

How microglia-astrocyte interaction affects neuronal functioning in the dopaminergic system. Analysis of protective potential of drugs changing the glial phenotype.

Changes in the functioning of brain glial cells (astrocytes and microglia) that regulate inflammation and dysfunction in the cellular metabolism are a common denominator of many chronic conditions and acute damages to the central nervous system, such as Parkinson's disease, Alzheimer's disease, Huntington's disease, epilepsy, amyotrophic lateral sclerosis, multiple sclerosis, stroke or injuries. The project will focus on the study of cells of the brain's dopaminergic system on the example of Parkinson's disease, but the results of these studies will find a very wide application in the future in the treatment of many other diseases.

The function of astrocytes and microglia is strictly interconnected and directly affects the activity and survival of neurons in the brain. Astrocytes constitute the basic neuronal support system. As the only ones, they can store extra energy supplies in the form of glycogen, provide neurons with energy substrates in the form of lactate, protect them by producing antioxidants and secrete growth factors. In response to stress or damage, astrocytes activate and adapt their functions by producing survival and regeneration factors. Therefore, a long-term disruption of astrocyte function may negatively affect the functioning of neurons. On the other hand, microglia is the main executor of inflammation in the brain. When activated it kills pathogens, removes the remains of dying cells, neutralizes toxic protein aggregates and then secretes trophic factors to protect neurons. At the same time, it also activates astrocytes to increase the tissue protection. The interaction of astrocytes and microglia is the basis of their proper functioning in the nervous system.

Recently, the existence of various forms of activated glial, both potentially dangerous for neurons and protective has been shown. The change in the form of astrocyte and microglia activation status is directly related to changes in the metabolism of these cells. The existence of different states of glia activation gives the possibility of inducing or inhibiting them with drugs, so that they are less harmful and work more protective.

Studies carried out so far have focused on culturing isolated cell types *in vitro* or analyzing tissue homogenates containing all types of cells simultaneously, not allowing for the separation of their specific functions depending on the state of their activation. In this project, we want to take a step forward and check which cells and in what form of activation are responsible for the observed effects. We will compare various pharmacological approaches, the total inhibition of microglia activity vs the modulation of its activity and a subtle change of its activation. We will investigate how this new approach will affect the interaction with astrocytes and neurons and check which drugs have a greater protective potential against the damage of the cells. We will conduct a detailed analysis of changes in the quality and quantity of proteins produced in particular subtypes of cells, to determine the mechanisms underlying the changes in the state of activity, associated cellular metabolism, potential protective action as well as mutual cellular interactions. In addition, we will check two groups of compounds that could also be protective towards the neurons and astrocytes. We will investigate whether their action also involves changing the form of glial cell activation.

Expanding the knowledge about the functioning of glia and detailed interactions between astrocytes, microglia and neurons has much to contribute in creating new therapies. Substances that change the state of glial activity have a very high therapeutic potential not only in diseases of the nervous system, but also in ophthalmology, asthma, cancer, diabetes and others. The new possibility of subtle pharmacological modulation of the function of glia, weakening the endogenous harmful effect and strengthening the protective is very promising and is the current global trend in the search for the new therapies for neurodegenerative diseases.