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TRACE ELEMENTS CHANGES IN FOREBRAIN AND THEIR INFLUENCE ON THE RATS BEHAVIOR IN ELEVATED PLUS MAZE IN ACUTE PERIOD OF MILD BLAST TRAUMATIC BRAIN INJURY

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Key words: *blast-induced trauma, iron, copper, zinc, forebrain, behavior, elevated plus maze*
Ключові слова: *вибухо-індукована травма, залізо, мідь, цинк, передній мозок, поведінка, піднесений хрестоподібний лабіринт*

Abstract. Trace elements changes in the forebrain and their influence on the rats behavior in elevated plus maze in acute period of mild blast-induced traumatic brain injury. Kozlova Yu.V. *The relevance of the study is related to the high frequency of blast-induced brain injury in both military and civilian populations, which is caused by the use of various types of explosives in military conflicts, including in Ukraine today. Changes of biometals in the acute period of a mild blast-induced traumatic brain injury, including forebrain that participates in the implementation of various behavioral and cognitive processes, remain unexplained. The study was carried out on 54 sexually mature male Wistar rats, which were divided into 3 groups: experimental (influenced by a baroacoustic wave with an excess pressure of 26-36 kPa, previously anesthetized with halothane and softly fixed), sham (under the influence of halothane and fixation), intact. Behavior was studied in an elevated plus maze. Biometals in the forebrain were determined using energy dispersive X-ray fluorescence analysis. Standard deviation, Mann-Whitney U test (p<0.01, p<0.05), Spearman's correlation coefficient (r, p<0.01) were statistically calculated. According to the results of the study, behavioral changes in the elevated plus maze were found in the rats of the experimental group, which indicate the absence of fear on day 1 and 3 and the increase of anxiety on day 7 of the post-traumatic period. Spectral analysis of the forebrain showed significant (p<0.01) changes in the Cu/Fe, Cu/Zn and Zn/Fe ratios, which are the result of iron accumulation due to disruption of the blood-brain barrier. The obtained changes in the ratio of biometals lead to the development of anxiety, which is confirmed by correlation analysis. This indicates that the imbalance of biometals is an important secondary factor in the pathogenesis of blast-induced brain traumatic injury, which is important to consider for diagnosis, treatment and prevention of complications.*

Реферат. Зміни мікроелементів у передньому мозку та їх вплив на поведінку щурів у піднесеному хрестоподібному лабіринті в гострому періоді легкої вибухо-індукованої травми головного мозку. Козлова Ю.В. *Актуальність дослідження пов'язана з високою частотою вибухо-індукованої травми головного мозку як у військових, так і в цивільних, до чого призводить застосування різних видів вибухівки у воєнних конфліктах, у тому числі і в Україні на сьогоднішній день. Нез'ясованими залишаються зміни біометалів у гострому періоді легкої вибухо-індукованої травми головного мозку, зокрема в передньому мозку, що бере участь у реалізації різних поведінково-когнітивних процесів. Дослідження проведено на 54 статевозрілих щурах-самцях лінії «Wistar», які були розподілені на 3 групи: експериментальна (впливали бароакустичною хвилею з надлишковим тиском 26-36 кПа, попередньо знеболювали галотаном і м'яко фіксували), контрольна (під дією галотану і з фіксацією), інтактні. Поведінку досліджували в піднесеному хрестоподібному лабіринті. Біометали в передньому мозку визначали за допомогою енергодисперсійного рентгенофлуоресцентного аналізу. Статистично розраховували стандартне відхилення, U-критерій Манна-Уїтні (p<0,01, p<0,05), коефіцієнт кореляції Спірмена (r, p<0,01). За результатами дослідження, у щурів експериментальної групи встановлені зміни поведінки в піднесеному хрестоподібному лабіринті, що свідчать про відсутність страху на 1 та 3 добу та наростання тривожності на 7 добу посттравматичного періоду. Спектральний аналіз переднього мозку показав достовірні (p<0.01) зміни співвідношень Cu/Fe, Cu/Zn та Zn/Fe, що є результатом накопичення заліза через порушення гематоенцефалічного бар'єру. Отримані зміни співвідношень біометалів призводять до розвитку тривожності, що підтверджено кореляційним аналізом. Це свідчить, що дисбаланс біометалів є вагомим фактором вторинного ушкодження головного мозку в патогенезі вибухо-індукованої травми головного мозку, що важливо враховувати для діагностики, лікування і профілактики ускладнень.*

