family of enzymes, and more specifically PKCγ isoform, regulates important aspects of synaptic plasticity and memory. In addition, PKCγ has been found to interact with cannabinoid receptors. In this study, we investigated the density and activity of cannabinoid receptors and the lipidomic profile of PKCγ knock-out mice, which show mild cognitive impairment. Brains from PKCγ knock-out mice (n = 9) and matched wild-type controls (n = 12) were used. Autoradiographies using [^{3}H]CP55,940 and [^{35}S]GTPγS stimulated by WIN55,212-2 were performed to study cannabinoid receptors density and activity, respectively. Mass spectrometry imaging (MSI) was used to study lipidomic changes. PKCγ knock-out mice showed markedly increased CB1 density in key brain areas for learning and memory, including the amygdala, the frontal and motor cortex and the hippocampus CA region. Importantly, in the dentate gyrus, where expression of PKCγ is very low, CB1 density did not increase, suggesting that changes in the eCB system are induced by the absence of PKCγ expression in a region-specific manner. Interestingly, regulations in receptor activity were more subtle and sometimes inverse to reported density changes. While in the *globus pallidus* CB1 activity increased too, in most CA regions it showed a tendency to decrease. Just like receptor density, CB1 activity was unaltered in the dentate gyrus. Divergent results between receptor density and activity suggest that compensatory mechanisms caused by the absence of PKCγ expression occur at different levels of the eCB signalling pathway. These results indicate that the eCB system adapts in the absence of PKCγ, highlighting that this isoform participates in the CB1-dependent signalling cascade and is thus key to better understand the dual effects of cannabinoids on memory.

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Topic: AS06 Neural Excitability, Synapses and Plasticity

IMPACT OF CHRONIC ETHANOL EXPOSURE ON INHIBITORY MODULATION OF CRF1-EXPRESSING NEURONS IN THE MOUSE VENTRAL BED NUCLEUS OF THE STRIA TERMINALIS

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The transition to alcohol dependence is associated with the recruitment of corticotropin releasing factor (CRF) and its CRF receptor 1 (CRF1) in the extended amygdala, including the bed nucleus of the stria terminalis (BNST). Here, we used an innovative transgenic mouse model in which CRF1 expressing (CRF1 +) neurons co-express green fluorescent protein (GFP) (CRF1:GFP mice) to assess the spontaneous GABAergic inhibitory postsynaptic currents (sIPSC) and acute alcohol responsivity of the CRF1 + neurons in the BNST in the development of alcohol dependence. To induce dependence, adult male CRF1:GFP mice were exposed to chronic intermittent ethanol (CIE) inhalation (16 h) followed by air (8 h) daily for ~5 weeks. Coronal BNST slices (300 μm) were prepared and whole-cell patch-clamp recordings of ventral BNST neurons were performed. We observed significantly higher basal sIPSC frequency in vBNST CRF1 + neurons relative to CRF1- neurons in both ethanol naïve and CIE mice. However, lower basal sIPSC frequency was observed in both neuronal populations from CIE mice compared with naïve mice. In addition, bath application of acute ethanol (44 mM) decreased sIPSC frequency in CRF1- vBNST neurons from naïve mice, but not in CIE mice. Acute ethanol had no effect on sIPSCs in CRF1 + neurons from naïve mice, but significantly decreased their frequency in CIE mice. Our results indicate that, independent of treatment, vBNST-CRF1 + neurons have higher GABAergic input compared with vBNST-CRF1- neurons and chronic ethanol decreases GABAergic input in both neuronal populations. Further, acute ethanol application decreases GABAergic input in CRF1- and CRF1 + vBNST neurons from naïve and CIE mice, respectively. To our knowledge, this is the first study to assess how acute and chronic ethanol alter the physiology of this unique CRF1 + population in the vBNST, and further research will produce insights into the neural mechanisms behind stress and alcohol dependence.

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Topic: AS06 Neural Excitability, Synapses and Plasticity

PHOTOACTIVATION OF INDIVIDUAL SYNAPSES IN VIVO WITH COVALENT PHOTOSWITCHES TARGETING ENDOGENOUS GLUTAMATE RECEPTORS

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Glutamate receptors (GluRs) play key roles in neurotransmission at excitatory synapses and in the regulation of synaptic plasticity. We have developed a targeted covalently-attached photoswitch (TCP,

Izquierdo-Serra et al., 2016) that allows the remote control of endogenous ionotropic GluRs using light. We here combined this photopharmacological effector with genetic and chemical calcium sensors to demonstrate all-optical reversible control of GluRs at multiple levels of spatial resolution in the brain: we achieved the photoactivation of multiple neurons, individual neurons, and single synapses in rat hippocampal slices and in intact *Xenopus laevis* brain *in vivo*, which is challenging using other methods. We show that this compound selectively targets AMPA and kainate receptors. Labeled receptors remained functional for long periods of time (>8 hours). This allowed us to longitudinally track endogenous receptor physiology during events of synaptic plasticity, such as long-term depression (LTD). We could monitor the loss of functionality of AMPA/kainate receptors during NMDAR-dependent LTD in hippocampal neurons. TCPs are, therefore, a unique optical tool to label, photocontrol and functionally track endogenous receptors in brain tissue without genetic manipulation.

