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R.S. Vastyanov, O.M. Stoyanov, V.V. Dobrovolskyi, O.L. Plakida, K.O. Talalayev, V.V. Babienko, G.F. Stepanov
Odesa National Medical University, Odesa

MONOAMINERGIC NEUROTRANSMISSION ACTIVITY MODULATION COULD ACTIVATE THE COMPENSATORY-ADAPTATION CAPACITIES IN CONDITIONS OF EXPERIMENTAL BRAIN TRAUMA

e-mail: rvastyanov@gmail.com

The purpose of the study was to evaluate the changes in motor and muscle activity in the dynamics of the post-traumatic period in conditions of serotonin-, dopamine- and noradrenergic neurotransmitter systems activity modulation. Experimental trials were performed on a model of brain trauma of medium severity. Prior to this, measures were taken to activate and suppress the activity of serotonin-, dopamine- and noradrenergic neurotransmitter systems in animals. The peculiarities of motor and muscle activity were determined 1, 7, 14, 21, 28 and 35 days after the brain trauma reproduction with rats' activity of monoaminergic neurotransmitter systems modulation of rats, the features of motor and muscle activity were determined. The data obtained confirm the motor and muscle disorders development in rats with brain trauma medium severity starting from the 1st day till the 35th day of the post-traumatic period. The post-traumatic period is characterized by evident neurological deficits and motor and muscle disorders which are manifested by muscle weakness, the inability to keep and maintain a natural position, as well as the inability to perform synchronous coordinated movements. Revealed motor and muscle dysfunctions are persistent and have their maximal expression during the first 14 days of the post-traumatic period. Serotoninergic and dopaminergic neurotransmitter systems activation in rats with brain trauma causes the motor and muscle functions of the body restoration and normalization. The authors stressed that serotoninergic and dopaminergic neurotransmission pathogenetic importance in conditions of traumatic brain damage should be taken into account when compiling and determining the clinical efficacy of complex pathogenetic therapy schemes for patients with brain trauma.

Key words: brain trauma, ischemia, monoaminergic neurotransmission, motor activity, muscle tone, compensatory activity, sanogenetic mechanisms.

Р.С. Вастьянов, О.М. Стоянов, В.В. Добровольський, О.Л. Плакіда, К.О. Талалаєв, В.В. Бабієнко, Г.Ф. Степанов

МОДУЛЯЦІЯ АКТИВНОСТІ МОНОАМІНЕРГІЧНОЇ НЕЙРОПЕРЕДАЧІ В ЯКОСТІ АКТИВАЦІЇ КОМПЕНСАТОРНО-АДАПТАЦІЙНИХ МОЖЛИВОСТЕЙ ЗА УМОВ ЕКСПЕРИМЕНТАЛЬНОЇ ЧЕРЕПНО-МОЗКОВОЇ ТРАВМИ

Метою дослідження було визначення зміни моторної та м'язової активності в динаміці посттравматичного періоду за умов модуляції активності серотонін-, дофамін- та норадренергічної нейромедіаторних систем. Експериментальні дослідження проводили на моделі черепно-мозкової травми середнього ступеня важкості. У тварин до цього були здійснені заходи по активації та пригніченню активності серотонін-, дофамін- та норадренергічної нейромедіаторних систем. Через 1, 7, 14, 21, 28 та 35 діб з моменту відтворення черепно-мозкової травми з модуляцією активності моноамінергічних нейромедіаторних систем щурів визначали особливості моторної та м'язової активності. Отримані дані підтверджують розвиток моторних та м'язових порушень, починаючи з 1-ї і до 35-ї доби посттравматичного періоду. Післятравматичний період характеризується вираженим неврологічним дефіцитом, моторними та м'язовими порушеннями, які проявляються м'язовою слабкістю, нездатністю приймати та утримувати природне положення, а також неспроможністю здійснювати синхронні координовані рухи. Відзначені моторні та м'язові дисфункції є стійкими та мають максимальне вираження протягом перших 14 діб посттравматичного періоду. У щурів після черепно-мозкової травми активація серотонінергічної та дофамінергічної нейромедіаторних систем спричиняють відновлення та нормалізацію функціонування моторної та м'язової функцій організму. Автори вважають, що висвітлене патогенетичне значення серотонінергічної та дофамінергічної нейротрансмісії за умов травматичного ураження мозку слід враховувати при складанні та визначенні клінічної ефективності лікувальних схем комплексної патогенетичної терапії хворих з черепно-мозковою травмою.

