T.V. Shulyatnikova
V.O. Tumanskiy

Zaporizhzhia State Medical University, Zaporizhzhia

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IMMUNOHISTOCHEMICAL ANALYSIS OF THE GLIAL FIBRILLARY ACIDIC PROTEIN EXPRESSION IN THE EXPERIMENTAL ACUTE HEPATIC ENCEPHALOPATHY

Shulyatnikova T.V. ✉, Tumanskiy V.O. Immunohistochemical analysis of the glial fibrillary acidic protein expression in the experimental acute hepatic encephalopathy.
Zaporizhzhia State Medical University, Zaporizhzhia, Ukraine.

ABSTRACT. Background. Pathophysiology of acute hepatic encephalopathy (AHE) is complex and fine links of its development are still to be recognized. It is believed that AHE mechanisms are commonly focused on the ammonia neurotoxicity associated with neuroinflammation, neurotransmitter disbalance and severe astrocytic swelling leads to generalized brain edema. Astroglia, principal homeostatic cell population in the brain are suggested to be the primary target for hyperammonemia in this condition. Being highly region- and context-dependently heterogenic, its response to various pathological actions is also supposed to be highly diverse. **The objective** determining the immunohistochemical features of glial fibrillary acidic protein (GFAP) expression in different rat brain regions in the conditions of experimental acute hepatic encephalopathy. **Methods.** The study was conducted in Wistar rats: 5 sham (control) animals and 10 rats with acetaminophen induced liver failure model (AILF). The immunohistochemical study of GFAP expression in the sensorimotor cortex, white matter, hippocampus, thalamus, caudate nucleus/putamen region was carried out in the period of 12-24 h after injection. **Results.** Beginning from the 6th hour after injection all animals of AILF-group showed the progressive increase in clinical signs of acute brain disfunction finished in 6 rats by comatose state up to 24 h; they constituted subgroup AILF-B, "non-survived". Four animals survived until the end of the experiment, 24 h (subgroup AILF-A "survived"). In the AILF-B group, starting from 16 to 24 hours after the AILF-procedure, a significant (relative to control) regionally-specific dynamic decrease in the level of GFAP expression was observed in the brain: in the subcortical white matter by 125.65%, in the thalamus by 526.66%, in the caudate nucleus/putamen by 103.12%, in the hippocampus by 176.31%, from 18th hour in the cortex, by 537.5% with the most substantive reduction in the cortex and thalamus: by 6.47 and 6.26 times, respectively. **Conclusion.** In the conditions of experimental AILF, there is early dynamic decrease in astroglial reactivity in the cortex, thalamus, hippocampus, white matter and caudate nucleus/putamen region. The most significant decrease in GFAP indices in the cortex and thalamus indicates these areas as more vulnerable to systemic aggressive factors and more susceptible to toxic and metabolic load in conditions of acute liver failure, and on the other hand, emphasizes relatively more pronounced sensitivity and reactivity of local astroglia to the action of damaging substances in this state and at this time period of the pathology development. The dynamic decrease in the level of GFAP in the rat brain, associated with the same dynamic deterioration in the state of animals, indicates the importance of such pathological astroglial remodeling in the mechanisms of AHE development in rats.

Key words: acute hepatic encephalopathy, astroglial reactivity, GFAP.

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Shulyatnikova T.V. 0000-0002-0196-9935
Tumanskiy V.O. 0000-0001-8267-2350
✉ shulyatnikova.tv@gmail.com

Background

Among the vast majority of reasons of endogenous toxicity, liver pathology plays one of the leading roles. Substantial liver damage is associated with the development of potentially reversible neurocognitive disorder termed hepatic encephalopathy (HE) ranging from Grade 0 "minimal" or latent HE to Grade IV coma state [1, 2]. HE determines a serious financial burden on health care system and linked to poor patient prognosis and high mortality rates [3].

Acute hepatic encephalopathy (AHE) occurs due to massive liver necrosis that complicates viral hepatitis and poisoning by hepatotoxic poisons, displaying the most prominent clinical manifestation of the acute liver failure (ALF) in these conditions [3].

The pathophysiology of HE is complex and fine links of its development are still to be recognized. It is believed that HE underlying mechanisms are commonly focused on the ammonia theory when urea cycle (ornithine cycle) abnormality in damaged hepatocytes causes rising of systemic ammonia levels. The highest levels of ammonia in systemic circulation have been observed in HE of types A and B according the World Congress of Gastroenterology in 1998, 2002 [1, 4]. Elevated blood ammonia that has not gone through liver detoxification, cross the blood-brain barrier (BBB) and induce increased level of ammonia in the brain [4, 5]. Among other factors implicated in the mechanisms of HE has been recognized systemic and neuroinflammation, disturbances in cerebral blood flow, electrolyte, pH, amino acids and neurotransmitter abnormalities [6, 3].