Analysis of modern literature indicates numerous studies of the pathogenesis features of primary and secondary brain damage as a result of the blast wave action [1]. This is due to the high frequency of blast-induced traumatic brain injury (bTBI) in both military and civilian populations, which occur due to applying of various types explosives in military conflicts [2], including in Ukraine today. Distinguishing bTBI as a separate type of craniocerebral trauma is associated with the specific action of the blast wave (BW) as the main pathological factor [3]. It is known that BW passes through the openings of the skull, changes the intracranial pressure, and leads to displacement of the brain. As a result, fluid pressure changes, cavitation, disruption of the blood-brain barrier (BBB) and neurons damage occur [4]. But clinically, these changes are not manifested by specific symptoms, the course of such injury is hidden in the acute period, victims without other injuries due to the influence of additional factors of the explosion (thermal, debris, etc.) go to the doctor rarely [5]. At the same time, behavioral and cognitive disorders, namely a decrease in concentration, signs of anxiety, depression and memory impairment in the acute post-traumatic period were established [6]. After primary damage, secondary pathological biochemical mechanisms are triggered, leading to irreversible changes and decrease in the life quality [7]. Known factors of secondary neurons damage in various diseases of the central nervous system are the imbalance of bioelements [8]. The participation of various micro- and macroelements, in particular iron, copper and zinc, in the processes of neurodegeneration in, for example, Alzheimer's disease has been proven [9]. However, the changes in biometals during the acute period of mild bTBI remain unclear, including in the forebrain, which is involved in the implementation of various behavioral and cognitive processes.

Therefore, the purpose of the study is to establish relationships between changes in the content of bioelements in the forebrain and behavioral and cognitive indicators.

MATERIALS AND METHODS OF RESEARCH

The study was carried out on 54 healthy, sexually mature male Wistar rats, body mass 220-270 g, aged 6-7 months in the laboratory of the Department of Pathological Anatomy, Forensic Medicine and Pathological Physiology of the Dnipro State Medical University (DSMU). Rats were kept in rectangular plastic cages (floor S=1500 cm^2) with a wire mesh on top and marked with a permanent marker. Wood shavings 2-3 cm thick were used as litter. In the room with rats, the air temperature was maintained in the range of 20-25°C, humidity – 50-60%. The daily light-dark cycle was 12:12 hours. Food and tap water were provided ad libitum. All rats were fed by commercial pellets, corn and wheat, identical in composition and quantity. The procedures followed the recommendations of the NIH Guide for the Care and Use of Laboratory Animals and the ARRIVE guidelines. Every effort was made to reduce both the suffering and the number of animals to a minimum, this is evidenced by an extract from the minutes of the meeting of the biomedical ethics commission DSMU No. 3, 02.11.2021.

The selected rats were randomly divided into 3 groups: I group – experimental (n=18), animals were anesthetized with halothane (Halothan Hoechst AG, Germany), softly fixed in a horizontal position on the abdomen, muzzle to the device opening at a distance of 5 cm and a baroacoustic wave with excess pressure 26-36 кPa was generated [10]. II group – sham (n=18), the animals of which were subjected only to inhalation anesthesia and fixation in a horizontal position, and III group – intact (n=18). Sham and intact groups were made to limit the influence of additional pathogenic factors on the behavior and composition of biometals (anesthesia, fixation). Behavioral studies in the elevated plus maze (EPM) were conducted on day 1, 3, and 7 after simulation of bTBI at the same time every day (11:00). Animals were brought to the laboratory 1 hour before the start of the study. After that, behavioral profiles were determined in the EPM (with crossed arms – 2 open, 2 closed, length – 50 cm, width – 14 cm, height of the walls of the closed arms – 30 cm, which creates sufficient darkness). At the intersection of the arms there was an open area, which is the starting point for the test. The arena is raised above the floor level by 55 cm [11]. The duration (in seconds) of staying in the open and closed arms, the number of stances (vertical motor activity – VMA), the duration of grooming (in seconds) were recorded in all groups of rats for 3 minutes.

