SECTION 19.
MEDICAL SCIENCES AND PUBLIC HEALTH

Shuliatnikova T.V.
Ph.D., Associate Professor,
department of pathological anatomy and forensic medicine
Zaporizhzhia State Medical University, Ukraine

REGION-DEPENDENT HETEROGENEITY IN GFAP EXPRESSION IN ACUTE HEPATIC ENCEPHALOPATHY

Acute hepatic encephalopathy (AHE) being one of the most dangerous complications of the severe liver pathologies, is supposed to be determined by complex pathophysiology including specific action of ammonia neurotoxicity [1]. It is believed that hyperammonemia targets primarily brain astrocytes causing their decompensated cytotoxic edema and swelling followed by generalized edema of the brain, coma and lethal outcome [2]. Considering growing body evidence on substantial phisiological region- and context-dependent heterogeneity of astroglial population throughout the entire brain, its reactivity to various triggers is also supposed to be diverse. In response to any changes in local homeostasis astroglia become reactive increasing expression of GFAP. Other studies have shown controversial results of brain hyperammonemia on expression of GFAP in astrocytes [3]. The purpose of the study was analyzing immunohistochemical (IHC) features of the astroglial reactivity in different brain regions in the conditions of experimental AHE. The study was performed in Wistar rats, which were subjected to acetaminophen induced liver failure (AILF) [4]. GFAP expression was determined by IHC method in the sensorimotor cortex, subcortical white matter, hippocampus, thalamus and caudate/putamen region as the relative area (S rel., %) of $GFAP^+$ labels from 16 up to 24 hours after AILF-procedure. At 12 hours after injection, non-survived animals showed slight, statistically unreliable increase in GFAP values in all studied regions ($p > 0.05$). In further time-points both survived and non-survived animals displayed substantial and dynamic decrease in GFAP immunolabeling in all studied regions compared to control values. Thus, beginning from the 12^{th} h, in the subcortical white matter of the non-survived rats up to 24 h after AILF-procedure, the indicators of GFAP expression was equal to 4.21 (3.21; 5.76) %, that mean reduction by 125.65% compared to control. In thalamus indicators were equal to 0.60 (0.31; 1.90) – decrease by 526.66%, in the caudate nucleus/putamen – 3.20 (3.10; 4.10), drop by 103.12%, in the hippocampus – 1.52 (0.90; 2.10), by 176.31% ($p < 0.05$). From the 18^{th} hour, cortical indicators showed the most substantive reduction among regions and were equal to 0.40 (0.11; 1.82) – reduce by 537.5% (6.47 times), $p < 0.05$. In sum, AHE development is associated with early dynamic attenuation of the astroglial reactivity in the cortical, thalamic, hippocampal, caudate/putamen and white matter rat brain regions. The most dramatic decrease in GFAP indices in the cortex and thalamus indicates these areas as more susceptible to fluxing systemic detrimental factors through the compromised systemic-brain barriers in the conditions of acute liver failure, as well as emphasizes the special kind of sensitivity and/or reactivity of local astroglia to the action of toxic factors. The reduced GFAP synthesis in the astrocytes positively associated with the dynamic deterioration of the

animal state, confirms the critical role of the altered astroglial reactivity in the AHE pathophysiology.

References:

1. Shulyatnikova T. & Shavrin V. (2017). Modern view on hepatic encephalopathy: basic terms and concepts of pathogenesis. *Pathologia*, 14(3), 371-380 (41). https://doi.org/10.14739/2310-1237.2017.3.118773
2. Liotta, E. M., & Kimberly, W. T. (2020). Cerebral edema and liver disease: Classic perspectives and contemporary hypotheses on mechanism. *Neuroscience letters*, 721, 134818. https://doi.org/10.1016/j.neulet.2020.134818
3. Jaeger, V., DeMorrow, S., & McMillin, M. (2019). The Direct Contribution of Astrocytes and Microglia to the Pathogenesis of Hepatic Encephalopathy. *Journal of clinical and translational hepatology*, 7(4), 352–361. https://doi.org/10.14218/JCTH.2019.00025
4. Shulyatnikova T, Shavrin V. (2021). Mobilisation and redistribution of multivesicular bodies to the endfeet of reactive astrocytes in acute endogenous toxic encephalopathies. *Brain Research*, 1751:147174. https://doi.org/10.1016/j.brainres.2020.147174.