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Topic: AS06 Neural Excitability, Synapses and Plasticity

ALTERED PREDICTIVE PROCESSING IN THE INFERIOR COLLICULUS OF A RAT MODEL OF AUTISM

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Autism spectrum disorder (ASD) refers to a range of conditions characterized by challenges in social communication and restrictive, repetitive behaviors. Within this repertoire, unusual reactivity to sensory inputs (*e.g.*, aversion or engagement to specific sounds) highlights as a diagnostic criterium. The predictive coding theory attempts to account for these symptoms, proposing a decreased ability to anticipate upcoming sensory information due to overly precise internal prediction models. Especially, when situations (*e.g.*, social) or stimuli (*e.g.*, sounds) become highly dynamic. Due to this, autistic people might display difficulties interpreting and responding to context-dependent stimuli (*e.g.*, social and environmental interactions), which become a daily-life challenge. Here, we studied the predictive processing of auditory stimuli at the subcortical level in a rat model of ASD. We injected valproic acid during pregnancy in rats to induce ASD in the offspring. We investigated the mechanisms that underlie the mismatch negativity generation, as it has been found to be different in autistic individuals. Specifically, we used female and male rats in prepubertal (PD 30-48) and adult (PD 65 and beyond) stages. We made single-unit recordings in the inferior colliculus in response to a classical oddball paradigm, which elicited the violation (deviant) of the regularity generated by the repetitive (standard) stimuli. Results so far show alterations in neuronal mismatch negativity responses at the midbrain level, supporting atypical low-level predictive processing in this model of ASD. These results support the notion of atypical predictive processing in autistic individuals, which may account for limited adaptive behavior under unexpected situations. Work supported by project PID2019-104570RB-I00 funded by MCIN/ AEI/10.13039/501100011033/ and The Foundation Ramón Areces grant CIVP20A6616 to MSM. SCS holds the grant FPU21/00124 funded by MCIN/AEI/ 10.13039/501100011033 and ESF. ABLR was supported by the EU's Horizon-2020 No.952378-BrainTwin.

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Topic: AS06 Neural Excitability, Synapses and Plasticity

INTERMITTENT COCAINE SELF-ADMINISTRATION AND PASSIVE INFUSIONS INCREASE SUBTHRESHOLD ACTIVITY IN MIDBRAIN DOPAMINERGIC NEURONS

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Substance use disorder (SUD) is a chronic brain disease characterized by transitioning from recreational to compulsive drug use. Intermittent Access (IntA) cocaine self-administration is a protocol suggested to simulate human drug consumption due to its intermittent patterns. IntA has been documented to produce incentive salience, psychomotor sensitization, and a neurochemical sensitization of the mesolimbic dopamine (DA) system by increasing DA release and neuron sensitivity to cocaine. DA neurons of the ventral tegmental area (VTA) display a mixed cation current conductance known as the hyperpolarization-activated cyclic nucleotide current (Ih). Neural processes like resting membrane potential and firing frequency modulation are influenced by the Ih. Previous results from our laboratory demonstrated that Ih amplitude and membrane capacitance (Cm) of VTA DA neurons is significantly reduced after cocaine sensitization. These reductions resulted in increased temporal summation. However, it is unknown how drug self-administration alters the intrinsic properties of VTA DA cells. This study explored if Ih, synaptic integration, Cm, and cell activity alterations are present after exposure to cocaine IntA. We hypothesize that a brief period of cocaine IntA enhances VTA DA cells' synaptic integration. Using in-vitro electrophysiology in rat brain slices, we analyzed the effects of cocaine IntA and passive cocaine infusions on synaptic integration. Our results demonstrate that cocaine IntA produces a significant Ih amplitude reduction of a higher magnitude than passive cocaine infusions. Animals in the cocaine IntA and yoke protocol have a significant increase in temporal summation at depolarized and negative potentials. These results suggest that the associative learning of drugs modulates the Ih of VTA DA neurons and that associative learning processes could enhance synaptic