Immediately after the study of behavior on day 1, 3 and 7 of the post-traumatic period, the animals were euthanized with halothane followed by removal of the brain. The forebrain was completely separated for spectral analysis using energy-dispersive X-ray fluorescence analysis (EDRFA) on the analyzer EXPERT 3 XL [12]. Regardless of the shape of the object, without the use of re-calibration and special sample preparation, direct express analysis with a wide measurement range of the spectrum of bioelements (from Na to U) allows you to quickly and highly accurately determine the elemental composition of any sample, in particular in the brain.

Fragments (forebrain) of the native unfixed brain were placed into the measuring chamber with radiation for 10 minutes (600 s). After that, with the help of software (manufacturer: LLC "Scientific and Production Enterprise Institute of Analytical Control Methods ("INAM" LLC), Kyiv, Ukraine) on the basis of the laboratory of the Communal Institution "Dnipropetrovsk Regional Bureau of Forensic Medical Examination" of the Dnipropetrovsk Regional Council, calculations were made in automated mode. The results are presented in the form of peak spectra and tables for each sample with the corresponding mass concentrations. After obtaining the quantitative mass fractions of biometals, the ratios of Cu/Fe, Cu/Zn, Zn/Fe were calculated based on the mass fractions of each element in percent and the data between the three groups were compared.

The numerical results were performed using Microsoft Office Excel-2003® (№ 74017-641-9475201-57075) (Microsoft Corporation, USA) and Statistica v6.1 (Statsoft Inc., USA) (ser. No. AGAR909E415822FA). Mathematical processing included calculations of average arithmetic values (M), standard deviations (SD). To determine the degree and nature of the relationship between the research parameters of the experimental and intact groups for each observation period, a comparative analysis (Mann-Whitney U-test) was used between the obtained results were considered statistically reliable when $p<0.01$ or $p<0.05$. Spearman's correlation coefficient was used to establish correlations between the studied parameters. The strength of correlation (r) was calculated, and the value of p was considered statistically significant $p<0.01$ [13].

RESULTS AND DISCUSSION

The analysis of behavior was carried out taking into account the known effect of halothane – analgesia, muscle relaxation and inhalation anesthesia [14]. The differences between the rats of the experimental and sham groups indicate an increase in adaptive and compensatory mechanisms in response to damage, and the reliability of the differences between the experimental and intact animals was further compared. Also, when comparing the results of the spectral analysis, an increase in the amount of bromine was found in days 1 and 3, which is related to its content in halothane, so this bioelement was not taken into account. Therefore, the results of the experimental and intact groups were compared.

It is known that the forebrain is involved in the regulation of behavior and motor activity [15] due to the presence of structural axonal connections with gray matter [16]. Primary brain damage established by previous studies in the form of ruptures of axonal connections, which lead to functional disorders of the behavioral-cognitive component [17], and also BBB disorders [18], which lead to metabolic disorders due to the penetration of compounds and substances that normally have a clearly controlled entry into the brain or do not penetrate at all, provide a basis for the study of changes in biometals (Cu, Fe, Zn) in the forebrain as factors of secondary damage [8]. And the application of EPM is widely used to determine behavioral and motor profiles [19].

Wave-like changes in the time the rats stay in the open and closed arms show the regularity of the animals' adaptation to the new environment. Normally, rats hide in a dark area, but spend some time exploring open, more lit areas [11]. We observed such dynamics in intact animals (Table 1).