It has been evidenced by multiply studies that hyperammonemia mostly target brain astrocytes likely because they are the only cell population that contain glutamine synthetase and metabolize ammonia [7]. An excessive ammonia level in the brain leads to glutamine overload of astrocytes, followed by their cytotoxic edema, development of generalized cerebral edema, intracranial hypertension and hernial dislocation of the brain hemispheres [1]. The noted facts suggest endowing astroglia with a unique and special role in the development of hyperosmolar brain edema in case of hyperammonemia. In response to high ammonia in the tissue, astrocytes undergo specific morphological changing called Alzheimer Type II astrocytosis, characterized by an enlarged nucleus with clear chromatin and the rim of the swollen cytoplasm around [8]. Astrocytes, the main homeostatic cells of the brain, being functionally disabled, cause critical disturbances in numerous fundamental processes including synaptic function and plasticity, neurotransmitter and water homeostasis, microcirculation, BBB permeability, etc. [9]. Astrocytic glial fibrillary acidic protein (GFAP) is critical for structural stability and integrity as well as motile activity and supporting homeostatic functions by astrocytes [10]. In response to any triggering factors astroglia rapidly underdo phenotypic remodeling and become reactive. Nevertheless, it was reported in earlier studies that GFAP is downregulated in astroglia during hyperammonemia states [11]. Considering substantive region-dependent and context-dependent constituent heterogeneity of astroglial population through the brain [12], its response to various pathological actions is also supposed to be highly diverse. The revealing this differential glial response during acute hepatic encephalopathy might shed more light on the processes of brain reactivity and adaptation to critical conditions that are created in the whole-body system in case of massive liver damage. Taking into account the intimate communication between glial cells in health and neuropathological states and the results of our previous study showing region-specific heterogeneity of microglial response in the experimental AHE [13], it would be imperative to study astroglial reactivity in the same brain regions and experimental model to compare glial responsiveness.

Acetaminophen one of the most widely used antipyretic drug worldwide and it's overdosing determines the leading cause of ALF in many countries [14]. Due to such overdosing causes ALF in rodents, this model can be used for explore fine links of AHE similar to that in humans [15, 16].

The objective determining the immunohistochemical features of GFAP expression in different rat brain regions in the conditions of experimental acute hepatic encephalopathy.

Materials and methods

For experimental purpose we used Wistar rats, 200-300 g body weight. All procedures were conducted according to the European convention for the protection of vertebrate animals (Strasbourg, 18 March 1986; ETS No. 123) and the Directive 2010/63/EU. For induction of AHE type "A" ("Acute liver failure" according to the American Association for the Study of Liver Disease updated guidelines), we used acetaminophen (paracetamol, N-acetyl-p-aminophenol [APAP]) induced liver failure (AILF) model [15, 16]. The detailed characteristics of all steps of the noted experimental model was described in the previous paper [17]. Rats were randomly divided into control group (n = 5) and AILF-group (n = 10). After intraperitoneal (i.p.) acetaminophen injection, rats were examined for signs of changed major physiological parameters, lethargy and loss of reflexes. Six rats were euthanized up to 24 h after the acetaminophen injection by an i.p. administration of sodium thiopental euthanasia solution due to the above severe clinical symptoms and constituted the group "AILF-B" decompensated AILF ("non-survived group"). Four animals that showed compensated clinical signs and survived up to 24 h after the injection were designated to group "AILF-A" compensated AILF (also indicated through the text as "survived group"). In control "AILF-C" group, all animals survived up to 24 h. At 24 h after AILF-procedure, all survived and control animals were euthanized by i.p. injection of sodium thiopental. The brain and liver samples were processed according to standard procedures with formation of paraffin blocks. For general histopathological analysis hematoxylin-eosin stained sections were used. Immunohistochemical (IHC) study involved detection of immunopositive labels using mouse monoclonal anti-GFAP primary antibody (clone ASTRO6, Thermo Scientific, USA) and Ultra Vision Quanto Detection imaging system with

diaminobenzidine (Thermo Scientific Inc., USA). The results of IHC reaction were assessed at x200 magnification in a standardized field of view (SFV) of the microscope Scope. A1 "Carl Zeiss" (Germany) using Jenoptik Progres Gryphax 60N-C1"1,0x426114 (Germany) camera and the program Videotest-Morphology 5.2.0.158 (Video Test LLC, Russia). The expression of GFAP was assessed as a percentage of the relative area (S rel., %) of immunopositive labels to the total area of the tissue section in the SFV. For the comparative analysis of the GFAP expression, such brain regions were selected as sensorimotor cortex, subcortical white matter, hippocampus, thalamus and caudate nucleus/putamen region. Five SFV of each mentioned region were analyzed for each animal. Digital data were statistically processed by Statistica® for Windows 13.0 (StatSoft Inc., license № JPZ804I382130ARCN10-J) with evaluating median (Me), lower and upper quartiles (Q1; Q3). For comparison between groups Mann-Whitney and Kruskal-Wallis tests were used. The results were considered significant at 95 % ($p < 0.05$).

Results

Beginning from the 6 h after injection all animals of AILF-group showed the dynamic increase in clinical signs of acute brain disfunction finished in 6 rats by comatose state up to 24 h. Pathohistological study of the liver samples of all AILF-rats have evidenced spread acute damage including centrilobular necrosis, focal hemorrhages and severe balloon dystrophy of hepatocytes, all presenting dynamic increase over time after injection. Conventional histopathological analysis of the samples from different brain regions of all experimental groups did not reveal prominent changes in size of astrocytic bodies and nuclei, while IHC study identified significant shifting of astroglial morphology.

Control AILF-C rats at 24 h after injection showed nonequivalence of the level of GFAP expression in different brain regions with the highest level in the white matter 9.50 (6.31; 10.69) % and the lowest in the sensorimotor cortex 2.59 (2.48; 3.33) % (Table 1).

