Laboratory title : CNRS UMR 5287 - Jean-René Cazalets

Supervisor

Name : Pascal BRANCHEREAU

Thesis title :
5-HT control of chloride homeostasis in spinal motoneurons of the ALS mouse model

Keywords : amyotrophic lateral sclerosis (ALS), spinal cord, development, electrophysiology, immunocytochemistry

Contact

Firstname : Pascal  Name : BRANCHEREAU

E-mail : pascal.branchereau@u-bordeaux.fr

phone number : 05 40 00 25 63

Fax : 05 40 00 25 61

Abstract

This project will focus on the ontogeny of motor spinal networks in two transgenic mice that develop symptoms resembling human Amyotrophic Lateral Sclerosis (ALS): the SOD1G93A mouse and TDP43 mouse. Our working hypothesis is that ALS disease is a neurodevelopmental disease that is the consequence of compensatory mechanisms, to date never considered. A PhD Thesis work just ended demonstrating that SOD1G93A motoneurons (MNs) exhibit 2 days before birth (E17.5) alterations of their morphological and electrical properties, leading to hyperexcitability (Martin et al. Neurobiology of Disease 2013). We also show that the chloride homeostasis is affected in SOD1G93A MNs. Because 5-HT has been described as modulating chloride homeostasis in spinal MNs, we looked at the level of 5-HT in SOD1G93A and found a significant reduction. We thus propose to analyze by which mechanisms 5-HT is involved in the deregulation of the chloride homeostasis and whether it is possible to restore the chloride homeostasis by up-regulating the 5-HT level during the embryonic maturation of spinal MNs in the SOD1G93A / TDP43 ALS mouse models. If acting on the 5-HT system allows a recovery of the chloride homeostasis, we will analyze whether the lifespan of treated mice is improved. This PhD work will be a first step towards new research strategies essential to diagnose SLA at early stages.

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Methodology: electrophysiology, visual patch-clamp, in vitro, immunocytochemistry, confocal microscopy, 3D reconstruction, western blotting, qPCR, computer simulation, Ca2+ imaging

Qualification required

Neuroscience background. Good knowledge in electrophysiology. Interest in developmental processes in pathological conditions.