

DESCRIPTION FOR THE GENERAL PUBLIC

Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome that typically develops as a result of acute liver failure or chronic liver disease. Therefore, removal of harmful substances from the circulation is highly reduced. During HE, a *plethora* of toxic substances, among which ammonia is a major toxin, accumulate in the blood and penetrate through the blood-brain barrier (BBB) leading to a subtle or severe structural and functional disruption of this structure. Brain edema (BE) is a common and often fatal complication of HE. Systemic inflammation and cerebral inflammation, next to ammonia, contributes to the pathogenesis of HE and seems to be accompanying factor in exaggerating HE symptoms. The mechanisms responsible for HE-induced development of BE are complex, however there is a consensus of coexistence two mechanistically unrelated components: cytotoxic and vasogenic. Although the cytotoxic mechanism of BE is relatively well known, the role of vasogenic factor, which involves a disruption of BBB remain to be inadequately characterized.

Cerebral edema in HE occurs with a strong participation of vascular factors resulting from altered BBB permeability. BBB forms a kind of barrier that prevents penetration of toxic substances from the bloodstream protect the environment. Total interplay of structures and factors ensuring the proper functioning of the BBB is considerable. Those structures are divided into mostly included – “horizontal” tight junction between endothelial cells along with protein adhesion, and so far almost entirely ignored – “vertical” and astrocytic endothelial receptor proteins of the extracellular matrix. Especially, an involvement of “vertical” component of BBB in HE-induced BE is unknown. Moreover, the knowledge of the effect of HE on changes in the structure and function of the BBB is incomplete, especially if one considers the interactions between endothelial cells, astrocytes, pericytes, and substance between them, known as extracellular matrix.

Increasingly, many physiological processes and pathological conditions associated with microRNA, a short, regulatory RNAs (18-24 nucleotides) that interferes with the specific fragment of RNA, and therefore regulate gene expression. The role of miRNAs in the context of BBB damage in HE is unknown.

In this project we want to analyze changes in the expression and function of proteins of “horizontal” and “vertical” components of the BBB during HE progression. Further, HE-altered expression of miRNAs, which potentially may regulate BBB function, will be determined. Finally, the association of BBB disturbances with an alterations in selected miRNAs expression will be assessed.

Experiments will be performed on: (1) rat model of acute HE, in different stages of BE and BBB damage (2) models *in vitro* using homogeneous or mixed cultures, reflecting the relationship between BBB building cells (rat brain endothelial cells (RBE-4) -, primary cultures of rat brain endothelial cells - astrocytes / pericytes). We will transfect endothelial cells with mimic-miRNA or anti-miRNA for pre-selected miRNA. In this way, we will investigate effects of miRNA on the structure and function of various BBB proteins.

It is well-known that miRNAs are quite stable and easily detected in plasma, therefore miRNAs associated either with BBB damage and/or inflammation status in HE patients, may offer as an effective and non-invasive biomarker, allowing for fast recognition of the degree of BBB damage. In the future, may be indicative in a rapid pharmacological interventions.