Table 1

The indicators of GFAP expression in different brain regions in animals of different experimental groups expressed in the percent of positive labels in standardized field of view of the microscope (S rel. (%) SFV). Data are presented as median (Me) with lower and upper quartiles (Q1; Q3)

Brain region	AILF-A	AILF-B	AILF-C
Cortex	0.82 (0.33; 1.91) *	0.40 (0.11; 1.82) *	2.59 (2.48; 3.33)
Subcortical white matter	5.26 (4.70; 5.92) *	4.21 (3.21; 5.76) *	9.50 (6.31; 10.69)
Hippocampus	1.90 (1.31; 2.10) *	1.52 (0.90; 2.10) *	4.20 (2.58; 4.89)
Thalamus	0.90 (0.41; 2.10) *	0.60 (0.31; 1.90) *	3.76 (2.90; 4.59)
Caudate/putamen	3.80 (3.23; 4,20) *	3.20 (3.10; 4.10) *	6.50 (5.70; 7.84)

Reliable differences in indicators of the same brain region compared to the control animals ($p < 0.05$) are marked with an asterisk (*).

Moreover, the morphology of control astrocytes also showed region-dependent diversity. Thus, cortical astroglial population mostly displayed signs of typical protoplasmic forms while astrocytes of the white matter shared morphological features of fibrous phenotypes, meanwhile hippocampal, thalamic and caudate nucleus/putamen regions were distinguished by a combination of the both mentioned morphological types with the prevalence of the fibrous one. All studied regions were characterized by non-overlapping territorial domain pattern of astroglia. (fig. 1).

Histopathological studying of ICH sections of all mentioned brain regions in rats after AILF-procedure revealed dramatic reduction in the numbers and sizes of GFAP-positive cells and their processes. The latter appeared to be thinner and shorter, mostly reflecting parenchymal non-vascular part of cellular processes and in much lesser degree represented by vascular astroglial endfeet (fig. 2).

Comparing to control, experimental AILF-A (survived) and AILF-B (non-survived) animals also showed variability of GFAP expression along the regions with the highest indicators in subcortical white matter, although, in general, in both groups there was revealed pronounced reliable decrease in the marker expression in all mentioned regions relative to control values of the same localization.

Thus, in the non-survived AILF-B group the relative area of $GFAP^+$ labels displayed the most prominent decrease in the cortical region comparing to control, respectively: 0.40 (0.11; 1.82) % and 2.59 (2.48; 3.33) %, $p < 0.05$, that was equal to 537.5% or 6.47-fold decrease if compare medians indicators. At 24 h of the experiment, AILF-A group also showed reliable the most profound among regions decrease in cortical GFAP expression, however with lesser degree compared with non-survived animals (Table 1).

Thalamic region of AILF-B group was the second most notable region of the rat brain where GFAP expression decrease substantially compared to control indicators 6.26-fold or 526.66%, respectively: 0.60 (0.31; 1.90) % and 3.76 (2.90; 4.59) %, ($p < 0.05$). For matching, in AILF-A survived group, as well as in case cortical region, the decline was

significant and reliable, although less expressed 0.90 (0.41; 2.10) % comparing to control 3.76 (2.90; 4.59) %, ($p < 0.05$).

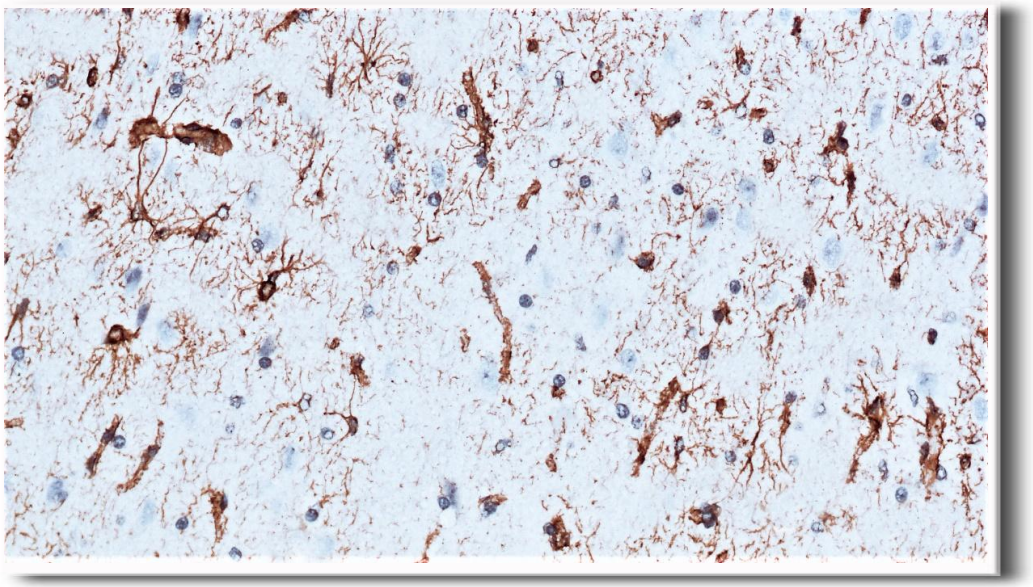

Fig. 1. GFAP expression in the cortex of the control rat (AILF-C group) 24 h after the sham procedure. (anti-GFAP, Thermo Scientific, USA). ×200.

