DESCRIPTION FOR THE GENERAL PUBLIC

The brain stores new information by creating an unimaginably complex network of connections between neurons. These connections form synapses. Their number and location change throughout life. Such reorganization of synaptic connections is called plasticity. It is well established that the neuronal plasticity includes both changes in learning and memory, as well as developmental and compensating (recovery following damage to the brain) changes. It is believed that these complex processes are regulated by structural modifications of individual synapses, which determine the efficiency of neurotransmission. Over the last two decades, a growing body of research evidence has been collected, suggesting an important role of extracellular matrix proteolysis in synaptic structural plasticity. It is known that proteases are secreted into the extracellular space in an activity-dependent manner. One of them is the extracellular matrix metalloproteinase-9, MMP-9. Several synaptic substrates of this enzyme have been characterized, but the importance of the controlled proteolysis of these proteins in the mechanisms of formation and remodeling of synapses is still unknown. Within this proposal we plan to focus on dystroglycan (DG), which is an important modulator of many signaling pathways in cells. This protein consists of two subunits. The extracellular α-DG is highly glycosylated and binds to numerous components of the extracellular matrix. On the other hand, the transmembrane β-DG anchors α-DG to the cell membrane and interacts with the cytoskeletal proteins. The importance of DG for brain function is confirmed by data showing that some mutations disrupting its glycosylation are associated with severe defects in the structure of cerebral cortex as well as mental retardation. Conflicting data exists regarding the location of DG in nerve cells. Some researchers believe that it occurs only in the inhibitory synapses, while others point to its presence in the postsynaptic membrane of excitatory synapses. Despite these contradictory reports, it can be assumed that DG plays an important role in structural plasticity. An important reason for this are results showing that DG interacts with the presynaptic neurexin and thus may contribute to the formation and stabilization of synapses.

In this project we propose to carry out studies that explain the location of DG in neuronal cells in the brain and answer to the question whether proteolytic cleavage of β-DG is necessary and sufficient for changes in the number and shape of synapses caused by enhanced MMP-9 activity. In addition, we will attempt to describe the mechanism responsible for the re-recruitment of β-DG to the postsynaptic membrane. We expect that our results will contribute to the understanding of the molecular mechanisms underlying the formation and stabilization of synaptic connections that determine both physiological and pathological plasticity.