

ABSTRACT FOR THE GENERAL PUBLIC

Stroke is the most common cause of death after myocardial infarction and cancer. The disease also leads to a long-term disability among adults. The most common cause of this disease is the interruption of the blood supply to the brain, within one or more of the arteries supplying this organ with blood. About 80% of stroke cases are ischemic. Unfortunately, until now there is no effective pharmacotherapy of brain ischemia. The only available therapy is the intravenous administration of tissue plasminogen activator (t-PA), which dissolves the thrombus and restores the blood flow in the arteries. However, reperfusion carries numerous disadvantages, including the risk of hemorrhagic stroke. Therefore, there is a great need to search for new compounds with a therapeutic effect, especially those whose administration after the onset of ischemic stroke will provide adequate neuroprotection, inhibiting the expansion of the necrosis zone in the brain.

The inhibition of the blood supply to a particular region of the brain results in the release of large amounts of glutamate from the brain cells. This amino acid is necessary for the proper functioning of the brain, however, in excessive amounts it leads to the death of neuronal cells. Therefore, the natural therapeutic procedure in ischemic stroke, it would seem, is to inhibit the release of this amino acid or block the site of interaction for glutamate, e.g. the NMDA receptor. However, clinical studies have shown that this procedure does not bring beneficial results, because it results not only in the abolition of the noxious effects of high concentrations of glutamate, but also blocks the physiological effect of the amino acid, leading to deepening brain dysfunction in stroke and causes cognitive disorders.

The reports of the last two years indicate that the most important factor in the pathomechanism of ischemic stroke is not the excessive activation of NMDA receptors by glutamate, but the formation of protein complexes in the extrasynaptic region, that is the NMDA receptor with the TRPM4 ion channel. The uncoupling of these complexes, using the only available dimerization inhibitor - compound 8, brings the desired effects, i.e. it reduces mitochondrial degeneration, improves energy balance, reduces stroke volume and diminishes neurological motor deficits that occur in the course of ischemic stroke in animals. Even though these reports are groundbreaking, show a new therapeutic target and, for the first time in many decades, allow us to wait with hope for new strategies of pharmacotherapy of ischemic stroke, still little is known about the role and mechanism of action of NMDA-TRPM4 complexes, in other than neurons central nervous system cells. It is also necessary to verify whether compounds that inhibit the interaction of TRPM4 with NMDA do not affect cognitive functions of the brain, as was the case with NMDA inhibitors. Compound 8 is a single chemical structure with a novel pharmacological activity. However, it is characterized by suboptimal pharmacokinetic parameters, which preclude its use, even in the long term, in clinical conditions. Therefore, the aim of this project is to thoroughly investigate the characteristics of the formation and the role of the complex of the TRPM4 channel with the NMDA receptor in the conditions of ischemic stroke, in individual cells of the central nervous system, such as neurons, astrocytes or endothelial cells. The effect of the complexes on the excitability of brain cells, energy metabolism and the blood-brain barrier will be assessed. In advanced behavioral tests, the possible effect of inhibiting the formation of NMDA-TRPM4 complexes on motor and cognitive skills will be determined. One of the most important tasks of the project is the design, synthesis, and verification of new compounds with increased potency to inhibit the formation of NMDA-TRPM4 complexes, with improved ADME parameters, meeting the requirements for compounds, drug candidates.

The project is interdisciplinary and involves experts in the fields of e.g. *in silico* design and chemical synthesis, experts in proteomics, metabolomics, molecular neurobiology, electrophysiological research, advanced imaging methods (MRP/PET, confocal microscopy), behavioral tests. In addition, the planned series of experiments has an international dimension, as some of the research will be carried out with the participation of scientists from leading European research institutes (King's College London and Karolinska Institute, Stockholm).

By carrying out a number of innovative studies, we will answer the question of the characteristics of the formation and the role of NMDA-TRPM4 complexes in ischemic stroke. The project will also provide new pharmacological tools with improved pharmacokinetic and pharmacodynamic properties, capable of uncoupling the above-mentioned protein complexes. The expected endpoint of this project is the definition of new therapeutic targets. Appropriate modulation of the formation of NMDA-TRPM4 complexes may bring a beneficial therapeutic effect in CNS diseases associated with glutamate homeostasis disorders. The results of this project may therefore significantly contribute to the development of a new class of drugs and therapeutic strategies for ischemic stroke and other CNS diseases associated with glutamate homeostasis disturbance in the brain.