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Research article

The effect of a traumatic brain injury on changes in the heart rate of rats subject to various modes of motor activity

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ABSTRACT

For the first time, studies have been conducted to study the reaction of animal heart rate to various modes of motor activity after a traumatic brain injury. It was revealed that on the first day after modeling an open head injury in rats of all age groups, a pronounced increase in heart rate was observed. In this case, the smallest heart rate response to brain injury is observed in animals of immature age. It was found that the implementation of systematic dynamic exercises by animals of mature and preschool age after modeling a craniocerebral injury contributes to a significant decrease in heart rate. A more pronounced formation of training bradycardia is observed in immature animals. It was revealed that limiting motor activity and performing isometric exercises after a traumatic brain injury maintain heart rate at an increased level in all age groups of animals and significantly inhibits the natural, age-related decrease in heart rate in immature animals.

Keywords: Heart rate, Traumatic brain injury, Modes of motor activity, Rat model

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INTRODUCTION

The modern approach to the interpretation of changes in the body during traumatic brain injury (TBI) is based on the following statement: the pathological effect on the brain at the moment of trauma has not ended but begun [1]. This is due to the fact that TBI immediately triggers a set of sanogenetic and pathological processes, which determine further recovery or secondary damage to the brain. The most important pathogenetic factors contributing to the formation of the named secondary injuries, according to S.V. Tsarenko [1], are hypoxemia and arterial hypotension. Studies [2, 3] have shown a significant increase in mortality among patients with TBI with oxygen and systemic hemodynamic disbalance.

Along with the blood system and the external respiration apparatus, blood oxygen saturation and its transport are determined by the state of the cardiovascular system. Oxygenation and perfusion of the brain and, consequently, the rate of recovery of its functions may depend on the state of the pumping function of the heart, under the autoregulation of cerebral blood flow disturbed in TBI [3].

A number of authors have devoted their studies to the investigation of the laws of influence of various modes of physical activity on heart functions in ontogenesis [1, 4, 6, 8, 9, 10]. At the same time, a significant number of works have been carried out to study the effect of enhanced motor activity on the heart functions of a mature organism. At the same time, the peculiarities of the functioning of the heart in immature animals subject to various modes of motor activity have not been sufficiently studied [2,3]. The literature has a few works devoted to the study of the characteristics of changes in the function of the heart of a developing organism subject to various modes of physical activity after suffering a brain injury are extremely rare. In this regard, we carried out studies to study the indicators of the pumping function of the heart of rats exposed to various modes of motor activity after modeling a traumatic brain injury.

MATERIALS AND METHODS

The experiments used white outbred laboratory rats aged 21-210 days. The basis for the age periodization of rats was anatomical and physiological characteristics of animals, proposed by Makhinko and Nikitin[5]. Work with laboratory animals complied with the basic regulatory and ethical requirements for laboratory and other experiments with the participation of experimental animals of different species.

Traumatic brain injury was modeled according to the method described in the article by Sharma et al., [11]: Sleep

deprivation exacerbates concussive head injury induced brain pathology: Neuroprotective effects of nanowired delivery of cerebrolysin with α-melanocyte-stimulating hormone.

The animals got concussion (cerebral edema) under anesthesia with etaminal (intraperitoneally 40-50 mg/kg). The surgical stage of anesthesia was determined by the absence of a corneal reflex in the animal. A median longitudinal incision (2 cm) was made in the right parietal region of the scalp shaved and treated with an aseptic solution, and trepanation was performed with a cutter of the skull bones (2 mm lateral to the midline). The dura mater was left intact. The weight, which is a steel cylinder weighing 114.6 g, was dropped from a height of 20 cm along a guide tube, thereby striking the area of the trepanation window in the right parietal region of the brain. After injury, the skin of the animals was tightly sutured with surgical thread (0.2 mm), the suture was treated with an antiseptic solution. Antibiotic therapy was carried out with a solution of gentamicin intramuscularly. With this weight and distance, the right parietal region of the brain was exposed to 0.224 N.

Experiments with animals after modeling traumatic brain injury were organized into four age groups. The first group included immature animals, i.e. from 21 to 51 days of age. The second group consisted of mature animals, from 70 to 100 days of age. The third group included pre-senile animals, from 180 to 210 days of age.