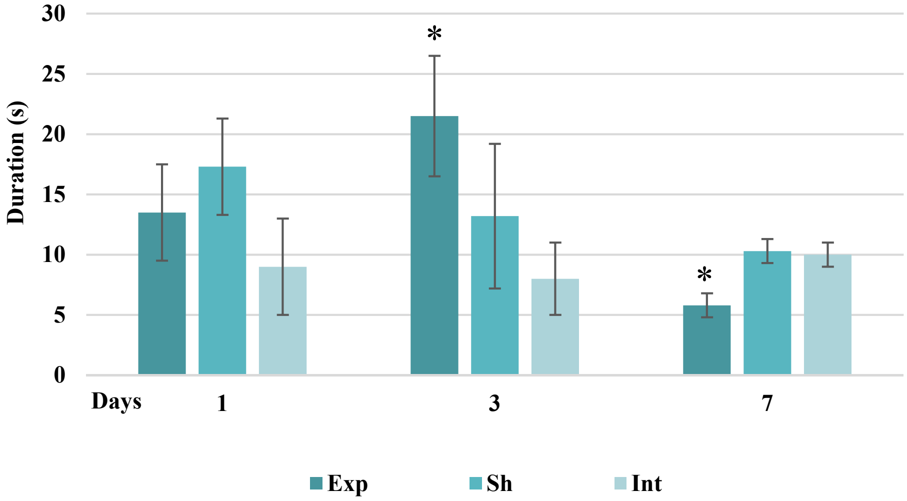
Table 1

Indicators of behavior in the elevated plus maze

Indicator	Day	1	3	7
Open arms (s) **(M±SD)**	**E**	**13.5±4**	**21.5±5***	**5.8±1***
	Sh	**17.3±4**	**13.2±6**	**10.3±2**
	I	**9±4**	**8±3**	**10±1**
Closed arms (s) **(M±SD)**	**E**	**142.5±3***	**155.7±3***	**161.7±3***
	Sh	**156.3±3**	**167.2±2**	**147.2±3**
	I	**154±3**	**164.5±2**	**150.3±2**
VMA (N) **(M±SD)**	**E**	**4.8±0.7***	**6.2±1.5***	**1.7±0.5***
	Sh	**1.2±0.7**	**4.2±1.2**	**4.3±0.5**
	I	**6±0.9**	**4±0.6**	**4.5±0.8**
Duration of grooming (s) **(M±SD)**	**E**	**10.5±2***	**17.3±1.6***	**24.2±2***
	Sh	**28.8±2**	**28.3±1**	**35.8±1.4**
	I	**30.5±1.8**	**29.2±1**	**36.8±1**

Notes: VMA – vertical motor activity; E – experimental group; Sh – sham group; I – intact group, * – the difference between the indicators of the experimental and intact groups — $p<0.01$, separately for each period of observation.

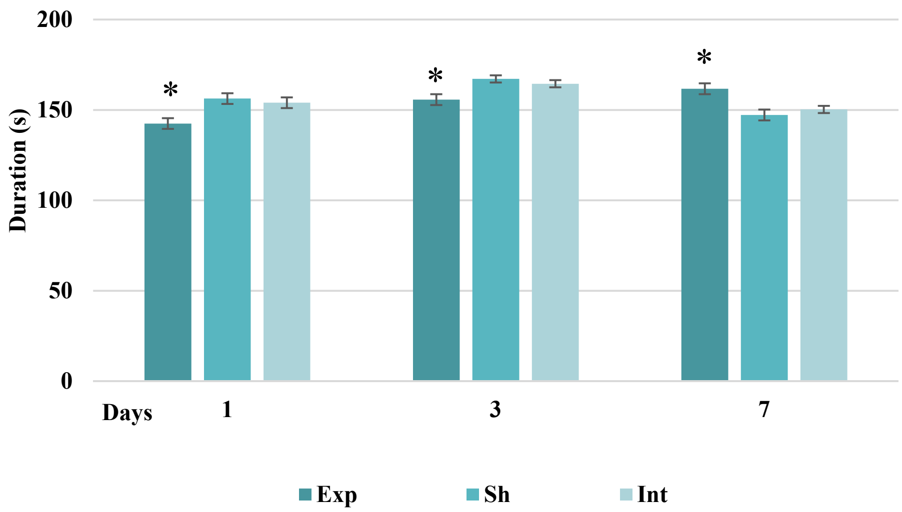
The study of motor activity in rats with bTBI, simulated using own device, showed significant ($p<0.01$) changes in the time spent in open (Fig. 1) and in closed arms (Fig. 2).



Exp – experimental group, Sh – sham; Int — intact group (* – the difference between the indicators of the experimental and intact groups – p<0.01, separately for each period of observation).

Fig. 1. Duration of staying in open arms

Comparison of our results with the results of other researchers provides a basis for concluding that rats with bTBI are more anxious on day 7, as evidenced by a 44% reduction in time spent in open arms and a 7% increase in closed arms.



