

Major depressive disorder is a debilitating mental illness characterized by prolonged depressed mood and inability to experience pleasure (anhedonia) from otherwise pleasurable activities. It affects significant part of the society (bigger, than all the other mental disorders combined) and can be fatal, either directly, due to increased likelihood of suicide, or indirectly, due to increased risk of cardiovascular and cerebrovascular diseases. The source of depression seems to be located in complex interactions between genetic and environmental factors, one of the major is undoubtedly stress. Stress, especially in its' chronic form may lead to maladaptive changes in vulnerable individuals, leading to increased morbidity for neuropsychiatric disorders.

Antidepressant drugs used these days are needed to be taken for weeks, to improve the patients' mental state. Moreover, they are often characterized by low clinical efficacy, or even lack of efficacy in case of some patients. That is why, since the half of XX century continues search for a „Holy Grail” of antidepressant drugs, a drug that would improve patients' mood from the first intake, and would have therapeutic effect also in patient resistant to classical anti-depressive drugs. Ketamine could be this drug, as it exhibits antidepressive properties only after couple of hours after intake, but it also possesses a plethora of adverse effects, which crosses it out as a universal drug in therapy of this disorder.

Research based on humans indicate, that this place could be filled with 5-HT_{2A} receptor agonists, known more commonly as psychedelics. Clinical research showed, that LSD or psilocybin can induce antidepressant effect as fast, as ketamine, and the improvement of mood can last up to 6 months, contrary to the week-long effect of ketamine. What is interesting, even though clinical efficacy of psychedelics was proven, there is lack of knowledge concerning mechanism behind their antidepressive properties.

In our project we would like to answer a couple of important questions regarding psychedelics. Using the procedure of chronic mild stress we would like to induce in rat behaviour, that is alike to depression in humans: anhedonia, anxiety and disruption of motivational and cognitive functions. A lot of peer-reviewed studies has been conducted to prove, that those changes can be reversed by both classical antidepressant drugs and ketamine. We'd like to evaluate if psilocybin or more selective compound, the 25I-NBOMe would reverse the changes induced by chronic mild stress. If so, we'd like to find out what changes in neurotransmission are the reason behind antidepressive properties of those two compounds. Furthermore, we'd like to investigate, if those drugs could normalize synaptic plasticity, a phenomenon strongly interrupted in depressive patients. What is more, we'd like to examine, if those compounds affect the hypothalamic-pituitary-adrenal axis, and if they could exert their action through reduction of levels of stress-related hormones.

To sum up, the research proposed could deliver new data concerning „virgin” area of neuropsychopharmacology, that is antidepressant action of psychedelic drugs. It could contribute then to invention of novel therapies in treatment of major depressive disorder and in consequence, to reduce the time needed to help patients suffering from this morbid mental disease.