Universidad de Navarra

Máster en Investigación Biomédica
Facultad de Ciencias

Research Project Proposal
Academic year 2015-2016

Project Nº 38
Title: Role of genetic manipulations of GluN3A-containing NMDA receptors in depression using a model of chronic stress.
Department/ Laboratory : Cellular Neurobiology Laboratory, CIMA, University of Navarra.
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Summary NMDA receptors are heteromers containing GluN1 subunits and combinations of four GluN2 (A–D) and two GluN3 (A–B) subunits. The function of GluN2A and GluN2B has been well established in brain plasticity, learning and memory, but little is known about GluN3A-subtypes. We have shown that altered GluN3A levels trigger synapse dysfunction and loss of cognitive abilities, and is associated to CNS pathologies such as Huntington disease or cocaine abuse (1,2,3). Suppressing aberrant expression restores normal plasticity, connectivity and behavior pointing towards GluN3A as a promising therapeutic target (1,3). More recent genetic evidence links mutations/polymorphisms in Grin3a (the GluN3A-encoding gene) to alcohol abuse and mental disorders including depression or schizophrenia, but a causal relationship is missing. This project seeks to determine the effects of genetic manipulations in GluN3A expression on depressive-like behaviors using a chronic (10 days) social defeat model of depression. We will use two different strains of genetically modified mice available in the laboratory: GluN3A transgenics and GluN3A KO mice. The goal will be to test if the mice present susceptible or resilient phenotypes when confronted to more aggressive congeners, and if this phenotype can be reversed by antidepressant treatment. Part of the work will be done in collaboration with Dr. Rosa Tordera, neuroscientist at the Pharmacology Department and expert in stress behaviors. These goals will be completed using: 1) behavioral tests such as: Sucrose Preference Test and Force Swimming Test; Social defeat paradigm with an aggressive CD1 mouse and Social Interaction Test with a novel CD1 aggressor, 2) DNA genotyping by PCR and, 3) evaluation of signaling pathways involved. The protocols for treatment with

antidepressants will be established during the study.

References

1. Marco, S., et al. Suppressing aberrant GluN3A expression rescues synaptic and behavioral impairments in Huntington's disease models. Nature medicine 19, 1030-1038 (2013).
2. Roberts, A.C., et al. Downregulation of NR3A-containing NMDARs is required for synapse maturation and memory consolidation. Neuron 63, 342-356 (2009).
3. Yuan, T., et al. Expression of Cocaine-Evoked Synaptic Plasticity by GluN3A-Containing NMDA Receptors. Neuron 80, 1-14 (2013).

POSSIBILITY OF PhD

YES*

* (PhD grant required)