УДК 616.831-001-092.9:614.83:612.821.2
DOI: 10.24061/1727-0847.21.1.2022.03

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THE IMPACT OF BLAST-INDUSED TRAUMATIC BRAIN INJURY ON PASSIVE AVOIDANCE RESPONSE

ВПЛИВ ВИБУХО-ІНДУКОВАНОЇ ТРАВМИ ГОЛОВНОГО МОЗКУ НА РЕАКЦІЮ ПАСИВНОГО УНИКНЕННЯ

Резюме. Серед військовослужбовців, що беруть участь у збройних конфліктах по усьому світі, частою є вибухо-індукована травма головного мозку. Для легкої вибухо-індукованої травми головного мозку характерними є клінічні ознаки у вигляді порушення когнітивних функцій, зокрема пам'яті. Тому метою стало дослідження особливостей впливу вибухо-індукованої травми головного мозку на умовно-рефлекторну діяльність в експерименті. Дослідження проведені на 18 білих щурах-самцях лінії Wistar віком 5-7 місяців, масою 180,0-220,0 г, що утримувались у стандартних умовах віварію Дніпровського державного медичного університету. Відібрані щури були розподілені на три групи: I група – експериментальна (n=6), тварин якої наркотизували галотаном (Halothan Hoechst AG, Germany), фіксували та моделювали вибухо-індуковану травму головного мозку шляхом генерації бароакустичної хвилі з надлишковим тиском 26,4±3,6 кПа на власноруч виготовленому пристрої. II група – контрольна (n=6), тварини якої піддавались тільки інгаляційному наркозу галотаном і фіксації в горизонтальному положенні та III група – інтактна (n=6). Умовну реакцію пасивного уникнення відтворювали за стандартною методикою у світло-темній камері з електрифікованою підлогою у темній камері. Визначали латентний період заходу у темну камеру у щурів, що пройшли попереднє навчання. В результаті проведеного аналізу отриманих у ході експерименту даних установлено, що легка вибухо-індукована травма головного мозку призводить до порушення пасивної умовно-рефлекторної діяльності на 3 добу після травми (подовження латентного часу на 28-31%, $p>0,05$), яке прогресувало у 21 (100-79%, $p>0,05$) та 28 (100-96%, $p<0,05$) доби посттравматичного періоду. Враховуючи попередні дослідження, отримані зміни свідчать про значне вторинне ушкодження біологічно-активними речовинами, що призводить до запуску нейродегенеративних процесів і, як результат, погіршення пам'яті.
Ключові слова: умовна реакція пасивного уникнення, головний мозок, вибух.

Blast-induced traumatic brain injury (bTBI) is common among military personnel who are involved in armed conflicts around the world [1]. Primarily, this is due to the widespread use of various blast devices. Regardless of the blast devices type, the main factor in the damage is the blast wave, which has a very specific multidirectional effect on the brain and is to displace brain structures and collide with the skull bones, extra- and intracellular hydraulic shock, as a result of which bubbles are formed and also damage cells (cavitation effect) [2, 3]. Depending on the strength of the explosion, the distance of the person from the epicenter of events and the subsequent level of brain damage, there are different degrees of severity: mild, moderate and severe. Moderate and severe injuries are diagnosed fairly quickly, because they have severe clinical symptoms (loss of consciousness, coma, reflex disorders and persistent cognitive impairment in the post-traumatic period) [4], have a more unfavorable prognosis. Mild bTBI often goes unnoticed by the victims themselves. This is due to the absence of significant symptoms. Most often patients notice stun or loss of consciousness, headache that gone quickly. In addition, when victims apply, doctors note excitement, short-term cognitive impairment. However, there are patients in whom even with mild bTBI there are persistent and long-term cognitive impairment, including disorders of various types of memory, the pathogenesis of which has not been well studied [2] and therefore subject to in-depth experimental and clinical research.

Objective was to investigate the features of the impact of explosion-induced brain injury on conditioned reflex activity in the experiment.

Material and methods. The studies were performed on 18 white male Wistar rats, age 5-7 months, weigh 180.0-220.0 g. Animals were kept in standard conditions and on the standard diet of the DSMU vivarium [5], all studies were conducted in accordance with modern international requirements and norms of humane treatment of animals (Council of Europe Convention of March 18, 1986 (Strasbourg); Helsinki Declaration of 1975, revised and supplemented in 2000, Law of Ukraine of 21.02.2006 № 3447-IV), as evidenced by an excerpt from the minutes of the meeting of the Commission on Biomedical Ethics of DSMU № 3 of 2.11.2021.

Selected rats were divided into three groups: I group – experimental (n=6), animals were anesthetized with halothane (Halothan Hoechst AG, Germany), recorded and simulated bTBI by generating a baroacoustic wave with an overpressure of 26.4±3.6 kPa on a self-made device [6]. Rats after anesthesia were fixed in a horizontal position on the abdomen with the main end to the muzzle of the device at a distance of 5 cm. II group – sham (n=6), animals were subjected only to inhalation anesthesia with halothane and fixation in a horizontal position and III group – intact (n=6). Control and intact groups are designed to refute the action of halothane.

The passive avoidance response (PAR) investigated by standard methods in a light-dark chamber, with an electrified floor in a dark chamber [7]. The animals underwent a 5-day training, after which the animals of the experimental group reproduced the bTBI and recorded the latent time of entry into the dark room on 1, 3, 7, 21 and 28 days of the post-traumatic period. Only animals that did not enter the dark room for 180 seconds after training, with a stable memory for pain in the darkroom, were selected to participate in the experiment.

