

Depression has been the leading cause of disability worldwide. It is estimated that over 400 million people worldwide suffer from depression during their lifetime. Since the serotonin hypothesis of depression was formulated dysregulation of serotonergic signalling has been considered a risk factor for the pathogenesis of depression and depressive-like behavior. The classical antidepressant drugs which were introduced into the clinic in the 1960s, affect the monoaminergic neurotransmitter system including serotonergic signaling. They have constituted a major breakthrough in the pharmacology of mental illnesses and confirmed that modulation of serotonin neurotransmission is a good target for antidepressant interventions. However, they are also characterized by a slow onset of action, severe adverse effects related with their chronic uptake, and a noticeable resistance rate. Therefore, there is a large need for searching of novel treatment strategies with faster onsets of action and greater remission rates.

Psychedelics such as psilocybin, LSD, DMT and 5-MeO-DMT belong to a group of psychoactive substances producing altered states of consciousness. What's interesting they had been known to exert rapid and prolonged antidepressant (AD) activity in humans even before the classical monoaminergic antidepressants were introduced into the clinic. It is worth noting that this was the first demonstration that fast and long-lasting AD effect is achievable by the direct modulation of serotonergic signalling. The new wave of clinical trials have confirmed promising AD potential of psychedelics. It should be noted however, that psychedelics may cause adverse effects and their medical use is still very controversial. Therefore, it is crucial to discover how psychedelics modulate neuronal circuits to understand their AD action, and thus establish their therapeutic safety profile.

The exact mechanism underlying AD efficacy of psychedelics is still an open question. It has been demonstrated that psychedelics interact directly with several serotonin receptors. Receptors are specialized membrane proteins that receive and transmit information to enable the body to respond to various stimuli and changes. Therefore, this project aims to elucidate the involvement of distinct serotonin receptors and its effects in the AD activity of psychedelics at the behavioral, functional, cellular, and molecular levels.

The results of our proposal may provide insights into the potential mechanisms underlying AD action of psychedelics and broaden knowledge about complex processes in the brain in the context of pathophysiology of depression. In the future our results may pave the way towards developing more efficient therapies as well as improved prevention strategies.