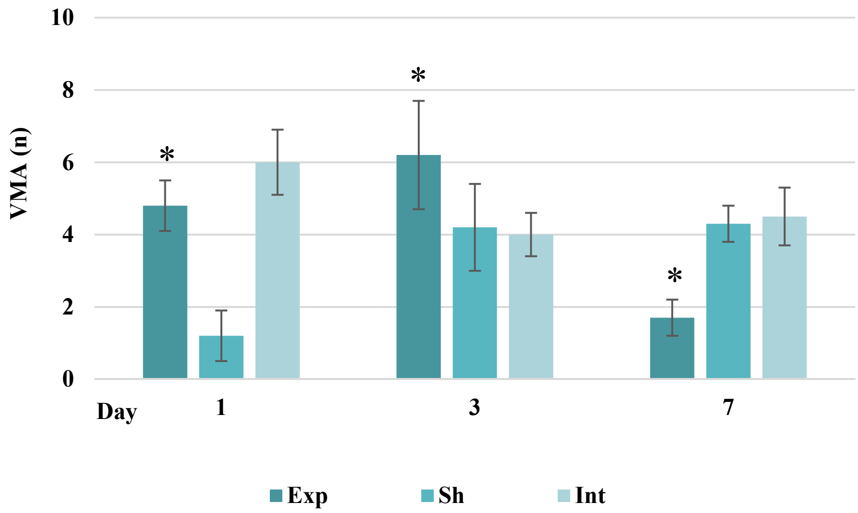
Exp – experimental group; Sh – sham; Int — intact group (* – the difference between the indicators of the experimental and intact groups — p<0.01, separately for each period of observation).

Fig. 2. Duration of staying in closed arms

However, in experimental rats there was an increase in the time of presence in the open arms by 33% on day 1 and by 63% on day 3, and a reduction in the time of presence in the closed arms by 8% on day 1 and by 5% on day 3. Such changes indicate the absence of fear and protective reactions with the maximum manifestation on day 3 of the bTBI course [19].

When comparing the data of the experimental group in separate periods of observation, a gradual lengthening of the time spent in closed arms is observed, this indicates the progression of anxiety in the dynamics of the acute post-traumatic period.

The number of vertical stands on the hind legs (Fig. 3), or vertical motor activity (VMA), which is an indicator of exploring a new territory and finding an exit from the maze, decreased significantly (p<0.01) by 20% on day 1 and by 64% on day 7, and increased by 35% on day 3.

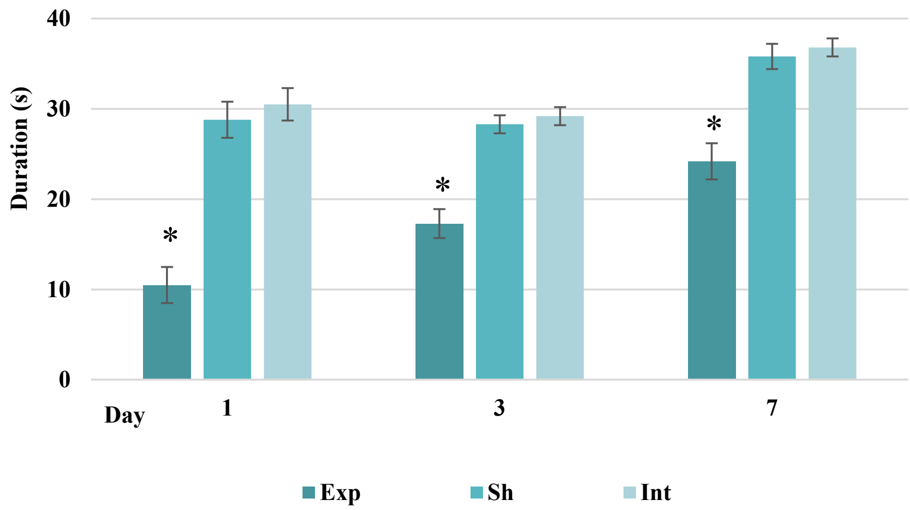


Exp – experimental group; Sh – sham; Int – intact group (* – the difference between the indicators of the experimental and intact groups – p<0.01, separately for each period of observation).