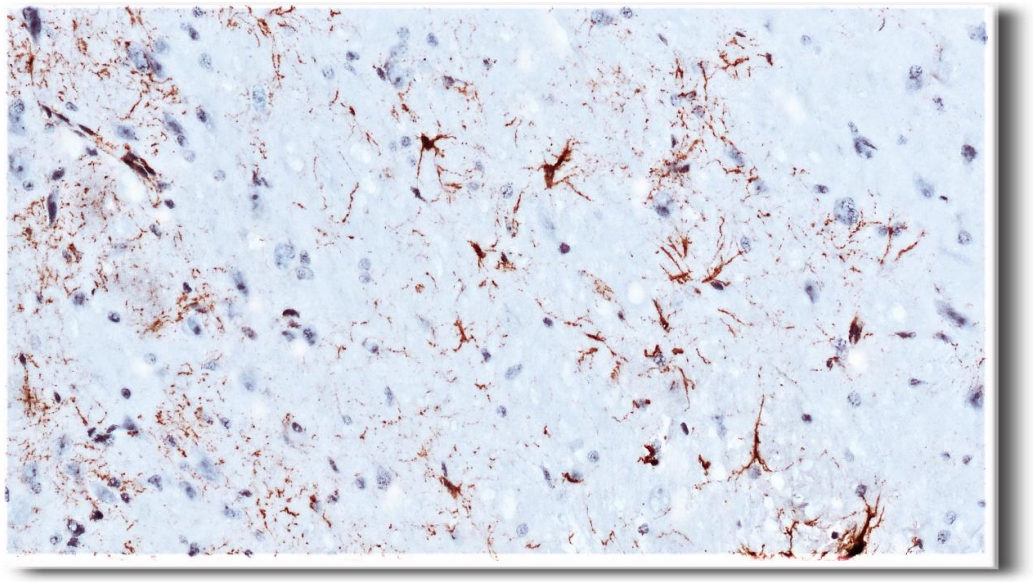

Fig. 2. GFAP expression in the cortex of the non-survived rat (AILF-B group) 24 h after the AILF procedure. (anti-GFAP, Thermo Scientific, USA). ×200.

The hippocampal, white matter and caudate/putamen regions of non-survived AILF-B rats during the whole period after AILF-procedure showed reliable decrease of GFAP expression by more than 2 times compared to control values of the same regions (by 176.31%, 125.65% and 103.12% respectively) (Table 1).

In all noted regions, survived AILF-A animals at 24 h also displayed serious decrease in GFAP expression, while these indicators were slightly higher comparing to total medians of AILF-B counterparts evaluated during the whole post-injectional period, with no statistical validity between AILF-A and AILF-B (Table 1).

In AILF-B group, during the post-injection period the decrease of GFAP values described dynamic curve (figs. 3-7). Depending on the time point after AILF-procedure when animals began display signs of severe suffering and were sacrificed, the indicators of GFAP expression also differed between regions. The lowest values of the GFAP S rel. (%) was found 24 h after the injection in all the studied re-

gions (figs. 3-7). The interesting feature of the first case of the animal death in AILF-B group at 12 h after the injection was represented by increased expression of GFAP in all studied brain regions compared to control values but with no statistical validity ($p > 0.05$) (figs. 3-7). Starting from 16 h of the experiment, all other animals displayed reliable decrease IHC indicators of GFAP relatively to control values, except the cortical region where decrease gained statistical validity only at 18 hours after AILF-procedure.

Overall, after AILF-procedure, the lowest indicators of $GFAP^+$ S rel. (%) in all studied regions were typical for the non-survived AILF-B animals with the most substantial decline in the cortex and thalamus (comparing to control rates). After insignificant elevation of the GFAP expression at 12 h of the experiment, the reliable and dramatic decrease in values of GFAP expression was noted from 16 h for all studied brain regions except the cortex, where it was revealed at 18 h after procedure.

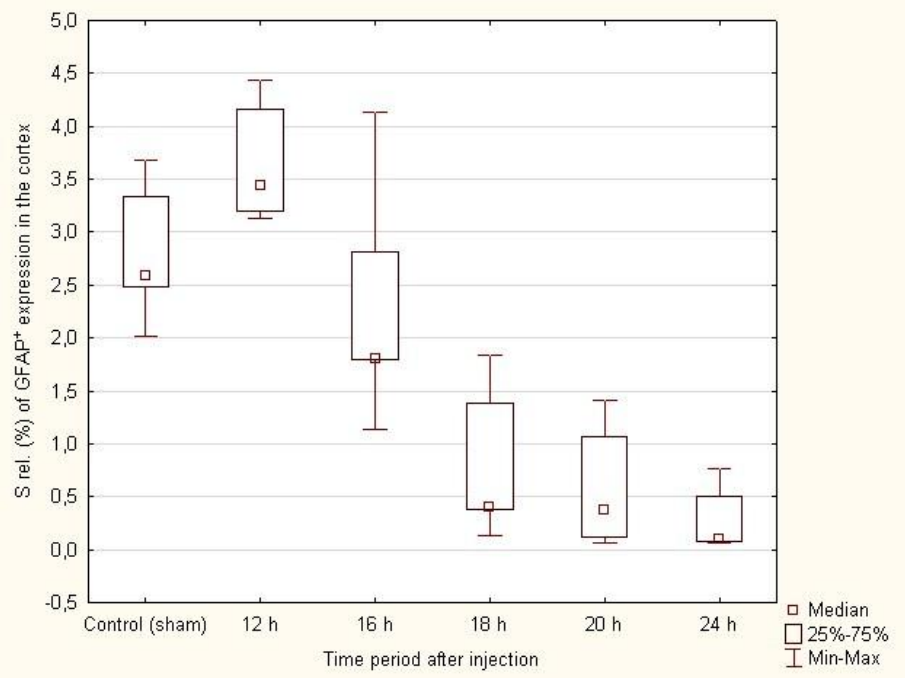

Fig. 3. Dynamics of the relative area of $GFAP^+$ expression (in the microscope SFV, %) in the cerebral cortex of AILF-B rats after injection.

