

Changes in the strength of connections between nerve cells are the foundations for adaptive capacity of the brain to respond appropriately to changing environmental conditions, e.g. in learning and memory. These changes are based on the so-called synaptic plasticity. Molecular mechanisms responsible for plastic changes of excitatory synapses that are located on nerve cells on the so-called dendritic spines, are still poorly known and are a field of intense research. Understanding these mechanisms is of fundamental importance for understanding the functioning of the brain and in particular the brain-mind relationship, both in physiology and pathology, as the mechanisms of synaptic plasticity are considered the key to understand the most serious brain diseases. It should be noted here that genetic studies in humans have repeatedly shown the importance of polymorphisms and mutations in genes encoding synaptic proteins for the development of mental disorders. In this context, enormous social and financial costs are worth emphasizing – estimated in the EU at 800 billion euros annually, including 500 billion euros on mental illnesses. Initiated by us 15 years ago, the studies on the extracellular proteolytic enzyme MMP-9 have shown that it can play a significant role in synaptic plasticity. We suspect that this is due to the involvement of MMP-9 in the control of dendritic spines. The aim of this project is to verify this hypothesis in a mechanistic way. The research will be conducted on neuronal cultures in which individual synapses will be stimulated by local release of glutamate, the excitatory neurotransmitter. We plan to investigate under what conditions and on what spines (that may vary in shape and size in accordance to their function), MMP-9 is secreted and may exhibit its activity. We postulate a direct link between MMP-9 and a well-known factor involved in plasticity control, BDNF. Hence, we plan to verify hypothesis that MMP-9 can activate BDNF outside the synapse by partially cleaving its latent form to produce the active one. Proposed research should bring a new knowledge in several areas: (i) in the field of the mechanisms of MMP-9 functioning at synapse level, which may lead to the use of this knowledge in the treatment of mental illness; (ii) in understanding the mechanisms of molecular synaptic plasticity, adding here an entirely new, extracellular, dimension of regulation of this phenomenon; (iii) in the field of functional connectomics (discovering connections and their functional modification by information processing) by providing and validating a potentially very attractive research tool in the form of a fluorescent marker (active MMP-9 and its biosensor) of synapses subjected to long-term plastic changes.