Fig. 3. Vertical motor activity

As is known, a decrease in VMA indicates anxiety, and an increase indicates the absence of fear and increased exploratory activity in rats [19]. Our results indicated to an increase in anxiety in rats on day 7 of the post-traumatic period.

During the 1 week, the duration of grooming acts (Fig. 4) was significantly (p<0.01) shorter in the rats of the experimental group compared to the data of the intact group rats: on day 1 – by 65%, on day 3 – by 41%, on day 7 – by 34%.



Exp — experimental group; Sh — sham; Int — intact group (* – the difference between the indicators of the experimental and intact groups — p<0.01, separately for each period of observation).

Fig. 4. Duration of grooming

Grooming, as an act of self-care and an indicator of social behavior, is also controlled by the forebrain [19]. The established reduction of grooming time in experimental rats indicates the presence of an anxiety feeling, which is increased by the unfamiliar environment of the EPM. Also, observing the grooming process itself, we found that the rats with bTBI washed themselves intermittently, the animals inconsistently cleaned separate parts of the face, same ear, which also indicates anxiety [20].

A comparison of the ratio of biometals in the forebrain of three groups of rats showed the presence of a significant imbalance of Cu/Fe, Cu/Zn, and Zn/Fe in the experimental group (Table 2).

Table 2

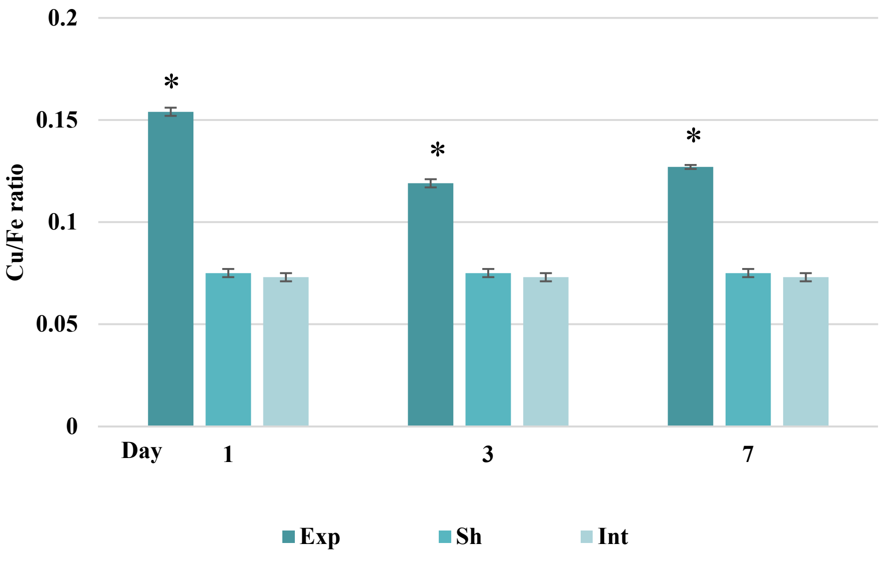
Changes in the ratio of biometals in the forebrain of rats

Indicator	Day	1	3	7
Cu/Fe (M±SD)	E	0.154±0.002*	0.119±0.002*	0.127±0.001*
	Sh	0.075±0.002	0.075±0.002	0.075±0.002
	I	0.730±0.002	0.730±0.002	0.730±0.002
Cu/Zn (M±SD)	E	0.394±0.002*	0.305±0.002*	0.265±0.002*
	Sh	0.207±0.002	0.207±0.002	0.207±0.002
	I	0.208±0.002	0.208±0.002	0.208±0.002
Zn/Fe (M±SD)	E	0.397±0.002*	0.403±0.002*	0.531±0.002*
	Sh	0.350±0.002	0.350±0.002	0.350±0.002
	I	0.353±0.001	0.353±0.001	0.353±0.001

Notes: E – experimental group; Sh – sham group; I – intact group, * – the difference between the indicators of the experimental and intact groups – p<0.01, separately for each period of observation.