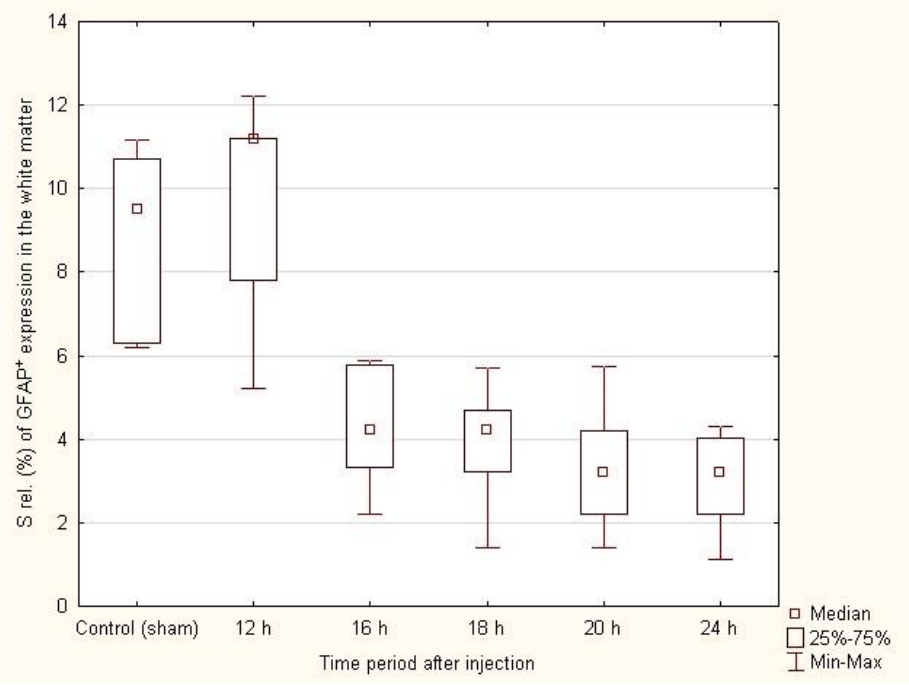

Fig. 4. Dynamics of the relative area of $GFAP^+$ expression (in the microscope SFV, %) in the subcortical white matter of AILF-B rats after injection.

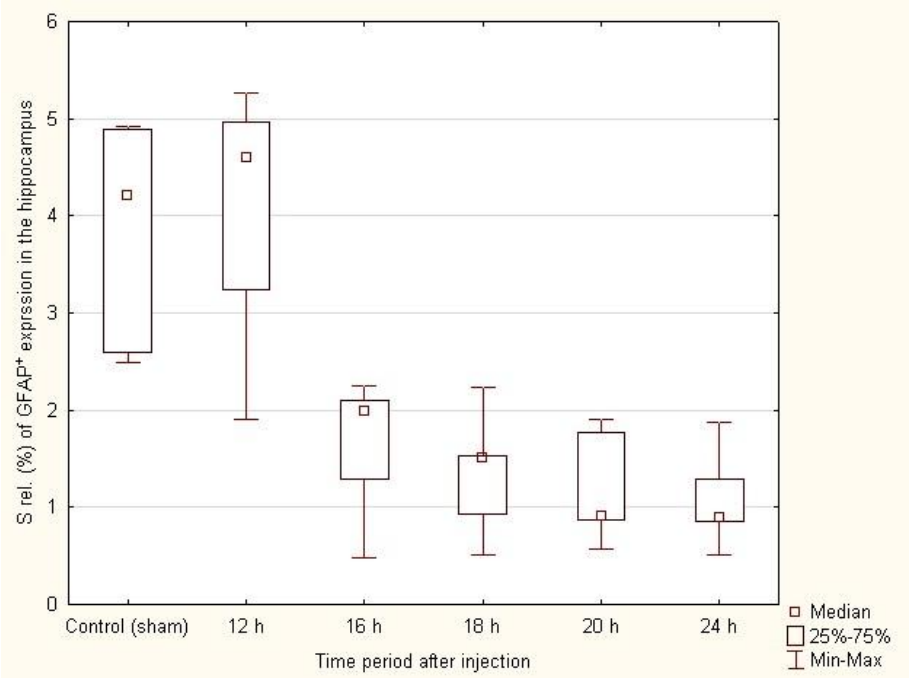

Fig. 5. Dynamics of the relative area of GFAP$^+$ expression (in the microscope SFV, %) in the hippocampus of AILF-B rats after injection.