Statistical analysis was performed using the software product STATISTICA 6.1 (StatSoftInc., serial № AGAR909E415822FA). Data are presented as the mean and standard error of the mean (mean ± SEM). Comparative analysis (Mann-Whitney U-test) was used to determine the degree and nature of the relationship between the study parameters. The obtained results were considered statistically significant at $p<0.05$ [8].

Research results and discussion. Under conditions of mild bTBI in rats, a tendency to prolong latency was observed at 3 and 21 days of the post-traumatic period. On day 3, the elongation was 31% ($p>0.05$) compared with the experimental (group I) and sham (group II) and 28% ($p>0.05$) between the rats of the experimental and intact group (group III) – table. At 21 days – 100% between groups I and II, 79% between groups I and III.

Table

Latent time of entry of rats into a dark room

	Training, latency (sec)					Experiment, latency (sec)					
Day Group	**1**	**2**	**3**	**4**	**5**	**1**	**3**	**7**	**14**	**21**	**28**
I	32,8	2,7	0	0	0	0	16,2	0,7	0,7	8,0	7,5*
II	27,5	2,5	0	0	0	0	5	0,8	0,5	0	0
III	27,0	2,5	0	0	0	0	4,7	1,2	0,8	1,7	0,3

Note: * – $p<0.05$ between I, II and III groups.

Significant ($p<0.05$) prolongation of the latent time of entry into the dark room was observed on the 28th day of the post-traumatic period between animals of groups I and II by 100%, between animals of groups I and III by 96%. The differences in latent time between groups II and III are not significant, which indicates a minimal effect of halothane on the brain in the experiment.

Due to the complex activity of brain higher functions the analysis, memorization and reproduction of information received. Thus, repetitive actions or negative situations lead to the formation of a memory trace in the form of passive reflexes, which are integrated, highly organized processes of the central nervous system adaptation to environmental changes. PAR is provided by the relationship between the cortex and subcortical structures, including the hippocampus, and reflects the cognitive function of the brain [9]. Therefore, the study of the effect of bTBI on PAR in the experiment allows to assess the functional state of the brain in acute and early post-traumatic periods.

Modern studies of the PAR in conditions of brain injury of various origins also indicate a prolongation of latency in rats of the experimental group at different times of the post-traumatic period, depending on the severity of the injury [10]. Our study showed the presence of both trends at 3 and 21 days, and a significant increase in latent time by 28 days, indicating a deterioration in memory due to secondary alteration (3 days), ie damage to biologically active substances released as a result of primary damage to neurons due to the action of the shock wave.

This coincides with the data of modern scientists studying the effects of inflammatory mediators (cytokines and chemokines) on the course of traumatic

brain injury [11-13]. Further prolongation of time indicates a deterioration in memory, which is probably associated with the development of neurodegenerative processes as a consequence of primary and secondary neuronal damage [14]. These have been found in war veterans affected by explosions [1, 4] and other types of even minor bTBI [15].

Thus, the results indicate a critical period after injury (3 days). We believe that timely pathogenetic effects on secondary factors of brain damage will contribute to the suppression of neurodegeneration.

Conclusion. As a result of the data analysis obtained during the experiment, it was found that mild blast-induced traumatic brain injury leads to impaired passive avoidance response on the 3rd day after injury, which progressed in 21 and 28 days of the post-traumatic period.

Prospects for further research. We believe that the study of histopathological and biochemical changes in rats with experimental blast-induced traumatic brain injury will be promising to establish the links of pathogenesis that affect changes in memory.

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THE IMPACT OF BLAST-INDUSED BRAIN TRAUMA ON PASSIVE AVOIDANCE RESPONSE

Abstract. Among military personnel participating in armed conflicts around the world, blast-induced traumatic brain injury is common. Mild blast-induced traumatic brain injury is characterized by clinical signs in the form of impaired cognitive functions, including memory. In this regard, the objective is to study the features of the influence of an blast-induced traumatic brain injury on conditioned reflex activity in the experiment. The studies were carried out on 18 white male Wistar rats aged 5-7 months, weighing 180.0-220.0 g, which were kept under standard vivarium conditions of Dnipro State Medical University. Selected rats were divided into three groups: I group – experimental (n=6), whose animals were anesthetized with halothane (Halothan Hoechst AG, Germany), fixed and simulated blast-induced traumatic brain injury by generating a baroacoustic wave with an excess pressure of 26.4±3.6 kPa on your own manufactured device. II group – sham (n=6), the animals of which were subjected only to inhalation anesthesia with halothane and fixation in a horizontal position, and III group – intact (n=6). The passive avoidance response was reproduced according to the standard method in a light-dark chamber with an electrified floor in a dark chamber. The latent period of entry into the dark chamber was determined in rats that had undergone preliminary training.
As a result of the data analysis obtained during the experiment, it was found that a mild blast-induced traumatic brain injury leads to a violation of passive avoidance response on the 3rd day after the injury (lengthening of the latent time by 28-31%, $p>0.05$), which progressed by 21 (100-79%, $p>0.05$) and 28 (100-96%, $p<0.05$) days of the post-traumatic period. Taking into previous studies, the changes which we obtained are indicate significant secondary damage by biologically active substances, which lead to the launch of neurodegenerative processes and, as a result, memory impairment.
Key words: passive avoidance response, brain, blast.

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Надійшла 28.01.2022 р.
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