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"Modulation of synaptic transmission in Nucleus Accumbens core by the activation of 5-HT_{2A} receptor in male mice"

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Serotonin (5-HT) is a neurotransmitter and neuromodulator that plays an essential role in physiological functions such as sleep, feeding, sexual behavior, temperature regulation, pain, and cognition. Also, it is involved in pathological states, including psychosis, pain management, mood and anxiety disorders. In the Central Nervous System (CNS), 5-HT acts through 14 different receptors once released by serotonergic neurons. These neurons belong in the midbrain Raphe nucleus and innervate many brain areas. Several studies have pointed out a role for serotonin in the reward system. Serotonergic projection neurons arising from dorsal and median Raphe nuclei innervate limbic brain areas involved in this system, such as the prefrontal cortex (PFC), ventral tegmental area (VTA), and nucleus accumbens (NAc), making the serotonergic system a modulator of synaptic transmission within mesocorticolimbic related areas. In PFC, this modulation is given by the activation of the 5-HT2A receptor (a G Coupled-Protein Receptor) that upon activation can produce increases in calcium and diacylglycerol intracellular levels, enhancing excitability and mediating endocannabinoid synthesis and release. In this regard, little is known about the serotonergic transmission in the NAc, where at least 6 types of 5-HT receptors (5-HT1A, 1B, 2C, 2A, and 4, 6) are expressed. In this nucleus, GABAergic medium spiny neurons (MSNs) comprise more than 90% of the neural population, but how serotonergic neurons modulate their activity is poorly understood when it comes to inhibitory transmission. To assess this question, we hypothesized that

5-HT modulates inhibitory transmission in the NAc core mainly through the activation of 5-HT2A receptor. Using a combination of electrophysiological and pharmacological techniques, such as whole-cell patch clamp, we evaluated evoked and spontaneous inhibitory transmission under the effect of different drugs. We discovered that 5-HT2A R activation produces a depression of the inhibitory synaptic transmission, also called iLTD (inhibitory long-term depression), that requires intracellular calcium rise upon GPCR activation (Gq), activation of PLCβ enzyme to form diacylglycerol (DAG) and inositol-1,4,5-triphosphate (IP3) and involves the production of endocannabinoids (e.g. 2-arachidonoylglycerol (2-AG)). 2-AG retrogradely decrease the release probability of GABA by the activation of presynaptic CB1 receptors. Therefore, acting in a pre and

post-synaptic manner. This effect could be translated into an altered excitation/inhibition balance, which relates directly with the neurophysiological processes that underlie neuropsychiatric disorders such as addiction, schizophrenia and depression.

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