Within each age group, animals were divided into four subgroups. Each subgroup was subjected to its own established regimen of physical activity. Animals of the first subgroup (control) were kept in the usual conditions of the vivarium for 9-12 animals, under unlimited motor activity (UPA). The second subgroup underwent enhanced motor regimen. The animals systematically and forcibly performed stepwise muscle swimming training (MST) increasing in time. The third subgroup of animals was limited in motor activity, i.e. hypokinesia (LMA). Animals of this group were subjected to daily long-hour restriction of physical activity by stretching and fixing the limbs on a special table. The fourth subgroup of animals was systematically subjected to the isometric exercise (IE) regimen. On the turntable, animals with fixed limbs hung upside down daily. The execution time gradually increased, from 5 minutes on the first day and up to about 2 hours at the end of the experiment [12, 13].

To determine the heart rate, the method of tetrapolar chest rheography was used [14]. The differentiated rheogram was recorded in dynamics in anesthetized animals during natural respiration using an RPG-204 device.

To assess the significance of differences, standard Student t-test values were calculated.

RESULTS AND DISCUSSION

Changes in HR in immature rats exposed to different modes of physical activity after a traumatic brain injury

As our studies have shown, the heart rate (HR) in 21-day-old rat pups of control group was 467.7±15.4 bpm ($P<0.05$) (Table 1). During the subsequent unlimited physical activity of these rat pups under for 30 days, i.e., by the age of 51 days, the heart rate indicators decreased by 32.0 bpm and amounted to 435.7±17.5 bpm ($P<0.05$). Consequently, immature rat pups undergo a natural age-related decrease in the heart rate in the process of natural growth and development from 21 to 51 days of age.

The UMA rat pups aged 21 days had their heart rate equal to 458.7±17.5 bpm. On the second day after modeling the traumatic brain injury, heart rate increased to 508.9± 11.5 bpm. This value was 50.2 bpm more than the initial data ($P<0.05$). During the subsequent maintenance of these rat pups under unrestricted motor activity (UMA) for 30 days, HR did not change significantly in comparison with the initial data, remaining approximately at the level of 460-470 bpm. Consequently, immature control animals with TBI had no age-related decrease in heart rate during the next 30 days under unlimited motor activity (UMA). In our opinion, this is due to a violation of the autonomic regulation of the cardiac function, caused traumatic brain injury.

In immature rat pups of MST group aged 21 days, heart rate was 457.4±16.8 bpm. On the second day after modeling the traumatic brain injury, heart rate was 509.7±15.8 bpm. This value was 52.5 bpm more than the initial data ($P<0.05$). In the process of dynamic swimming exercises over the next 30 days, these rat pups had a significant decrease in their heart rate. Enhanced motor regimen (MST) by the age of 51 days caused an increase in heart rate by 42.9 bpm compared with the initial data ($P<0.05$). Consequently, it can be argued that in immature animals that underwent a craniocerebral injury at 21 days of age, the performance in the subsequent gradually increasing dynamic exercises in the form of swimming causes a decrease in their heart rate, i.e. bradycardia.

At 21 days of age, in immature rat pups of LMA group, heart rate was 461.2±15.6 bpm. On the second day after modeling the traumatic brain injury, heart rate was 512.5±14.6 bpm. This value was 51.3 bpm more than the initial data ($P<0.05$). In the process of daily long-hour restriction of physical activity, by stretching and fixing the limbs on a special table for 30 days in these rat pups, heart rate increased in comparison with the initial data by 25.5 bpm and amounted to 486.7±12.9 bpm ($P<0.05$). Thus, in immature rat pups with traumatic brain injury, the subsequent limitation of motor activity (LMA) from 21 to 51 days of age caused a significant increase in heart rate. Therefore, it can be argued that in immature animals that got traumatic brain injury at 21 days of age, the subsequent 30-day restriction of motor activity restrains the natural age-related decrease in heart rate.

