Depression is the most common mental disorder. Statistics indicate that approximately 15-18% of the population manifested symptoms of depression, including up to 2% of children and 4% of young people. Depression can be a fatal disease, which confirms the increased number of suicide deaths among patients. This is a problem, not only to the nature of clinical, but also social and economic. Due to the "malaise" patients have a limited ability to work, resulting in their absences and generates billions in losses for businesses around the world. It should be noted that it is a chronic and dominant disease, especially in developed countries.

Despite over 60 years of research on depression and attempts to develop better and better medicines, there is still no medication that would display high efficiency and, above all, quick anti-depressant action. Modern antidepressants despite a wide spectrum of activities require long-term use, which is necessary to achieve satisfactory therapeutic effect. Moreover, there is no certainty that received drug will be effective, since about 30% of patients are resistant to antidepressant treatments. Difficulties in the treatment and diagnosis of depression follow by poorly known patomechanisms of this disease.

The studies in recent years show the importance of impaired (hyperactivity) glutamatergic transmission in the course of depression, in particular the significant involvement of the NMDA and AMPA receptors. These receptors are an important element in the exchange of information between neurons (excitatory neurotransmission) and are involved in learning and memory. However, an excessive activity of NMDA and AMPA is a phenomenon detrimental to the cells and can lead to excitotoxicity, which is also observed in the course of depression. Traditionally it was believed that a sufficient explanation of the functional changes is modifications of the synaptic transduction (eg. addition of phosphate groups) existing in cell membrane receptors, leading to changes in the conductivity, or permeability to ions (including calcium). Studies in recent years have destabilized the static image synapses, revealed its dynamic structure in which the receptors constantly circulate between the inside of the cell (spot synthesis) and cell membrane. Moreover, even within the same membrane receptors can move, adjusting their amount to the current needs of the cell. The concomitant protein identified as protein scaffolds device largely determines mobility of the receptors. These include proteins which various functions (e.g. attach / detach various functional groups to the other proteins retain other proteins in the vicinity of the cell membrane). In pathological processes (disease) may disturb the cyclization of the various receptors including NMDA and AMPA, which may be associated with impairment of the interaction between mobile scaffolding proteins.

All those conditions meant that, the main objective of the project is to determine the dynamics of changes in excitatory synapses in the course of depression. Accordingly, in the first part of the project will examine how the location and subunit composition of the NMDA and AMPA receptors and their interaction with specific cell protein scaffold (such as PSD-95, Shank / ProSAP3 Homer 1, CaMKII, ZnT-1) is changing. Analyses will be conducted in the 2 brain structures (the frontal cortex and hippocampus - a well-documented role in depression; rich in glutamatergic innervation) collected from depressed patients and healthy volunteers and from animals with induced depression (animal models). The research will be carried out using modern and carefully selected biochemical methods (ELISA, co-immunoprecipitation, surface receptors cross-linking assay, Western Blot or proximity ligation assay) in different cellular fractions (intracellular, membrane: synaptic, outside / extra synaptic). In the second part of the project it is planned to provide the animals inhibitors of the NMDA receptor subunits - GluN2A and GluN2B and cell scaffolding proteins - PSD-95 and CaMKII. Use of tests to evaluate antidepressant activity of the compounds in an animal will be able to verify that inhibition of the function of these proteins, which will result in major changes in animal behavior. Concomitant use of inhibitors and different antidepressants (LPD) will indicate whether the protein (GluN2A, GluN2B, PSD-95 and CaMKII) play important roles in the mechanism of antidepressants action (LPD).

Results of this project will increase the current knowledge about the significance of the functional changes in the excitatory synapses in the pathophysiology of depression. On the other hand, this project will answer the question of whether and which proteins or signal transduction pathways are involved in the mechanisms of the antidepressants activity.