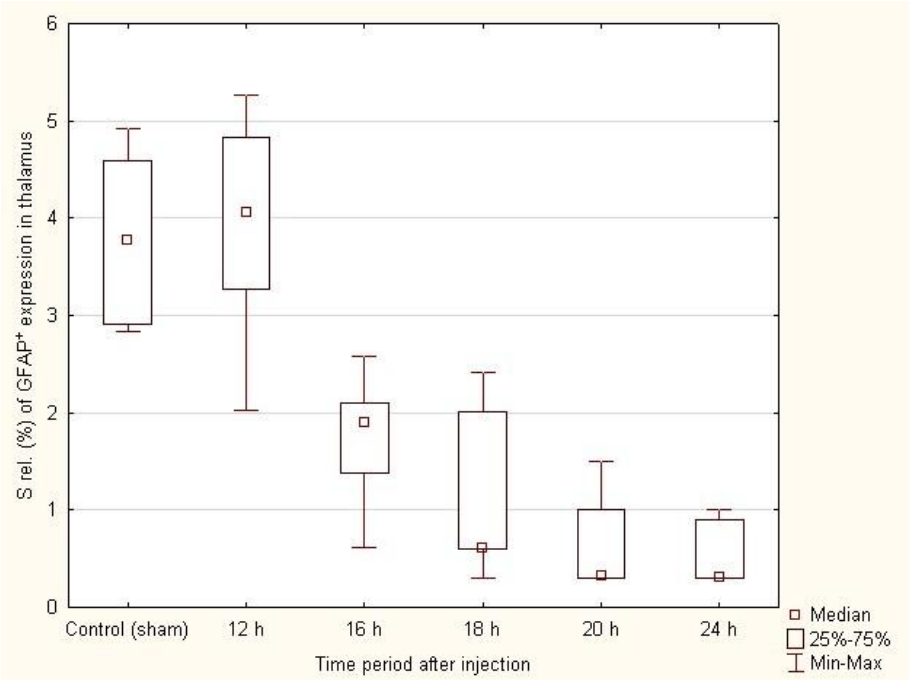

Fig. 6. Dynamics of the relative area of GFAP$^+$ expression (in the microscope SFV, %) in the thalamus of AILF-B rats after injection.

Discussion

Except the ammonia theory as a leading conception of the AHE development, the neuroinflammatory mechanistic component in the tissue reactivity has also been emphasized [18]. It was displayed in many previous studies that astroglia rapidly become reactive in response to various inflammatory signals both systemic and local, accompanied with upregulation of the main astrocytic "reactive" marker GFAP [9]. On the background of the general picture of the dramatic decrease in the levels of GFAP protein during immunostaining of the all mentioned brain regions, we eventually revealed the interesting phenomenon

of the temporary increase in the level of expression in rats scarified at 12 hours after acetaminophen injection, although with no statistical validity compared to control. Such synchronic rising of the level of GFAP in the all taken regions can be indirectly corresponded to the results of our previous study where in the cecum ligation and puncture model of sepsis-associated encephalopathy we observed the early activation of microglia cell type which is evidenced to be intimately interrelated with astroglia in orchestrating the neuroinflammatory reactiveness in the brain and often showing simultaneous reactivity [19].

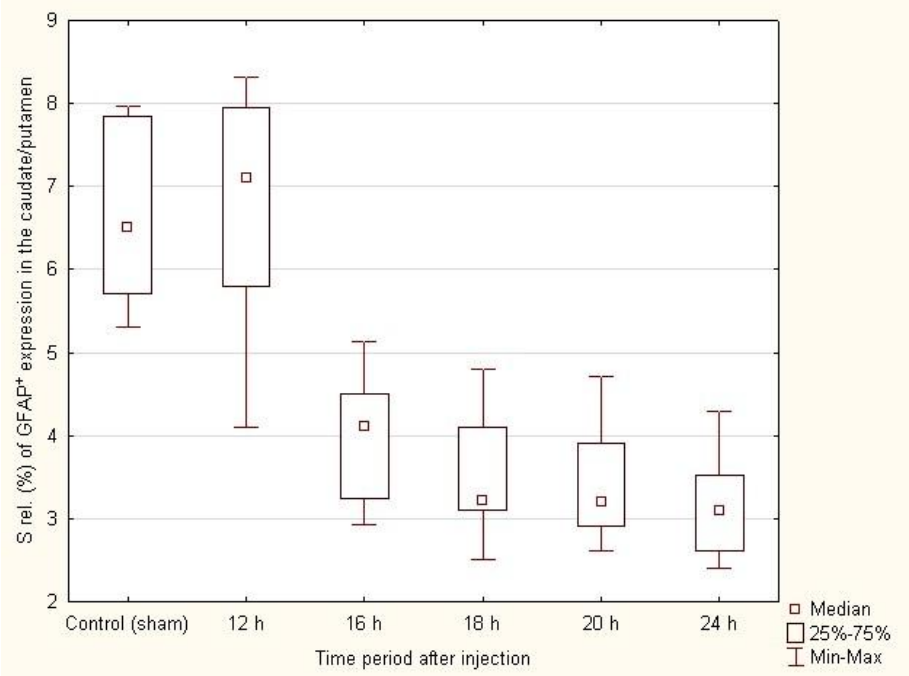

Fig. 7. Dynamics of the relative area of GFAP$^+$ expression (in the microscope SFV, %) in the caudate nucleus/putamen of AILF-B rats after injection.

