Project 1.2 Molecular mechanisms of 5-HT7R-mediated resilience in stress-related disorders

Supervisor: prof. dr hab. Jakub Włodarczyk

Laboratory: Cell Biophysics
www: https://www.nencki.edu.pl/laboratories/laboratory-of-cell-biophysics/

Background:

Stress resilience is a dynamic process whereby an individual can withstand stressful events while still maintaining normal, physiological functioning. Resilience is inferred from an observed level of cognitive performance higher than expected in the face of a demonstrated stressful event. The neural rewiring that leads to stress resilience resides in structural and functional synaptic plasticity. The importance of studying stress resilience has become more evident in the last years, considering the frequency and variety of stressors that humans have to cope with and the attendant stress-related disorders, and especially now more than ever due to the COVID-19 worldwide crisis. The molecular basis for stress resilience and the factors that modulate it are important research areas in neuropsychiatry and contemporary neuroscience. Numerous clinical observations as well as our own data (Bijata et al., Cell Rep. 2017; Gorinski et al., Nat. Comm. 2019) suggest that the serotonergic system may be critically involved in the regulation of the stress response. Stress resilience is considered to be the adaptive maintenance of homeostasis in the face of stress or adversity, but the exact molecular mechanisms are still enigmatic. Our recent results suggest that the resilience phenomenon is associated with the inactivation of the postsynaptic serotonin 5-HT7 receptor-mediated signaling. Supporting this view, we found that activation of the 5-HT7 receptor in the hippocampus leads to the development of depressive behavior, while its selective inhibition promotes stress resilience (Bijata et al., in rev.). Additionally, in resilient animals, we observed a compensatory remodeling of the dendritic spines of pyramidal neurons in the Stratum Oriens, which correlates with changes in the S Palmitoylation pattern of engaged proteins and the lack of activation of the 5-HT7R/MMP-9/Cdc42 signaling pathway in the hippocampus (preliminary results; Zareba-Koziol et al., Mol Cell Proteom., 2019) Taken together, we hypothesize that changes in the palmitoylation of proteins associated with 5-HT7R downstream signaling within a specific hippocampal region (namely Stratum Oriens or Stratum Radiatum) promote resilient behavior.

Aim:

The overall goal of the proposed project is to assess the molecular mechanisms of neural processes that underlie the phenomenon of resilience to chronic stress. We hypothesize that specific changes in the palmitoylation of proteins associated with 5-HT7R downstream signaling in the context of brain regions (namely in Stratum Oriens and Stratum Radiatum of the CA1 hippocampal region) are responsible for the behavioral switch between the resilient and depressive-like phenotype during stressful conditions. In this proposal, we will use an animal model of chronic unpredictable stress (CUS), in vitro cell culture, and human induced pluripotent stem cells (hiPSCs) to: (i) Assess the in vivo behavioral fingerprint of stress resilience; (ii) Define changes in synaptic plasticity at the structural and molecular levels associated with stress resilience; (iii) Determine in vitro molecular mechanisms underlying stress resilience; (iv) Evaluate if changes in human iPSC-derived neuronal model parallel those seen in the CUS paradigm and whether those changes differ within men and women.

Requirements:

For the implementation of the project we will use cell culture technique, molecular biology techniques, visualization techniques using light and confocal microscopy, bioinformatics methods and behavioral and memory tests. Thus the experimental background in at least two above mentioned techniques is required.