Molecular mechanisms of 5-HT$_7$R-mediated resilience in stress-related disorders

Major depressive disorder (MDD) is currently one of the main civilization diseases in the world and it is predicted that will rank first by 2030. The importance of studying stress-related disorders has become more than ever evident now due to the spiked depressive episodes with the COVID-19 pandemic. One of the most effective approaches to treating depression is long-term psychotherapy combined with pharmacotherapy. Currently, there are several anti-depressant products available on the market manufactured by different companies, which mechanism of action based on reversing the symptoms of depression by restoring the balance of excitatory neurotransmission in the brain. An example of such drugs is new-generation antidepressants, the so-called SSRIs (*selective serotonin reuptake inhibitors*) which, by inhibiting the reuptake of serotonin, maintain its high concentration, thereby modulating the plasticity of synaptic connections. Unfortunately, each drug has a success rate of merely about 60%. This is due to the fact that depression is a very complex disease, its development is influenced by a variety of factors, including genetic predisposition and environmental conditions. Chronic stress is a key factor for developing a neuropsychiatric disease such as MDD and affects limbic structures including the hippocampus. Due to the connectivity with other limbic regions and increased sensitivity for stress hormones, the hippocampus displays marked structural atrophy of neuronal complexity, volume, and disturbed neurogenesis and is associated with cognitive deficits in MDD patients. However, stress alone is often not sufficient to induce disease, as a large contribution comes from synaptic changes depending on our individual vulnerabilities to stress. Although many individuals experience stressful events and are exposed to trauma during life, most of them do not develop psychiatric illnesses such as MDD – these individuals are stress-resilient. Stress resilience is the capacity and dynamic process of adaptively overcoming stress and adversity while maintaining normal cognitive functioning. While resilient behavior has been extensively investigated in the context of psychological, sociological, psychobiological, and neurobiological studies, research aimed at understanding the molecular bases of this behavioral phenotype is sparse.

The molecular theory of depression indicates that depression develops due to abnormalities in the synaptic plasticity of neurons. Dendritic spines make up the postsynaptic part of most excitatory synapses in the brain, and their shape reflects the strength of synaptic connections. Thin spines are classified as immature synaptic connections. In contrast, mushroom spines, forming more stable connections. Numerous neurological and neuropsychiatric diseases (including MDD) contribute to abnormalities in dendritic spine density and morphology. The similarities in morphological changes of dendritic spines in many diseases suggest that in pathological conditions there is often a problem with the transformation of immature spines into mature ones. Of importance, we have observed that animals resilient to stress reveal structural compensatory mechanism in the hippocampus (spine maturation), therefore the studies on mechanisms that modulate the shape of dendritic spines are important for understanding aberrant synaptic plasticity underlying stress-related disorders.

Although the effects of 5-HT receptors on synaptic plasticity have been studied for decades, the underlying molecular mechanisms of action of individual receptors on various forms of synaptic plasticity remain poorly understood. Up to this time, the most intensively studied was the 5-HT$_1$ and 5-HT$_2$ receptors. Recently, scientists have focused on 5-HT$_7$R. The studies have shown that the pharmacological blockade of 5-HT$_7$R results in antidepressive effect. Moreover, many antipsychotic or antidepressant drugs (e.g., clozapine and risperidone) interact directly with 5-HT$_7$R. Our studies suggest that stress resilience is associated with serotoninergic signaling in which 5-HT$_7$-R and posttranslational modification of synaptic proteins play a key role. The presented studies focus on the relation between serotoninergic signaling, dendritic spines remodeling, and stress resilience behavior.

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-HT$_7$R downstream signaling are responsible for the behavioral switch between the resilient and depressive-like phenotype during stressful conditions. This approach opens a new direction in pharmacology in which newly designed antidepressants will improve compensatory mechanisms during or before stressful conditions, without the need to reverse the depressive state as is commonly practiced. Delineation of the molecular factors associated with a resilient phenotype may not only lead to a better understanding of the pathogenesis of stress-related disorders but may also pave the way for the development of new and better-acting antidepressants.