DESCRIPTION FOR THE GENERAL PUBLIC (IN ENGLISH)

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome related to liver damage. Latent and overt forms of HE are distinguished, whereby the former is characterized by discrete neuropsychiatric symptoms and affects approximately 70% of patients with HE and the second is associated with appearance of acute symptoms, often concluded by comatous state and/or brain edema as a leading cause of death. Acute HE develops due to bleeding into the gastrointestinal tract, viral hepatitis, drug overdose or poisoning by toxic substances, whereas chronic HE is a consequence of liver cirrhosis or alcohol overdose. HE affects both physical and mental patient status, and the severity of symptoms is rated using the West Haven scale. Stage 1 is characterized by alteration in sleep cycle and wakefulness, problems with concentration and agitation, that pass into stage 2, causing disorientation, impaired memory and subtle personality change, stage 3, is characterized by severe slowness of movement, drowsiness, anxiety, dementia, nystagmus until phase 4 ending in coma leading to death. The pathomechanism of HE is not fully understood, therefore therapies are not specifically focused, and based on the reduction of proteins intake, as a source of ammonia (low protein diet), elimination of toxins from the blood (dialysis, antibiotics) or liver transplantation considered as the last opportunity.

There is a consensus that high concentration of ammonia due to dysfunctional liver is a main factor in HE development. An increase of ammonia in the brain causes a number of physiological and morphological changes, including mainly astrocyte dysfunction. The current view assumes that disturbances in neurotransmissions, which are responsible for HE symptoms, are caused by the alterations of astrocytic proteins, such as ion channels and neurotransmitter transporters. Some reports and also our preliminary results lead us to formulate the hypothesis, that changes in the expression and localization of synaptic proteins, synaptic morphology and some electrophysiological characteristics may impair neurotransmission by themselves.

As a result of liver damage, an increase of the cytokine TGF-β1 in the blood was observed. TGF-β1 controls cell growth, proliferation, differentiation and apoptosis, including regulation of neuronal survival. This cytokine presents neuroprotective features in excitotoxicity-evoked brain injury. Overexpression TGF-β1 mice model was associated with increased expression of ionotropic, AMPA and NMDA receptor subunits , and synaptophysin in hippocampus , which may affects glutamatergic synapses. We therefore assume, that this protein may be involved in the development of HE. Consequently, we want to investigate its role in the development of HE-induced changes of synaptic protein expression and their cellular/subcellular localization, as well as morphology of synapses.

In the present project we will use a mouse model of hepatic encephalopathy, based on i.p. injection of azoxymethane (AOM). We will examine the expression of proteins from the pre- and post-synaptic zone, their cellular localization, morphology of synapses and basic electrophysiological parameters, characterizing neuronal function. The effect of TGF-β1 neutralization on mentioned above factors will be conducted in control and AOM mice. The expression of proteins involved in docking of synaptic vesicles to the membrane, such as synaptophysin, synaptotagmin, syntaxin-1 and proteins forming PSD-95 nNOS-NMDA receptor complex in the postsynaptic zone, will be measured. Using the confocal microscope, cellular localization of these proteins will be studied. Images from electron microscopy reveals the morphology of synapses. Using the method of registration whole-cell patch-clamp will current-voltage characteristics of the studied neurons be determined. Then we will record spontaneous excitatory (sEPSC) and inhibitory (sIPSC) postsynaptic currents, miniature EPSC and IPSC will be recorded in the presence of tetrodotoxin, a sodium channel blocker. In addition, long-term potentiation (LTP) will be recorded.

Explanation of TGF-β1 role in the pathomechanism of HE, may further provide a knowledge for faster and more effective pharmacological interventions, particularly to stop or delay changes in neurotransmission, which in patients in the later stage of disease, results in a cognitive, mobility and coordination impairment. It is hoped that the study will enable the design of therapies aimed at cytokine TGF-β1, and at the same time expand our general knowledge about its role in the development of neuronal changes and about the underlying mechanisms.