Ключові слова: черепно-мозкова травма, ішемія, моноамінергічна нейропередача, рухова активність, м'язовий тонус, компенсаторна активність, саногенетичні механізми.

The study is a fragment of the research project "To investigate the chronic convulsive syndrome pathogenetic mechanisms on the model of pharmacological kindling and to study the efficacy of its complex pathogenetical correction by anticonvulsant mechanisms activation", state registration No. 0122U000081.

The relevance of the problem of traumatic brain injury, and especially brain trauma (BT), is categorical and is explained by high absolute rates of prevalence and mortality from it, episodes of disability of survivors, poor long-term prognosis, development of consequences and residual phenomena with quality of life decrease throughout the postponed period. It is also necessary to consider the high medical, social, and economic significance and direct and indirect losses due to the loss of the so-called "working potential", not only with the victims but also the whole society [3, 6].

The majority of BT cases are well known to occur in the young working age, with a maximum in the range of 14–24 years, and are the main cause of disability and mortality in people from 20 to 40 years. The lethality index exceeds the same for cardiovascular diseases 10 times and for oncology 20 times [8].

More than 11000 people die from BT every year in Ukraine; 55 % of them die before admission to a hospital, and 42 % die in a hospital, which is 1.5 times higher than in developed countries [4].

The increase in life duration expands the age range of BT receiving possibilities, and the life rhythm acceleration, scientific and technical progress, urbanization and military conflicts, which are quite frequent today, act, unfortunately, as such factors that will contribute to increasing the cases of body traumatic damage in general and the brain in particular.

We started to study this problem, taking into account the complexity of the post-traumatic period with the certain number of factors that directly characterize the traumatization process itself – the weight of the load and the intensity of the alterative factor, the area of the brain undergone to mechanical influence, the age of the patients, the presence of concomitant pathology, etc. Currently, existing schemes for patients with BT pharmacological correction effectively affect the cause of the disease and are completely able to prevent the development of certain complications throughout the post-traumatic period.

To a greater extent, we are interested in adaptive and compensatory mechanisms that provide a sufficiently effective regulatory potential to resist the powerful alterative power in BT conditions for a certain period. Since the body's motor functions are often disabled in a certain range during traumatic brain injury, it is important to recall the existing neurotransmitter mechanisms of both the pyramidal and extrapyramidal pathways functioning and muscle system functioning regulation. We believe that both subcortical and brainstem area monoaminergic neurotransmission activity modulation might cause a certain regulatory effect that can mobilize energy resources or activate motor function without the pharmacological compounds with neuroprotective properties injection. Subsequently, we are talking about a direct sanogenetic effect of serotoninergic, dopaminergic, and noradrenergic neurotransmission activity modulation, which is the expression we decided to test in conditions of experimental BT.

The purpose of the study was to evaluate the changes in motor and muscle activity in the dynamics of the post-traumatic period in conditions of serotonin-, dopamine- and noradrenergic neurotransmitter systems activity modulation.

Materials and methods. Experimental studies were performed on 126 mature white male Wistar rats. The animals were kept in standard vivarium conditions. Experimental animals keeping and manipulation was done in accordance with the "General Ethical Principles of Animal Experiments" adopted by the Fifth National Congress on Bioethics (Kyiv, 2013) and was guided by the recommendations of the European Convention for the Protection of Vertebrate Animals for Experimental and Other Scientific Purposes (Strasbourg, 1985) and guidelines of the State Pharmacological Center of the Ministry of Health of Ukraine on "Preclinical studies of drugs" (2001) as well as rules of humane treatment of experimental animals and conditions approved by the Committee on Bioethics of Odesa National Medical University (Prot. N17-C from 12.10.2021).

