C.1 DESCRIPTION FOR THE GENERAL PUBLIC

1. Research project objectives

The aim of the project is to investigate the antidepressant activity of scopolamine combined with selected ligands interacting with metabotropic glutamate (mGlu) receptors in animal models of depression. All the tested substances will be used at sub-effective doses in order to reduce the risk of occurrence of adverse effects during the treatment. In addition, it is planned to determine the mechanism responsible for the potential therapeutic effects, as well as to examine the effect of those compounds on memory and learning processes in mice.

2. Research project methodology

The assessment of antidepressant effects of sub-effective doses of scopolamine and sub-effective doses of selected mGlu receptor ligands (MTEP, LY341495, AMN082) will be performed using two behavioural tests: the forced swim test and the tail suspension test. They are widely used rodent models of despair. Furthermore, it is planned to determine the mechanism of antidepressant action of tested compounds, including the role of a AMPA receptor, as well as mTOR kinase pathway and synaptic proteins level in prefrontal cortex and hippocampus of mice, using molecular biology methods: qPCR (quantitative Polymerase Chain Reaction) and Western blot technique. As scopolamine blocks the action of acetylcholine, which is a neurotransmitter involved in the process of gaining new information, the important part of the experiment will be to assess the effects of the sub-effective doses of scopolamine and mGlu receptor ligands on learning and memory by the use of the Morris water maze test. All planned experiments will be carried out on male CD1 and C57BL/6J mice and all the tested compounds will be administered intraperitoneally.

3. Expected impact of the research project on development of science, civilization and society

According to the epidemiological data, 350 million people of all ages suffer from depression. Furthermore, it becomes increasingly widespread, especially in developed countries and pharmacological strategies are effective only in approximately 60-65% of patients. Pharmacotherapy of depression is based on the monoamine hypothesis and requires long-term treatment (4-6 weeks) in order to achieve first therapeutic effects. It is thought that the main problem of therapy is the lack of compliance as well as suicidal attempts. Clinical studies reveal that after single intravenous infusion of ketamine (an antagonist of NMDA receptor) the antidepressant effects in patients could be rapid and long-lasting. **Those results underlined the significant role of glutamate in the pathogenesis of depression.** Glutamate is the major excitatory neurotransmitter in the central nervous system. It interacts both with ionotropic glutamate receptors (NMDA, AMPA and kainate) and metabotropic ones (8 subtypes: mGluR1- mGluR8). However, ketamine is a psychoactive substance and its usage is associated with a high risk of adverse effects, including hallucinations and psychosis. It has been presumed that the usage of compounds interacting only with mGlu receptors, which exhibit antidepressant activity in animal models of depression, is associated with the lower risk of adverse effects. Recent clinical studies suggest that similar therapeutic effects to ketamine can be achieved by the administration of scopolamine**.** It occurs naturally in the leaves of *Datura stramonium* (known by the common name Devil's snare) and *Atropa belladonna* (known as belladonna, deadly nightshade). Unfortunately, the use of scopolamine might be also connected with several adverse effects.

Hence we focus on the assessment of the antidepressant potential of the a combination of the sub-effective doses of scopolamine and selected ligands of mGlu receptors which possess antidepressant activity. The project also aims at investigation of the mechanism of antidepressant activity, especially at determination of the role of AMPA receptors and activation of mTOR pathway, which could help to compare those effects with the action of ketamine. Enhancing the antidepressant activity of scopolamine by the use of mGlu receptor ligands will help to reduce the risk of adverse effects associated with blockade of cholinergic system. Therefore, we will examine the influence of the tested compounds on learning and memory in mice. Examples of ketamine and scopolamine deny the hypothesis that a long time lag is necessary to produce therapeutic effects of antidepressants. The greatest challenge of modern neuropsychopharmacology is to discover novel antidepressant drugs characterized by a high efficacy, rapid onset of action, long-lasting activity and low risk of adverse effects. The research planned in this project may help in the achievement of this great goal.