The results of another our study have displayed that in the condition of AILF, the microglial phagocytic marker CD68, one of the most critical indicators of its reactive state, was not significantly changed compared to the control values reflecting relative inconsistency of microglial response to incoming aggressive factors at 12 hours after acetaminophen injection in the same regions which are studied in the current research [13]. The noted facts may suggest the early (12 h after AILF-procedure) microglia-independent reactivation of astroglial population in all studied brain regions in response to acute liver failure and accompanying critical changes in systemic homeostasis. The exact significance of such a reactive astroglia on other participants of the pathologic events in these terms of the disease remains to be clarified, since it is impossible to interpret the pathogenetic action of astrocytes only by increased GFAP expression. It is likely that on the first stages of the ALF when the wide spectrum of systemic damaging factors attacks the BBB, enter the brain parenchyma and accumulate inside, astroglia being the crucial and the main homeostatic cell population, attempts to compensate the progressively deteriorating water and osmotic tissue balance and thus distinguished by elevated GFAP, the common feature of astrocytic reactiveness. Consequently, due to exacerbation of the harmful action of the incoming aggressive factors through the BBB, it is supposed that astrocytes lose their reactive capabilities (with beneficial and/or unfavorable functional effect on the microenvironment) became insufficient and show decreased levels of GFAP comparing to control values which was observed in later time periods, beginning from the 16 hours in the white matter, hippocampus, thalamus and caudate/putamen and at 18 hours in the sensorimotor cortex.

As well as in the physiological conditions, in the AILF-model of ALF, astroglia displayed heterogenous reactivity with the most substantive decrease of GFAP levels in the cortical and thalamic regions compared to control values. Apparently, these brain regions might be suggested as more passable for the entry of systemic aggressive molecules or/and regions more susceptible to toxic-metabolic imbalance in conditions of ALF, as well as may indicate the special reactive response of regional astroglia on the action of detrimental substances in this condition and time point.

In general, our current observations correspond with earlier studies reported about GFAP downregulation in other animal models of HE, while some differences and contradictions also present. Thus, Jaeger V. and coauthors have reviewed the

data from earlier study of Suarez I. et al. showing heterogeneous reduce in GFAP expression in the rat brain, including perivascular astrocytic processes of different hippocampal layers in the long-term portacaval anastomosis model of HE [11]. Despite this, the same review referred other paper authored by Wright G. et al. where it was shown increased GFAP expression in corpus callosum from day 1 to 4 weeks after bile duct-ligation in rat model of cirrhosis. Lost GFAP expression in the brain cortex was also revealed in the postmortem study of patients who died as a result of brain edema due to ALF [20]. GFAP being important cell volume regulator, in downregulation state could contribute to the development of cerebral oedema in the conditions of AHE. The mechanism of the GFAP downregulation during HE is supposed to be linked to the mechanism where ammonia interfering with the cellular metabolism is followed by falling ATP levels and decrease GFAP synthesis [11]. Finally, brain dysfunction in AHE grading up to coma state seems to be conditioned by aggravation of oxidative and nitrosative stress in the brain tissue, followed by loss of GFAP protein and severe astrocyte swelling [21, 22].

Conclusion

Beginning from the 16th hours after the AILF procedure (from the 18th h in the cortex) up to 24-hours end-point of the experiment, the reliable (compared to control) region-specific dynamic reduce in GFAP expression was observed in the cortical, thalamic, subcortical white matter, hippocampal, caudate nucleus/putamen regions of the rat brain with the most substantive decrease of indicators in the cortex and thalamus. The latter potentially may indicate brain regions more passable for entering systemic aggressive factors and/or areas more susceptible to toxic-metabolic imbalance in conditions of ALF, as well as may indicate the special sensitivity and kind of reactive response of regional astroglia on the action of detrimental substances in this condition and time point. The dynamic decrease of the GFAP level in the rat brain associated with deterioration of animal state, indicate involvement of astroglial failure in the mechanisms of AHE in rats.

Prospects for further research

Given the mechanisms of AHE are still to be investigated and suggesting critical role of astroglial participance in brain adaptive reactions to various factors, it is reasonable to proceed further studies in the field of glial intercellular communication in response to systemic endogenous toxic challenges.

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Conflicts of interest: authors have no conflict of interest to declare.

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Шулятнікова Т.В., Туманський В.О. Імуногістохімічний аналіз експресії гліального фібрилярного кислого протеїну при експериментальній гострій печінковій енцефалопатії.

РЕФЕРАТ. Актуальність. Патогенез гострої печінкової енцефалопатії (ОПЕ) представляється комплексним, і тонкі ланки її розвитку все ще вимагають свого з'ясування. Вважається, що механізми ОПЕ в цілому зосереджені на нейротоксичности аміаку, нейрозапаленні, дисбалансі нейромедіаторів і важкому астроцитарному набуханні, що приводить до генерализованного набряку мозку. Вважається, що астроглія, будучи основною популяцією клітин мозку, що відповідає за всі види тканинного гомеостазу, є основною мішенню для підвищених рівнів аміаку в даних умовах. Будучи досить неоднорідною в залежності від мозкового регіону і контексту подій, астрогліальная реакція на різні патологічні впливи також представляється гетерогенною. **Мета** визначення імуногістохімічних особливостей експресії гліального фібрилярного кислого протеїну (GFAP) в різних відділах мозку щурів в умовах експериментальної гострої печінкової енцефалопатії. **Матеріали та методи.** Дослідження проводилося на щурах лінії Вістар: 5 контрольних і 10 щурів з відтворенням моделі ацетамінофен індукованої печінкової недостатності (AILF). Імуногістохімічне дослідження експресії GFAP в сенсомоторної корі, білій речовині, гіпокампі, таламусі, хвостатому ядрі/скорлупі проводили в період 12-24 год після ін'єкції. **Результати.** Починаючи з 6-ї години після ін'єкції у всіх тварин AILF-групи спостерігалося прогресуюче наростання клінічних ознак гострої мозкової дисфункції, яка завершилася у 6 щурів до 24 годин коматозним станом; вони склали підгрупу AILF-B, «загиблі тварини». Чотири тварини вижили до кінця експерименту, 24 ч (підгрупа AILF-A «тварини, що вижили»). У групі AILF-B, починаючи з 16-24 годин після процедури AILF, в головному мозку спостерігалося статистично значуще (щодо контролю) регіон-залежне динамічне зниження рівня експресії GFAP: в підкірковій білій речовині на 125,65%, в таламусі на 526,66%, в хвостато-

