRAIN INJURY AND THE ROLE OF TOLL-LIKE RECEPTOR SIGNALING**

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