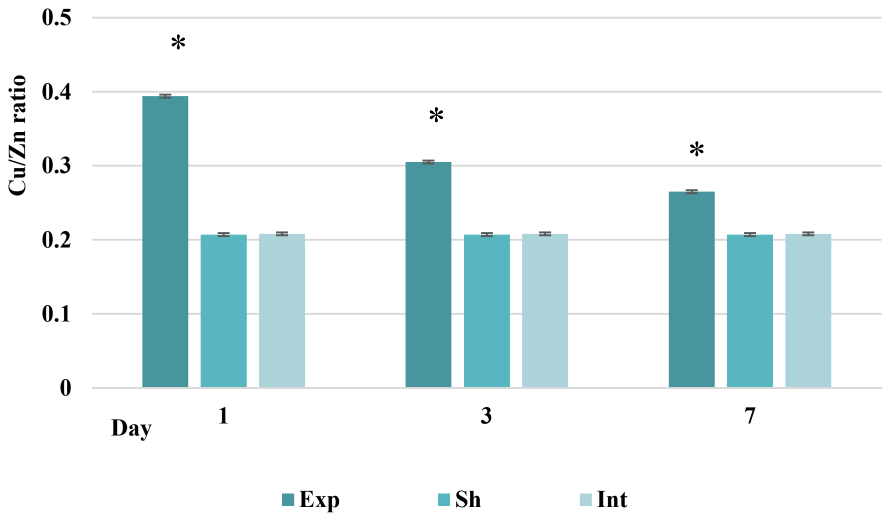
During the study period, a significant (p<0.01) increase in the ratio of Cu/Fe (Fig. 5) in the forebrain of experimental rats in comparison with the indicators of rats in the intact group was established: on day 1 – by 51%, on day 3 – by 39%, on day 7 – by 56%.

Changes in the Cu/Zn ratio (Fig. 6) during the entire observation period had a significant (p<0.01) increase in the rats of the experimental group: on day 1 – by 46%, on day 3 – by 32%, on day 7 – by 19%.



Exp – experimental group; Sh – sham; Int – intact group (* – the difference between the indicators of the experimental and intact groups – p<0.01, separately for each period of observation).

Fig. 5. Changes in the ratio of Cu/Fe in the forebrain of rats

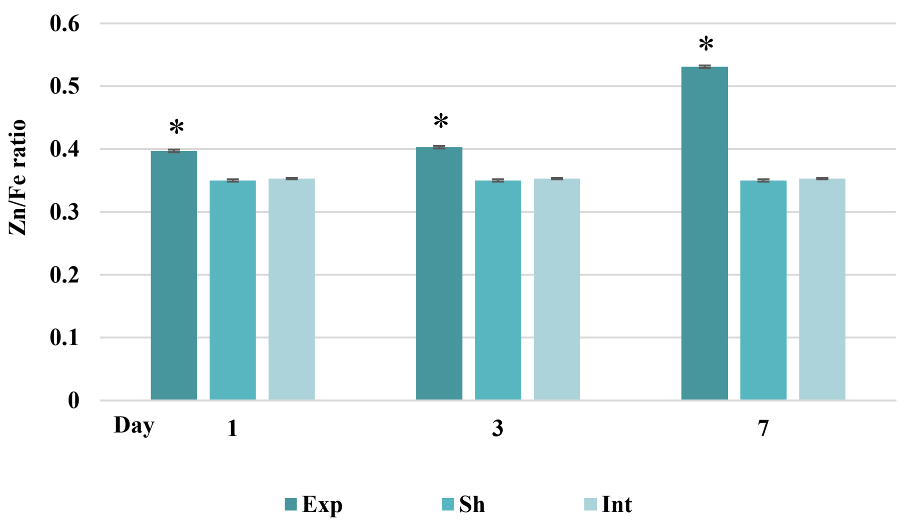


Exp – experimental group; Sh – sham; Int – intact group (* – the difference between the indicators of the experimental and intact groups – p<0.01, separately for each period of observation).

Fig. 6. Changes in the ratio of Cu/Zn in the forebrain of rats

The indicators of the Zn/Fe ratio (Fig. 7) in the rats of the experimental group increased significantly (p<0.01): on day 1 – by 20%, on day 3 – by 12.5%, and on day 7 – by 34%.

