NAWA (NARODOWY PROGRAM WYMIANY AKADEMICKIEJ)

Homeostasis between synaptic inputs and intrinsic motoneuron excitability in physiological and pathological conditions

POPULAR SCIENCE ABSTRACT

The long goal of the collaboration between the polish and french partners aims at investigating how the homeostasis between synaptic inputs and intrinsic excitability of motoneurons, which is essential to maintain an adequate motoneuron firing, is challenged in physiological and in pathological conditions. This is a critical issue given that motoneurons are the output neurons that drive the muscles and that are thereby responsible for every motor act. Recent findings made by the team of Daniel Zytnicki in Paris show that "inputs - excitability homeostasis" is impaired in the SOD1 G93A mouse, i.e. a model of amyotrophic lateral sclerosis (ALS) that is a fatal neurodegenerative disease. In this model, the degeneration-vulnerable fast motoneurons become intrinsically hypoexcitable at presymptomatic stage as shown by their inability to produce sustained firing in response to stationary input (4) while the degeneration resistant slow motoneurons display intrinsic hyperexcitability in neonates (6). What is striking is that hypoexcitability of the vulnerable motoneurons is not counteracted by an increase of synaptic excitation. On the contrary, monosynaptic excitation of mutant motoneurons is decreased as shown by the recent investigation made by Marcin Baczyk during his Post-Doc stay in the french laboratory. He demonstrated that the monosynaptic EPSPs are about 30% smaller in mutant animals when compared to non mutated controls (2). This weakening of the synaptic strength is not caused by a reduced density of excitatory synapses but more likely by post-synaptic impairments. On the other hand experiments made on wild type rats in the polish laboratory indicate that motoneuron intrinsic excitability can be increased by modifications of the levels of physiological activation of motoneurons which occur during physical training. However how this intrinsic excitability affects synaptic excitation of the trained motoneurons has never been determined.

During the few coming years, the polish and french teams plan to investigate homeostasis between synaptic inputs and intrinsic excitability of motoneurons in two different models and with the use of two complementary methods. The Polish and French partners mastered complementary in vivo techniques which combined together create an unique opportunity to extensively study the problem of motoneuron homeostatic regulation. The french unit masters the intracellular recordings of the mouse motoneurons in vivo (7, 8). Furthermore within the animal facility of this unit it is possible to perform viral injections which are not possible in the polish institution. In Paris, we plan to manipulate the motoneuron excitability using intramuscular injections of adeno-associated virus (AAV). The virus will carry shRNAs to silence specific genes involved in the motoneuron intrinsic excitability. The shRNAs have already been validated on cellular systems and AAVs, holding these genetic sequences, have already been constructed. We will investigate the changes in synaptic excitation induced by alterations of the motoneuron intrinsic excitability by virus. This will allow to understand how the homeostatic mechanisms regulate the equilibrium between the motoneuron intrinsic excitability and the synaptic excitation thereby controlling the motoneuron firing.

The Poznan laboratory mastered the procedures of rat physical training aimed at modifying motoneuron firing properties. This laboratory has already proven that training protocols can induce hyperexcitability of motoneurons of rat subjected to Whole Body Vibration training (1) or muscle overload (5). One should be aware that it is possible to selectively target specific types of motoneurons with the use of proper training protocol. For example WBV training causes adaptation in motoneuron threshold and firing properties that are limited to the fast motoneuron subpopulation only while on the other hand endurance training influences predominantly slow motoneurons (3). We plan to induce alterations in motoneuron intrinsic properties by using known training protocols, and then test the impact of these manipulations on motoneuron synaptic excitation with the use of In vivo electrophysiological techniques. The experiments in Paris and in Poznan will allow us to understand the role of homeostasis between synaptic inputs and intrinsic excitability in the improvement of motor performances in physiological conditions or in the motoneuron degeneration in pathological conditions. We expect that the results will provide the scientific grounds to apply to competitive grants (EU programs like JPND or grants provided by international organization such as Thierry Latran Foundation, TARGET ALS or ALS Association to further develop our collaborative work. We also plan to apply for HARMONIA grant of the Polish National Center in order to be able to

reinforce our collaboration. Major part of this project is intended to be done by the PhD students and young Post-Docs with Polish and French applicants acting as project coordinators. Polish students and researchers will travel to Paris in order to learn and perform the AAV injections and mouse in vivo electrophysiological techniques, while french students and researchers will travel to Poznan to learn and perform the rat training and rat in vivo experiments. We plan that each member of the team to visit the collaborating lab 2 times during 2 years of the project, each stay lasting 30 days (in total 180 days for 3 members of the Polish team in 2 years). This kind of bilateral collaboration is essential for scientific staff mobility and development and fits well within the Mobility and Cross-Border Cooperation strategy of the European Council. At the Polish University side a stipend program financing up to 3 months scientific stay per applicant has been recently initiated in order to further support young researchers mobility. If successful, this financing source will be used to further support this collaboration and increase the duration of scientific stay. In the long perspective we also plan to bilaterally introduce the respective Polish and French experimental methods to our collaborating labs. Working on both mouse and rat preparations and the use of complementary methods will enable us to conduct large scale research project which would be impossible to perform by the partners separately. As a result we will create a strong binational team based not only on established researchers but also on young scientists trained in an international environment.