



Research Project Proposal

Academic year 2015-2016

Project Nº 43
Title: Regulation of serotonin (5-HT) function by a VGLUT1 dependent glutamate pathway.
Department/ Laboratory Department of Pharmacology and Toxicology (Neurpharmacology research area)
Director 1 Dr Rosa M Tordera Baviera Contact: rtordera@unav.es (948 425600, ext. 806624) Codirector: Dr Elena Puerta Contact: epuerta@unav.es
Summary: <p>It is widely accepted that in many patients altered serotonergic function may contribute to the aetiology and pathophysiology of affective disorders and frequently co-morbid with anxiety disorders. Moreover, drugs affecting the serotonergic function have had success in the treatment of major depression. Still, although the molecular mechanisms underlying the 5-HT dysfunction are unknown, experimental evidences suggest an important role for both local and long-loop feed back mechanisms of control over the 5-HT activity in the brain stem including the excitatory (glutamate) and inhibitory (GABA) neurotransmitter systems. Further, clinical and pre-clinical studies have linked major depression to an imbalance in the excitatory-inhibitory ratio in different brain areas. In keeping with this, unraveling the mechanisms of 5-HT neuron control might provide new insights into depression pathophysiology. In addition to the inhibitory 5-HT_{1A} autoreceptors, cortico-raphé glutamatergic descending pathways are suggested to modulate 5-HT activity in the DRN. Here we will study how decreased VGLUT1 levels in the brain stem affect glutamate regulation of 5-HT function.</p> <p>VGLUT1+/- mice (C57BL/6) and wild type (WT) littermates will be used. In addition, adenovirus overexpressing VGLUT1 (pDEST-B1-pSyn-B5-VGLUT1Venus-B2 y pDEST-B1-pSyn-B5-VGLUT1mCherryminisog -B2) will be used to rescue the phenotype observed in VGLUT1+/- mice. Specifically, the functionality of the inhibitory 5-HT_{1A} autoreceptor will be assessed using biochemical (5-HT levels by HPLC, 5-HT_{1A} mRNA expression) and pharmacological approaches (GTP-Gamma binding, in vivo recording of body temperatura) in all the groups.</p>



References

García-García AL, Venzala E, Elizalde N, Ramírez MJ, Urbiola A, Del Rio J, Lanfumey L, Tordera RM. Regulation of serotonin (5-HT) function by a VGLUT1 dependent glutamate pathway. *Neuropharmacology*. 2013 Jul;70:190-9.

Tordera RM, Garcia-Garcia AL, Elizalde N, Segura V, Aso E, Venzala E, Ramirez MJ, Del Rio J Chronic stress and impaired glutamate function elicit a depressive-like phenotype and common changes in gene expression in the mouse frontal cortex. *Eur Neuropsychopharmacol* 21:23-32. 2013

García-García AL, Elizalde N, Matrov D, Harro J, Wojcik SM, Venzala E, Ramirez MJ, Del Rio J, Tordera RM (2009) Increased vulnerability to depressive-like behavior of mice with decreased expression of VGLUT1. *Biol Psychiatry* 66:275-282.

POSSIBILITY OF PhD

YES*

* (PhD grant required)