With the help of correlation analysis, it was established the presence of a strong positive relationship between Cu/Zn in the forebrain and VMA on day 1 (r=0.8, p<0.01) and an average positive relationship on day 7 (r=0.6, p<0.01). In turn, a strong negative relationship was found between Cu/Fe in the forebrain and VMA on day 3 (r= -0.7, p<0.01), medium positive relationships with the duration of presence in closed arms on day 3 (r=0.5, p<0.01) and on day 7 (r=0.6, p<0.01), and with grooming time (r=0.5, p<0.01). Correlation analysis between the ratio of Zn/Fe in the forebrain and behavioral indicators showed a strong positive relationship with VMA on 7 day (r=0.7, p<0.01), time of presence in closed arms on day 7 (r=0.7, p< 0.01), negative average degree of connection on day 1 with grooming (r= -0.5, p<0.01) and on day 3 with VMA (r= -0.6, p<0.01).



Exp – experimental group; Sh – sham; Int – intact group (* – the difference between the indicators of the experimental and intact groups – p<0.01, separately for each period of observation).

Fig. 7. Changes in the ratio of Zn/Fe in the forebrain of rats

The life quality of people with various types of craniocerebral injury deteriorates due to impaired behavioral and cognitive functions of the brain. Thus, brain trauma victims, in particular as a result of the blast wave, experience anxiety and general excitement in the acute post-traumatic period [21]. Experimental studies of mild bTBI in the acute period also indicate anxiety, emotional and motor arousal [22], which coincides with our results of behavioral indicators assessment.

In previous publications, we demonstrated that BBB disorders with diapedesis hemorrhages were determined in rats with bTBI and established the presence of oxidative stress during the first two weeks of the post-traumatic period [18]. Similar results were obtained by other scientists under the conditions of using different models of bTBI simulation [23]. We consider that these factors contribute to the accumulation of iron, in particular in the forebrain. It is known that iron is a part of antioxidant enzymes, participates in the cycle of tricarboxylic acids and oxidative phosphorylation and it also participates in the metabolism of catecholamines, the processes of nerve fibers myelination, and besides regulates the balance of copper and zinc [24]. Copper is involved in the regulation of iron homeostasis, myelination of nerve fibers, transmission of nerve impulses and is a part of some enzymes [25]. In turn, zinc participates in the transmission of intercellular signals, catalytic processes [26].

In addition to the physiological significance, it has been shown that the gradual, age-related imbalance of these biometals leads to neuroaging and neurodegeneration, resulting in the development of Alzheimer's and Parkinson's diseases [9]. Also, a number of studies notes the dependence of behavior on the balance of iron, copper and zinc, in particular, the development of anxiety during their accumulation [27, 28].

At the same time, studies of the changes in these biometals in craniocerebral injuries of other genesis show the imbalance of Fe, Cu and Zn in the dynamics of the post-traumatic period, which is part of the pathogenesis of anxiety and play a leading role in the development of neurodegeneration [29, 30]. It has been proven that the imbalance of Fe, Cu and Zn is associated with neuroinflammation as a result of trauma and leads to disruption of mitochondrial processes of energy generation, oxidative stress and triggers the accumulation of β-amyloid [31].

Considering the established functions of the investigated biometals and the indisputable data regarding their involvement in the secondary damage of neurons in traumatic brain injury and other brain diseases, we think that the key link in the pathogenesis of the biometals disruption in the forebrain in the case of bTBI is primarily the BBB disorder, which leads to the accumulation of iron, and this, in turn, leads to the violation of other iron-dependent biometals. In combination, these changes cause metabolic disturbances with subsequent energy deficit and interruption of the neuron excitation processes and nerve impulse transport. Signs of these disorders became markers of anxiety in the study of behavior in EPM and were confirmed by data of correlation analysis.

CONCLUSIONS

1. Rats with blast-induced traumatic brain injury showed behavioral changes in the elevated plus maze, indicating the absence of fear on day 1 and 3 and increased anxiety on day 7 of the post-traumatic period.
2. Spectral analysis of the forebrain showed significant ($p<0.01$) changes in Cu/Fe, Cu/Zn and Zn/Fe ratios, which are the results of iron accumulation due to a disorder of the blood-brain barrier.
3. The obtained changes in the ratio of biometals lead to the development of anxiety, which is confirmed by correlation analysis. This indicates that the imbalance of biometals is an important factor of secondary brain damage in the pathogenesis of blast-induced traumatic brain injury, which is important to consider for diagnosis, treatment and prevention of complications.

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