L-tryptophan (LT; intravenously (i.v.) 100 mg/kg, during 14 days) and parachlorophenylalanine (PCPA; i.v.; 300 mg/kg, during 3 days), correspondently, we used to activate and inhibit the activity of the serotoninergic neurotransmitter system (NS). The dopaminergic NS activity, both activation and suppression, were achieved via the use of deprenyl (DP; intraperitoneally (i.p.); 3 mg/kg, during 14 days) and haloperidol (HP; i.p.; 2.5 mg/kg, during 3 days), respectively. Ludiomil (LD; i.p.; 20 mg/kg, during 14 days) and α-methyl-paratyrosine MP; i.p.; 80 mg/kg, during 3 days) were used for activation and inhibition of noradrenergic NS activity [5].

The rats were randomized as follows: group 1 – control (falsely injured, n=7); group 2 – 11 rats with BT; group 3 – LT+control (n=9); group 4 – LT+BT (n=9); group 5 – PCPA+control (n=9); group 6 – PCPA+BT (n=9); group 7 – DP+control (n=9); group 8 – DP+BT (n=9); group 9 – HP+control (n=9); group 10 – HP +BT (n=9); group 11 – LD+control (n=9); group 12 – LD+BT (n=9); group 13 – MP+control (n=9); group 14 – MP+BT (n=9).

After the rat's NS activity activation/suppression BT of medium severity was reproduced by falling load (m=50 g) impact from a height of 50 cm on the occipito-parietal part of the skull. For this purpose, rats under ether Rausch anaesthesia were fixed in such a way that the trajectory of the load was perpendicular to the surface of their skull. After that, autoblood (100 μl) was stereotaxically injected bilaterally into the parietal-temporal area of both hemispheres according to the coordinates of the stereotaxic atlas (AP=2.7; L=3.5; H=5.7) under nembutal (30–35 mg/kg, i.p.l) anesthesia [9]. Intact (pseudo-injured) animals were observed as a control group, which were fixed shortly in conditions of ether Rausch anesthesia without mechanical impact.

Animals were observed on an open plane 1, 7, 14, 21, 28 and 35 days after the BT induction, and the number of rats that kept a vertical posture, the duration of their uncomfortable posture holding on their back or on their side and the muscle activity change dynamics were determined together with rats' coordination movements and neurological status.

Muscle activity was determined by the time during which the rats were able to hold on to two horizontally located sticks with the help of their forelimbs and hindlimbs [13]. The rat's motor coordination was tested according to their ability to hold a horizontally rotating rod (rotarod; diameter = 25 mm, length = 60 cm) divided by 5 discs into 6 parts [13]. The number of animals that were able to stay on a rod rotated with the frequency of 15 turns per minute for 120 sec was determined. Neurological status was evaluated by the neurological deficit expression determination according to the scale of motor shift estimation [1].

The data obtained were statistically analyzed with the help of the parametric ANOVA test followed by Newman-Keulls test and the non-parametric Krushkal-Wallis test. The minimal statistical probability was determined at $p<0.05$.

Results of the study and their discussion. Hypodynamia was registered in rats after BT. In the "open field" test, there was a significant decrease in crossed squares and vertical stands and looking into the holes of the "open field". Thus, the absolute indices of the abovementioned motor behaviour parameters in the "open field" 1 day after BT were less pertaining to the equivalent control data by 2.90 times, 2.94 times and 4.39 times (in all cases $p<0.001$; Table 1).

Table 1

The dynamics of rats after brain trauma motor activity in the "open field" in conditions of monoaminergic neurotransmitter systems activity modulation

