

Depression is the most common and one of the most debilitating disorders of the central nervous system. It's estimated that over 300 million people worldwide suffer from depression. Nevertheless, the mechanisms associated with the pathogenesis of depression are still not fully understood. Furthermore, despite the availability of effective pharmacological therapies as well as psychotherapy, remission rates are low. Numerous antidepressant drugs that modulate serotonergic and norepinephrine neurotransmission, introduced into the clinic almost 70 years ago, are characterized by a slow onset of action, numerous side effects, and a noticeable resistance rate.

Therefore, there is a great need for new treatment strategies with faster and long-lasting effects, higher remission rates, and fewer side effects. Serotonergic psychedelics such as psilocybin, LSD and DMT are one of the most fascinating groups of psychotropic substances. They have been shown to be effective in the treatment of post-traumatic stress disorder and alcohol addiction. Interestingly, they were known to exert rapid and enduring antidepressant activity along with anxiolytic potential in humans even before the classical monoaminergic antidepressants were introduced into the clinic. In the past 15 years, renewed interest in serotonergic psychedelics has led to the accumulation of new evidence confirming their great antidepressant potential. It should be emphasized, however, that psychedelics used in doses required in monotherapy can cause side effects that are difficult for many patients to accept. Therefore, their medical use is controversial. Considering the above, there is a great need to look after pharmacotherapeutic solutions to reduce the doses of administered psychedelics in order to reduce their side effects while maintaining their therapeutic potential.

The results of preclinical studies have shown that the blockade of metabotropic glutamate receptors type 2/3 (mGlu2/3 receptors) induce rapid and prolonged antidepressant effects in rodents. What is important in the context of the following project, the potential therapeutic effects of mGluR2/3 blockers are functionally dependent on the activity of the serotonergic system. It should also be noted that several studies including our own findings indicate that modulation of mGlu2/3 receptors activity increases the antidepressant effects of hallucinogens, including serotonergic psychedelics, along with a significant reduction in their side effects.

Considering the above, the main goal of this project is to evaluate the antidepressant activity of combined administration of serotonergic psychedelics with compounds affecting mGlu2/3 receptors activity in animal models of depression. Due to the fact that the causal relationship between the modulation of mGlu2/3 receptors, serotonergic psychedelics and the antidepressant effects are not fully understood, this project will attempt to elucidate the molecular and cellular mechanisms involved in the antidepressant activity of selected compounds. As the subject of research is very complex, the project will be highly interdisciplinary. In the first step, behavioral effects of selected compounds will be assessed. Next, a series of molecular, neuroanatomical and electrophysiological studies will be performed to unravel the biological mechanisms related to the therapeutic effects of tested compounds in the context of simultaneous modulation of the serotonergic and glutamatergic systems.

The following project may thus lead to a better understanding molecular mechanisms associated with the pathophysiology of depression and open new avenues towards developing more effective and safer therapies for depression.