PROGETTO

Supervisore: Danilo De Gregorio

Titolo/*Title*: Targeting the 5-HT_{2A} receptor for treating alcohol use disorder (AUD)

Curriculum: Neuroscienze e Neurologia Sperimentale

Link alla pagina personale del sito web di Ateneo o del polo ospedaliero di riferimento:

https://www.unisr.it/docenti/d/degregorio-danilo

Descrizione del progetto (max 3.000 caratteri spazi inclusi)

Background/gap of knowledge

Alcohol use disorder (AUD) is a growing phenomenon affecting populations. In 2020, in Italy, 65000 new accesses to care have been registered, accounting for 5.9 million euros only for pharmacological treatment. AUD is further burdened by disability and increased morbidity and mortality due to both mental and physical conditions, as well as accidents[1,2]. Pharmacological treatments for AUD are limited in their effectiveness, and the development of novel targets is essential[3]. AUD involves a variety of neurotransmitter systems in interaction, but dopamine (DA) and serotonin (5-HT) are critical in mediating alcohol reward and dependence. A substrate of AUD is the mesocorticolimbic DA system, consisting of the ventral tegmental area (VTA) DA neurons projecting to the medial prefrontal cortex (mPFC)[4]. 5-HT dysfunction involves several receptors and transporters; interestingly, 5-HT_{2A} receptor agonists showed promising therapeutic potential in AUD[5]. However, the neural mechanism linking 5-HT_{2A} receptor to both AUD aetiology and treatment remains elusive.

Rationale and hypothesis

The overarching aim of this proposal is to examine the role of the 5-HT_{2A} receptor in the modulation of alcohol consumption in an approved and validated murine model of alcohol use disorder (AUD), the drinking in the dark (DID) protocol. This procedure consists of a limited-access paradigm whereby high-drinking strains, such as C57BL6/J mice, lose control over

ethanol intake when the water bottle is replaced with 20% ethanol in the home cage for a limited period of time (2 hours) for 4 consecutive days, beginning 3 hours into the dark cycle[6,7,8]. We hypothesize that the pharmacological activation of this receptor reduces the consumption of alcohol in the DID model in male and female mice through the modulation of the neuronal activity in the VTA and and in the mPFC. This study would not only have positive implications for the treatment of patients dealing with AUD, but also from a future drug discovery perspective.

Objectives and specific aims

Employing a multidisciplinary approach spanning from behavioral paradigms, electrophysiology, morphology and biomolecular analysis, we will first i) investigate the impact of the AUD on the 5-HT_{2A} mRNA levels in the mPFC and in the ventral VTA of male and female mice following 6 weeks of DID procedure. By employing the local field potential (LFP) recordings, we ii) will then use a selective agonist of the 5-HT_{2A} receptor, the 2,5-dimethoxy-4-iodoamphetamine (DOI, 1 mg/kg, intraperitoneally injected)to assess the impact of the pharmacological activation of the 5-HT_{2A} receptor on the VTA and mPFC neuronal activity in freely-moving male and female mice following the chronic alcohol consumption. Finally iii), we will test if the treatment with the DOI will impact the dendritic spines in the mPFC of male and female mice following chronic alcohol consumption.

Expected outcomes

We expect statistically significant data (SSD) about the impact of chronic alcohol consumption on the mRNA levels of the 5-HT_{2A} receptor in male and female rodents. Moreover, we expect SSD about the effect of the pharmacological activation of the 5-HT_{2A} receptor in both male and female rodents following chronic alcohol consumption and that this effect will be accompanied by the modulation of neuronal activity in the VTA-mPFC circuit.

Competenze che deve acquisire lo studente (Max 600 caratteri spazi inclusi):

The PhD student will learn how to perform translational research to treat a psychiatric condition such as alcohol use disorder. In particular, the student will acquire various skills spanning from behavioral pharmacology, in vivo electrophysiology and morphological analysis.

Bibliografia (max. 15)

1. J. Rehm et al., Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. The lancet 373, 2223-2233 (2009).

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4. B. Juarez et al., Midbrain circuit regulation of individual alcohol drinking behaviors in mice. Nature communications 8, 2220 (2017).

5. Calleja-Conde, J., Morales-García, J. A., Echeverry-Alzate, V., Bühler, K. M., Gine, E., & López-Moreno, J. A. (2022). Classic psychedelics and alcohol use disorders: A systematic review of human and animal studies. Addiction Biology, 27(6), e13229.

6. T. E. Thiele, M. Navarro, "Drinking in the dark"(DID) procedures: a model of binge-like ethanol drinking in non-dependent mice. Alcohol 48, 235-241 (2014).

7. J. S. Rhodes, K. Best, J. K. Belknap, D. A. Finn, J. C. Crabbe, Evaluation of a simple model of ethanol drinking to intoxication in C57BL/6J mice. Physiology & behavior 84, 53-63 (2005).

8. B. R. Cox et al., Repeated Cycles of Binge-Like Ethanol (E t OH)-Drinking in Male C 57 BL/6 J Mice Augments Subsequent Voluntary E t OH Intake But Not Other Dependence-Like Phenotypes. Alcoholism: clinical and experimental research 37, 1688-1695 (2013).