Small Changes - Huge Impact: The Role of S-palmitoylation and S-nitrosylation interplay in the mice model of depression

Depression is the most common psychiatric disorder in the world. Depression treatment consist of psychotherpy and pharmacotherapy. Unfortunately, more than half of patients is treatment resistant. Still there is little known about the role of S-nitrosylation (S-NO) and S-pamitoylation (S-PALM) – two posttranslational modification of proteins (PTM) in development of depression. S-PALM is lipid modification where palmitate is being attached to the protein what regulates many signaling pathways critical for proper brain functions. Importantly, S-PALM is necessary for isomerization of serotonin receptors (5-HT), what activates them. Ligands for 5-HT receptors such as serotonin, are targets for standard antidepressive medications. S-PALM is regulated by S-NO, another PTM in which nitric oxide (NO) is attached to proteins. In brains of rodents that have depression like symptoms lower number of neurons producing NO can be found. Moreover, in the blood serum of suicide victims elevated levels of NO metabolites have been detected. Disruption of NO metabolism associated with depression may influence regulation of PTMs and could be important factor in development of depression. Recently, it has been shown that ketamine – anesthetic and analgesic drug has remarkable antidepressive properties causing quick and lasting relieve of depressive symptoms in animals and humans. One of the mechanisms by which ketamine influence brain activity is by activating NO synthesis in neurons.

The aim of our project is to check if and how S-PALM and S-NO profile changes in the brain of mice, which developed depression like symptoms. First we will induce depressive like behavior in mice by exposing them to chronic stress. After achieving behavioral effect animals will receive ketamine at different concentrations in order to achieve antidepressive effect. Finally we will perform sophisticated and powerful proteomic analysis of PTM on proteins isolated from different brain structures associated with depression. We believe that above-mentioned PTMs, both in qualitative and quantitative manner, play critical role in the pathogenesis of depression as well as other psychiatric disorders. Results obtained by us will help in understanding the function of posttranslational modifications in the nervous system, what may bring us closer to development of more efficient antidepressive therapies.