PROGETTO

Supervisore: Danilo De Gregorio

Titolo/*Title*: The additive effect of ketamine in combination with electroconvulsive stimulation (ECS) in major depressive disorder

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

Major depressive disorder (MDD) is a debilitating disease that is characterized by at least one depressive episode lasting at least 2 weeks and involving changes in mood and in cognition. The brain neurocircuitries of MDD involve several regions including the hippocampus[1] and the medial prefrontal cortex (mPFC)[2]. Current pharmacological treatments for depression have a delayed therapeutic onset, ranging from several weeks to months, and there is a high percentage of individuals who never respond to treatment [3]. National Institute for Health recommends electroconvulsive stimulation (ECS), known in humans as electroconvulsive therapy, as an option for patients with MDD if they have not responded to multiple drug and psychological treatments. However, critics contend that ECS invariably results in cognitive impairments [4]. Ketamine is an anaesthetic that has been used in ECS anaesthesia. Intriguingly, ketamine at sub-anaesthetic dose is a rapid-acting antidepressant with efficacy for treatment-resistant symptoms of depression [5]. Despite these findings, the proof of concept is lacking that ketamine at sub-anaesthetic dose can potentiate the antidepressant effects of ECS and at the same time can alleviate cognitive adverse effects ECS-related, thus accelerating symptomatic improvement. To this end, we here propose to perform a preclinical study to assess the additive effect of ketamine with ECS in a murine model of depression.

Rationale and hypothesis

We hypothesize that the add on of a sub-anaesthetic dose of ketamine to ECS reverts the depressive phenotype of male mice under chronic stress with higher efficacy compared to ECS or ketamine alone and limits cognitive impairments related to the ECS stimulation and that this effect is accompanied by a modulation of hippocampal and cortical biomarkers, increased neurogenesis and modulation of neuronal activity in the hippocampus.

Objectives and specific aims

Employing a multidisciplinary approach spanning from behavioral paradigms, electrophysiology, optogenetics, morphology and biochemical analysis, we will i) first investigate the ability of ketamine to potentiate the antidepressant effect of the ECS without causing cognitive impairment related to ECS in a mouse model of depression. Moreover, we will study ii) the ability of ketamine in combination to ECS to modulate biomarkers and neurogenesis in the mPFC and hippocampus of mice following chronic stress. Finally, we will iii) investigate the role of cortico-hippocampal circuitry in the mechanism of action of ketamine/ECS by recording the neuronal activity of hippocampal neurons in combination with the optogenetic photo-inhibition of the mPFC.

Expected outcomes

Our data will provide: behavioural, morphological and neurochemical data unveiling the mechanism of the combination of ketamine and ECS in mice under chronic stress and the correlation between electrophysiological alterations and behavioural outcomes.

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 major depressive disorder. In particular, the student will acquire various skills spanning from behavioralparadigms of depression, in vivo electrophysiology, optogenetics and morphological analysis.

Bibliografia (max. 15)

1 Campbell S. Journal of psychiatry & neuroscience. 2004.

2 Belleau EL et al. Biological psychiatry. 2019;85(6):443-53.

3 Otte C et al. Nature reviews Disease primers. 2016;2(1):1-20.

4 Argyelan M et al. Translational Psychiatry. 2021;11(1):1-7.

5 Krystal JH et al. Neuron. 2019;101(5):774-78.

6 Krishnan V et al. Cell. 2007;131(2):391-404.

7 Abelaira HM et al. Molecular neurobiology. 2022:1-24.

8 Aguilar-Valles A. Nature. 2021;590(7845):315-19.

9 Aguilar-Valles A. Nature communications. 2018;9(1):1-14.

10 Messaoud A. The World Journal of Biological Psychiatry. 2018.

11 De Gregorio D et al. Proceedings of the National Academy of Sciences. 2021;118(5).