Experimental groups	Indices of motor activity in "open field" test (M±m)		
	The number of squares crossed	The number of vertical posts	The number of peeks into the floor holes
1st day after brain trauma			
Control, n=7	24.1±2.6	4.7±0.6	2.46±0.24
BT, n=11	8.3±1.3***	1.6±0.2***	0.56±0.06***
LT+BT, n=9	9.1±1.4***	1.3±0.2***	0.67±0.07***
PCPA+BT, n=9	8.7±1.1***	1.4±0.2***	0.58±0.07***
DP+BT, n=9	10.1±1.3***	1.8±0.3***	0.71±0.07***
HP+BT, n=9	9.2±1.3***	1.7±0.2***	0.59±0.06***
LD+BT, n=9	9.4±1.2***	1.7±0.3***	0.63±0.06***
MP+BT, n=9	8.9±1.4***	1.9±0.2***	0.64±0.06***
7th day after brain trauma			
Control, n=7	22.9±2.4	4.4±0.4	2.28±0.21
BT, n=11	7.2±1.1***	1.2±0.2***	0.38±0.04***
LT+BT, n=9	15.3±1.6#	2.4±0.3*#	1.32±0.19*#
PCPA+BT, n=9	9.1±1.1***	1.3±0.2***	0.47±0.05***
DP+BT, n=9	14.1±1.7#	2.6±0.4*#	1.37±0.18*#
HP+BT, n=9	8.4±1.3***	1.7±0.3***	0.56±0.06***
LD+BT, n=9	7.1±1.1***	1.6±0.2***	0.43±0.04***
MP+BT, n=9	8.7±1.3***	1.4±0.3***	0.51±0.06***
14th day after brain trauma			
Control, n=7	20.3±1.9	4.1±0.4	2.16±0.17
BT, n=10	9.1±1.3*	1.3±0.3**	0.53±0.06***
LT+BT, n=9	17.1±1.8#	2.9±0.4#	1.84±0.21##
PCPA+BT, n=9	10.3±1.2**	1.7±0.3**	0.56±0.06***
DP+BT, n=9	14.9±1.7#	3.4±0.4##	1.91±0.22##
HP+BT, n=8	9.7±1.2**	1.8±0.2**	0.76±0.08***
LD+BT, n=9	8.6±1.2**	2.1±0.3**	0.59±0.06***
MP+BT, n=8	10.6±1.3**	1.6±0.2**	0.61±0.06***

Notes: * – P<0.05, ** – P<0.01 and *** – P<0.001 – statistical differences of the investigated parameters compared with the same in the control group; # – P<0.05 and ## – P<0.01 – statistical differences of the investigated indexes compared with the same in rats with brain trauma (ANOVA + Newmann Keuls criteria).

All the investigated indices of motor activity at this time of the trial did not differ from those recorded in rats with BT and were significantly less vs. the corresponding control data.

The number of the "open field" crossed squares was 2.1 times higher in rats with serotoninergic NS activation than in rats with BT ($p<0.05$) on the 7th day of the trial. At the same time, rats demonstrated vertical postures twice as often and looked into the "open field" holes 3.47 times more often than rats with BT ($p<0.05$). Significant differences in the investigated indices being compared with the corresponding ones in rats with BT were registered in rats with dopaminergic NS activation ($p<0.05$). All investigated parameters in the rest of the experimental groups did not differ significantly from those demonstrated by the injured rats.

On the 14th day of the post-traumatic period, rats with BT and the serotoninergic NS activation crossed on average 88 % more squares and demonstrated 2.2 times more vertical stands as well as 3.5 times more often looked into the "open field" holes (in all cases $p<0.05$) when compared with such indices in rats with BT. At the same time, rats after BT with the dopaminergic NS activation also crossed an average of 64 % more the "open field" squares ($p<0.05$) and demonstrated 2.6 times more vertical stands and 3.6 times more looking into the "open field" holes ($p<0.01$). All investigated indices of motor activity in the "open field" in the rats of the remaining groups were revealed to be identical to those in the injured rats.

Similar dynamics of investigated motor activity indices in injured rats with monoaminergic NS activity modulation in the "open field" test were registered throughout the 21–35 days of the trial.

Rats demonstrated neurological disorders during the first day after BT in the form of lethargy, slowness of movements, limb weakness, and varying degrees of the limbs both paresis and paralysis. The studied indices of neurological status in rats of all groups had approximately the same expression and were significantly worse than in control animals ($p<0.05$; Table 2).

Table 2

The dynamics of neurological deficit expression in rats after brain trauma in conditions of monoaminergic neurotransmitter systems activity modulation

