Universidad de Navarra

Máster en Investigación Biomédica
Facultad de Ciencias

Research Project Proposal
Academic year 2016-2017

Project Nº 32 ASIGNADO
Title: Roles of juvenile NMDA receptors containing juvenile GluN3A subunits in anxiety, stress and social behaviors: Implication of the oxytocin/vasopressin balance?
Department/ Laboratory Cellular Neurobiology Laboratory, Center for Applied Medical Research(CIMA), University of Navarra.
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Summary During critical periods of postnatal development, immature neural networks are intensively rearranged (or "refined") by external experience. Refinements involve stabilization of some synapses but pruning of many others, resulting in irreversible changes in brain function that will determine adult patterns of behavior. Failures in activity-dependent rearrangements of neural circuits are emerging as major causes of neurodevelopmental disorders including autistic spectrum disorders (ASD), mental retardation and schizophrenia. Three events have remarkably important roles on the timing, extent and coupling to experience of synaptic refinements during critical periods of postnatal development: 1) Maturation of the composition and function of NMDA-type glutamate receptors (NMDARs) where juvenile NMDARs containing GluN3A subunits are replaced by mature subtypes lacking GluN3A (1); 2) Oligodendrocyte proliferation, differentiation and myelination of central axons; and, 3) maturation of axonal projections of oxytocinergic neurons to cortical areas or other mechanisms modulating oxytocin release (2). This project seek to perform a comprehensive behavioral analysis of memory and stress-related behaviors in transgenic mice with altered GluN3A expression. To do this we will use two different strains of genetically modified mice available in the laboratory: GluN3A double transgenics and GluN3A KO mice (3). The goal will be to test if the mice present a behavioral phenotype that could be predicted from an early maturation of the oxytocin/vasopressin system (OT/AVP) and whether supression of

GluN3A expression could produce biochemical changes in the OT/AVP system.

These goals will be completed using: 1) behavioral tests such as: Open Field, Elevated Plus Maze, Three Chamber, Sucrose Preference Test, Novelty suppressed feeding Test and Force Swimming Test; to generate chronic stress we will perform chronic restraint in adults and early-life stress in juvenile mice, 2) DNA genotyping by PCR and, 3) evaluation of signaling pathways involved by immunohistochemisry and in situ hybridation. The protocols to rescue the phenotype will be established during the study.

References

1. Pérez-Otaño, I., Luján, R., Tavalin, S.J., Plomann, M., Modregger, J., Liu, X.B., Jones, E.G., Heinemann, S.F., Lo, D.C., Ehlers, M.D. Endocytosis and synaptic removal of NR3A-containing NMDA receptors by PACSIN1/syndapin1. Nature Neuroscience 9(5): 611-21 (2006).

2. Grinevich, V., Knobloch-Bollmann, H.S., Eliava, M., Busnelli, M., Chini, B. Assembling the Puzzle: Pathways of Oxytocin Signaling in the Brain. Biological Psychiatry 79(3): 155-64 (2016).

3. Roberts, A.C., Díez-García, J., Rodriguiz, R.M., López, I.P., Luján, R., Martínez-Turrillas, R., Picó, E., Henson, M.A., Bernardo, D.R., Jarrett, T.M., Clendeninn, D.J., López-Mascaraque, L., Feng, G., Lo, D.C., Wesseling, J.F., Wetsel, W.C., Philpot, B.D., Pérez-Otaño, I. Downregulation of NR3A-containing NMDARs is required for synapse maturation and memory consolidation. Neuron 63(3): 342-56 (2009).

POSSIBILITY OF PhD

YES*

* (PhD grant required)