The place does matter
- 5-HT$_7$R-mediated structural plasticity in the specific hippocampal subregions

Nowadays, we are constantly exposed to stress. Sometimes it is a mobilizing stress, but more often - especially when the state of tension lasts for a long time, it can adversely affect our health. Chronic stress weakens the functioning of many systems in the body (eg. the immune system), but most importantly it affects the functioning of the brain. A healthy body can cope with a certain level of stress and restore balance to him, but when is it too much stress, it can lead to an overload of these mechanisms. Stress causes an increase in corticosteroids levels, called stress hormones, and a simultaneous decrease in serotonin in the brain, which may lead to development of neuropsychiatric disorders like depression. Symptoms related to depression such as sadness, loss of interest and enjoyment, and reduced activity, sleeplessness, feelings of guilt or low self-worth, poor concentration, have been described already in ancient times by Hippocrates. In medical practice this disease today is one of the most common mental illnesses. According to World Health Organization the number of people suffering from depression increased by nearly 50% over the past 30 years. Over the course of decades of research, no highly effective antidepressant therapy has been found. Depression is a growing health problem in today's society. Epidemiological studies conducted throughout the world indicate that over the course of a lifetime, about 16% of the general population suffers from depression and close to 800 000 people die due to suicide every year. Depression is not only a chronic illness that threatens the lives and proper functioning of individuals in society but also entails enormous costs of treatment, social care and incapacity. World Health Organization estimates that annual global economic burden of depression is approximately 1 trillion $. It is estimated to be the most expensive brain disease in Europe. In addition to social and emotional costs, it now consumes a significant share of the health care budget. Affected patients require constant care.

Thus, the numbers speak for themselves. Great economic and social burden associated with depression is growing every year, mainly due to low efficacy of standard anti-depressive treatment. This may be due to poor understanding of the mechanisms underlying the pathogenesis of depression. Most of the therapy still focuses on the signaling pathways described many years ago. It is vitally important to find more effective and faster therapies. In order to achieve this, we need to better understand the molecular, cellular and network pathways involved in the pathophysiology of depression. The long history of research on serotonin receptors has contributed to the wide recognition of the extremely important and comprehensive role of serotonin receptor signaling in maintaining the physiological functioning of the organism. Although the effects of 5-HT receptors on synaptic plasticity has been studied for decades, the underlying molecular mechanisms of action of individual receptors on various forms of synaptic plasticity remain poorly understood. Over the last 60 years more and more studies have shown that the majority of all known serotonin receptors have a role to play in the pathophysiology of depression or depressive-like behavior. In the last decades the most intensively studied were the 5-HT$_1$ and 5-HT$_2$ receptors. Recently, increasing scientific attention has been shifting towards the 5-HT$_7$R. However, the exact mechanism of action of the 5-HT$_7$R in the pathogenesis of depression is still mysterious. Therefore, we have decided to expand our knowledge about this receptor function as part of this proposal.

It is currently believed that depression results from structural changes in the specific brain regions. Those changes are a result of impaired neuronal plasticity. Numerous neurological and neuropsychiatric diseases (including depression) contribute to anomalies in density and morphology of small protrusions on dendritic shaft (dendritic spines). The shape of dendritic spines usually correlates with their function and physiological strength of the synaptic connection. Recently, we have found a similarity between changes in the shape of dendritic spines caused by exposure of the animal to chronic stress and changes caused by activation of the serotonin 5-HT$_7$ receptor in the hippocampus. Uncovering the precise mechanisms regulating the formation and disappearance as well as the plasticity and stability of dendritic spines is extremely important for our understanding how the brain functions. Understanding the mechanisms that modulate the shape of the spines is absolutely important and could be a breakthrough in the treatment of depression. The proposal focuses on investigating the mechanisms behind structural plasticity in specific regions of the hippocampus following 5-HT$_7$ serotonin receptor activation. We will investigate the 5-HT$_7$R-mediated profiles of activation proteins involved in regulation of actin cytoskeleton in different hippocampal subregions and determining their role in structural plasticity. Moreover, we will characterize the types of neurons expressing the 5-HT7R in different hippocampal subregions and examining their electrophysiological properties.