Experimental groups	Parameters of neurological deficit expression, %				
	Lethargy, slowness of movements	Weakness of movements	"Manege" movements	Paresis of 1–4 limbs	Paralysis of 1–4 limbs
1st day after brain trauma					
Control, n=7	14	14	0	0	0
BT, n=11	91**	100***	46*	27	9
LT+BT, n=9	78**	78**	22	0	0
PCPA+BT, n=9	89**	100***	44*	33	11
DP+BT, n=9	78**	67**	22	0	0
HP+BT, n=9	100***	100***	56*	44*	0
LD+BT, n=9	78**	100***	44*	33	11
MP+BT, n=9	89**	100***	56*	44*	0
7th day after brain trauma					
Control, n=7	14	0	0	0	0
BT, n=11	64**	73**	46*	18	0
LT+BT, n=9	33#	44#	22	0	0
PCPA + BT, n=9	78**	67**	44*	11	11
DP+BT, n=9	33#	33#	22	0	0
HP+BT, n=9	89**	78**	44*	33	0
LD+BT, n=9	67**	67**	44	22	0
MP+BT, n=9	67**	56**	44*	11	0
14th day after brain trauma					
Control, n=7	0	0	0	0	0
BT, n=10	30	40*	30	10	0
LT+BT, n=9	11#	22#	11	0	0
PCPA+BT, n=9	33	33	0	0	0
DP+BT, n=9	11#	11##	11	0	0
HP+BT, n=8	38*	25	38*	13	0
LD+BT, n=9	33	33	11	0	0
MP+BT, n=8	38*	25	13	0	0

Notes: * – P<0.05, ** – P<0.01 and *** – P<0.001 – statistical differences of the investigated parameters compared with the same in the control group; # – P<0.05 and ## – P<0.01 – statistical differences of the investigated indexes compared with the same in rats with brain trauma (Kruscall-Wallis criterion).

After BT, the rats preserved the neurological deficit indices on the 7th day of the trial. However, 3 out of 9 animals showed lethargy and weakness of movement groups with both the serotoninergic and dopaminergic NS activation, which was significantly less when compared with the same indices in injured rats ($p<0.05$). The investigated neurological deficit indices in rats of the remaining groups did not differ significantly from those revealed by the injured rats.

Only 1 rat with BT and the serotoninergic NS activation showed slowness of movements, and 2 rats showed weakness of movements on the 14th day of the post-traumatic period, significantly less pertaining to the same indices in rats with BT ($p<0.05$). 1 rat from each group showed lethargy and weakness of movements in animals with BT and dopaminergic NS activation, which also had probable differences with similar indices in rats with BT ($p<0.05$). All animals in the other groups showed neurological deficits comparable to those in injured rats.

A similar nature of neurological deficit demonstration was preserved in rats after BT with the monoaminergic NS activity modulation until the 35th day of the trial.

1 day after BT induction, the injured rats were in an uncomfortable position for more than 4 min average which was 36 times higher than the corresponding control index ($p<0.001$). None of the traumatized rats was able to hold on either on two horizontally located sticks or on the rotarod ($p<0.001$). Similar muscle adynamia was characteristic of all rats in other investigated groups.

The duration of uncomfortable posture maintenance in rats with BT with both serotonin and dopaminergic NS activation seven days after BT was 66.4±7.3 sec and 43.1±4.6 sec, correspondingly, which was 2.68 and 4.13 times less vs the same data in traumatized rats ($p<0.001$). All rats of these two groups could not simultaneously hold on to two horizontally located sticks on the rotarod. In the rats of the remaining groups, the investigated indices also did not differ from the same in the injured rats and stayed significantly changed when compared with control data ($p<0.001$).

The duration of uncomfortable posture maintenance in rats with BT with the serotoninergic NS activation on the 14th day of the trial was 11 times less than in injured rats ($p<0.001$). 6 rats of this group were able to hold on to two horizontally located sticks, which was also twice high vs the corresponding rate in rats with BT ($p<0.05$). The duration of uncomfortable posture maintenance in rats after BT with dopaminergic NS activation was 15.5 times less than in injured rats ($p<0.001$). At the same time, 6 rats of this group were able to stay on two horizontal sticks and 2 rats – on a rotarod, which turned out to be more than in rats traumatized without the monoaminergic NS activity modulation ($p<0.05$). All muscle activity investigated parameters in rats of the remaining groups were identical to those in rats with BT.

We recorded the analogous data characterizing muscle tone in rats after BT with monoaminergic NS activity modulation until the end of the trial.

