PROJECT

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1) Project title
Targeting melatonin receptors for neuropsychiatric disorders
2)Abstract (max 500 words)
Melatonin (MLT), a neuromodulator mainly acting through two G-protein coupled receptors named MT1 and MT2, regulates many brain functions, including circadian rhythms, mood, pain and sleep. MLT and non-selective MT1/MT2 receptor agonists are clinically used in neuropsychiatric and/or sleep disorders although their efficacy is still debated. Ongoing research in our lab is showing the importance of selectively targeting only one of the two MLT receptors in terms of both disease pathophysiology and psychopharmacology drug discovery. This is due to the fact that 1) there are changes in the density across the light/dark cycle and in the relative distribution of MLT receptors in the brain, and 2) MT1 and MT2 receptors control unique physiological responses as example in sleep, anxiety, pain, and depression. However, the selective role of MT1 and MT2 receptors in the brain as well as their potential to be target of novel therapies for neuropsychiatric diseases still need to be clarified. In this project, we will thus investigate in mice the neuropsychopharmacological properties of novel and selective ligands for MT1 and/or MT2 receptors using well validated animal paradigms for depression, anxiety, social behavior, and cognitive and motor functions. We will also explore their neuronal mechanism of action using in-vivo electrophysiology in anesthetized or freely moving mice and neurochemistry (determination of neurotransmitter release and metabolism using high performance liquid chromatography (HPLC) technique). In particular, we will study their effects at the level of serotonergic, dopaminergic and prefrontal cortex pyramidal neurons that are known to modulate emotions and behavior, and to be dysfunctional in several neuropsychiatric disorders. These pharmacological studies will be performed in specific animal models of unipolar and bipolar depression. Finally, preclinical findings will be supported by data in unipolar and bipolar patients in which we will examine the correlations between plasma and genetic biomarkers of the melatonin system and psychopathology. Collectively, this project will provide the neurobiological and pharmacological basis for developing selective MT1 and/or MT2 receptors ligands as novel drugs in neuropsychopharmacology.