му ядрі/скорлупі на 103,12%, в гіпокампі на 176,31%, з 18-ої години в корі головного мозку, на 537,5% при найбільш значному зниженні показників в корі і таламусі: відповідно в 6,47 і 6,26 рази. **Висновки.** В умовах експериментальної AILF спостерігається раннє динамічне зниження реактивності астроглії в корі, таламусі, гіпокампі, білій речовині й області хвостатого ядра/скорлупи. Найбільш істотне зниження показників GFAP в корі і таламусі позначає ці області як більш уразливі для системних агресивних чинників і токсико-метаболічного навантаження в умовах гострої печінкової недостатності, з іншого боку, підкреслює відносно більш виражену чутливість і реактивність місцевої астроглії у відповідь на дію пошкоджуючих речовин в цьому стані і на даному часовому етапі розвитку патології. Динамічне зниження рівня GFAP в головному мозку щурів, асоційоване з таким же динамічним погіршенням стану тварин, вказує на значення такого патологічного астрогліального ремоделювання в механізмах розвитку ОПЕ у щурів.

Ключові слова: гостра печінкова енцефалопатія, астрогліальна реактивність, GFAP.

Шулятникова Т.В., Туманский В.А. Иммуногистохимический анализ экспрессии глиального фибриллярного кислого протеина при экспериментальной острой печеночной энцефалопатии.

РЕФЕРАТ. Актуальность. Патогенез острой печеночной энцефалопатии (ОПЭ) представляется комплексным, и тонкие звенья ее развития все еще требуют своего выяснения. Считается, что механизмы ОПЭ в целом сосредоточены на нейротоксичности аммиака, нейровоспалении, дисбалансе нейромедиаторов и выраженном астроцитарном набухании, приводящем к генерализованному отеку мозга. Предполагается, что астроглия, будучи основной популяцией клеток мозга, ответственной за все виды тканевого гомеостаза, является основной мишенью для повышенных уровней аммиака в данных условиях. Будучи достаточно неоднородной в зависимости от мозгового региона и контекста событий, астроглиальная реакция на различные патологические воздействия также представляется гетерогенной. **Цель** определение иммуногистохимических особенностей экспрессии глиального фибриллярного кислого протеина (GFAP) в различных отделах мозга крыс в условиях экспериментальной острой печеночной энцефалопатии. **Методы.** Исследование проводилось на крысах линии Вистар: 5 контрольных и 10 крыс с воспроизведением модели ацетаминофен индуцированной печеночной недостаточности (AILF). Иммуногистохимическое исследование экспрессии GFAP в сенсомоторной коре, белом веществе, гиппокампе, таламусе, хвостатом ядре/скорлупе проводили в период 12-24 ч после инъекции. **Результаты.** Начиная с 6-го часа после инъекции у всех животных AILF-группы наблюдалось прогрессирующее нарастание клинических признаков острой мозговой дисфункции, завершившейся у 6 крыс до 24 часов коматозным состоянием; они составили подгруппу AILF-B, «погибшие животные». Четыре животных выжили до конца эксперимента, 24 ч (подгруппа AILF-A «выжившие животные»). В группе AILF-B, начиная с 16-24 часов после процедуры AILF, в головном мозге наблюдалось статистически значимое (относительно контроля) регионзависимое динамическое снижение уровня экспрессии GFAP: в подкорковом белом веществе на 125,65%, в таламусе на 526,66%, в хвостатом ядре/скорлупе на 103,12%, в гиппокампе на 176,31%, с 18-го часа в коре головного мозга на 537,5% при наиболее значительном снижении показателей в коре и таламусе: соответственно в 6,47 и 6,26 раза. **Выводы.** В условиях экспериментальной AILF наблюдается раннее динамическое снижение реактивности астроглии в коре, таламусе, гиппокампе, белом веществе и области хвостатого ядра/скорлупы. Наиболее существенное снижение показателей GFAP в коре и таламусе обозначает эти области как более уязвимые для системных агрессивных факторов и более подверженные токсико-метаболической нагрузке в условиях острой печеночной недостаточности, с другой стороны, подчеркивает относительно более выраженную чувствительность и реактивность местной астроглии в ответ на действие повреждающих веществ в этом состоянии и на данном временном этапе развития патологии. Динамическое снижение уровня GFAP в головном мозге крыс, ассоциированное с таким же динамическим ухудшением состояния животных, указывает на значение такого патологического астроглиального ремоделирования в механизмах развития ОПЭ у крыс.

Ключевые слова: острая печеночная энцефалопатия, астроглиальная реактивность, GFAP.