Thus, the data obtained indicate a mean degree of motor and muscle disorder formation in rats with BT. The revealed disorders were registered starting from the 1st day of the post-traumatic period and lasted for 5 weeks. The studied indices on the 5th week of the trial without pharmacological correction have a tendency towards recovery, which we most likely explain by regulatory antioxidant mechanisms activation and energy resources mobilization in case of brain sanogenetic mechanisms activation [2]. Finalizing this idea, we note that the tendency to both motor and muscle dysfunctions self-recovery is experimental evidence of the reasonability of pathogenetic neuroprotective pharmacocorrection initiation as early as possible.

Our data proved that the post-traumatic period is characterized by expressed neurological deficits and motor and muscle disorders which are manifested by muscle weakness, the inability to keep and maintain a natural position, as well as the inability to perform synchronous coordinated movements. The expressed motor and muscle dysfunctions are persistent and have their maximal appearance during the first fortnight of the post-traumatic period.

The most interesting component of the obtained results is that both serotoninergic and dopaminergic NS activation in BT rats causes the motor and muscle functions of the body restoration and normalization. We did not register evident changes in motor and muscle functions during the post-traumatic period in conditions of serotonin and dopaminergic NS activity inhibition just as with noradrenergic NS activity modulation.

The data obtained in a certain way correlate with clinical observations that prove muscle weakness, adynamia and emotional poverty in patients in the acute period after a traumatic brain injury [11]. Some experts emphasize the motor disorders' dominance and muscle function preservation after BT [8], but this is a rather controversial point [11].

There is interesting evidence of brain serotoninergic and dopaminergic systems activity modulation in conditions of chronic convulsive syndrome [15], during the relevant association's formation for the avoidance strategy in the shuttle [10], during the periods of cognitive deficits recovery [12] and others.

The fundamental importance of both serotonin and dopaminergic NS activity modulation was proved in muscle fatigue development as well as in the body's physical ability restoration [7].

In any case, we are talking about the promising possibility of regulating brain excitability processes by monoaminergic NS activity modulation, which we consider a necessary and sufficient component of activating sanogenetic mechanisms in traumatic and ischemic brain damage. The protective mechanisms of endogenous activation might be achieved in this case, which initiates a complex cascade of physiological and biochemical sanogenetic processes.

Monoaminergic NS intrastriatal modulation enabled an anticonvulsant effect in conditions of the kindling-induced model of epilepsy, which also highlights these NS pathogenetic significance in brain excitability regulation [14].

In this aspect, we consider it suitable to call attention to the fact that pathogenetically determined pharmacological correction should take into account the need to activate serotonin and dopaminergic

neurotransmission in the case of BT and together with endogenous regulatory processes in the case of their preservation could outline a single protective impact on traumatic factor.

Proved pathogenetic importance of serotoninergic and dopaminergic neurotransmission in conditions of traumatic brain damage should be taken into account when compiling and determining the clinical efficacy of complex pathogenetic therapy schemes for patients with BT.

Conclusions

1. Motor and muscle disorders in rats with BT of medium severity were registered starting from the 1st day of the post-traumatic period and lasted for 5 weeks.

2. Post-traumatic period is characterized by evident neurological deficits and motor and muscle disorders, which are manifested by muscle weakness, the inability to keep and maintain a natural position, as well as the inability to perform synchronous coordinated movements.

3. Revealed motor and muscle dysfunctions are persistent and have their maximal expression during the first 14 days of the post-traumatic period.

4. The studied indexes on the 5th week of the trial without pharmacological correction have a tendency towards recovery, which we most likely explain by regulatory antioxidant mechanisms activation and energy resources mobilization in case of brain sanogenetic mechanisms activation.

5. Serotoninergic and dopaminergic NS activation in BT rats causes the motor and muscle functions of the body restoration and normalization.

6. Pathogenetically determined pharmacological correction should consider the need to activate serotonin and dopaminergic neurotransmission in the case of BT.

7. Proved pathogenetic importance of serotoninergic and dopaminergic neurotransmission in conditions of traumatic brain damage should be considered when compiling and determining the clinical efficacy of complex pathogenetic therapy schemes for patients with BT.

Prospects for further research aimed at prospective experimental verification of the probability of injured animals' other functions recovery by modulating the monoaminergic neurotransmission, as well as identifying the efficacy of traumatic brain damage correction using the original scheme of pathogenetic pharmacological correction via certain monoaminergic neurotransmission modulation.

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