In immature rat pups of IE group aged 21 days, heart rate

was 460.9±18.7 bpm. On the second day after modeling the traumatic brain injury, heart rate was 510.9±15.7 bpm. This value was 50.0 bpm more than the initial data (P<0.05). Starting from the age of 21 days after a traumatic brain injury, over the next 30 days, the animals were tightly fixed on the turntable and gradually accustomed to hanging upside down (antiorthostasis). The performance of systematically increasing isometric exercises for 30 days led to a significant increase in heart rate. Heart rate in these animals by the age of 51 days was 503.6±19.3 bpm, which was 42.7 bpm more than the initial data (P<0.05). Consequently, the performance of isometric exercises after a traumatic brain injury leads to a significant increase in heart rate.

Thus, the results obtained indicate that, after a traumatic brain injury, the most favorable mode of physical activity for immature rat pups is the performance of dynamic exercises in the form of systematic swimming. Restriction of motor activity and performance of isometric exercises after a traumatic brain injury maintain high levels of heart rate and to a significant extent restrain the natural age-related decrease in heart rate of immature animals.

Changes in HR in mature rats exposed to different modes of physical activity after a traumatic brain injury

In 70-day-old mature animals of control group, the heart rate was 415.7±11.7 bpm (Table 2). In the process of natural growth and development of animals, heart rate indicators gradually decreased and by the age of 100 days reached 405.7±11.5 bpm (P<0.05). The difference between the initial values of heart rate at 70 and 100 days of age was 10.0 bpm (P<0.05). Consequently, mature rats have a natural age-related decrease in their heart rate in the process of natural growth and development from 70 to 100 days of age.

The UMA rats aged 70 days had their heart rate equal to 417.3±12.5 bpm. On the second day after modeling the traumatic brain injury, heart rate in these animals increased to 479.7±10.3 bpm. This value was 62.4 bpm more than the initial data (P<0.05). During the subsequent maintenance of rats under UMA conditions for 30 days, heart rate remained at a high level. By day 100 of age, heart rate of these animals was 438.7±11.8 bpm. This value is 21.4 bpm more than the initial data. Consequently, in control animals who had a traumatic brain injury at 70 days of age and kept under the UMA conditions until 100 days of age, heart rate remain at a high level, i.e., no natural age-related decrease in heart rate is observed in these animals.

In mature rats of MST group aged 70 days, heart rate was 419.6±15.8 bpm. On the second day after modeling the traumatic brain injury, heart rate was 480.2±11.6 bpm. This value was 60.6 bpm more than the initial data (P<0.05). In the process of dynamic swimming exercises, after a traumatic brain injury, these rats had a significant decrease in their heart rate within 30 days. Enhanced motor mode (MST) by day 100 of age caused an increase in heart rate by 25.7 bpm compared to the initial data (P<0.05). Consequently, in mature animals that underwent traumatic brain injury at the age of 70 days, the subsequent systematic performance of dynamic exercises leads to a significant decrease in heart rate. These animals, against the background of a natural age-related decrease in heart rate, had a more significant decrease in heart rate due to the systematic performance of dynamic exercises.

At 70 days of age, in mature rat pups of LMA group, heart rate was 416.9±13.7 bpm. On the second day after modeling the traumatic brain injury, heart rate was 478.5±12.3 bpm. This value was 61.6 bpm more than the initial data (P<0.05). In the process of daily restriction of physical activity for 30 days in these rat pups, heart rate increased in comparison with the initial data by 53.4 bpm and amounted to 470.3±15.5 bpm (P<0.05). Thus, in immature rat pups with traumatic brain injury, the subsequent restriction of motor activity (LMA) from 70 to 100 days of age causes a significant increase in heart rate, i.e. the LMA mode inhibits the natural process of slowing down the heart rate.

In mature animals of IE group aged 70 days of age, heart rate was 418.4±14.2 bpm. On the second day after modeling the traumatic brain injury, heart rate in these animals was 482.6±11.8 bpm. This value was 64.2 bpm more than the initial data (P<0.05). Starting at 70 days of age after suffering a traumatic brain injury, the animals hung upside down on the turntable for the next 30 days (antiorthostasis). The performance of systematically increasing isometric exercises by these animals for 30 days led to a significant increase in heart rate. By 100 days of age, heart rate was 492.6± 16.4 bpm, which was 74.2 bpm more than the initial data (P<0.05). Consequently, performing isometric exercises after a traumatic brain injury leads to a significant increase in heart rate.

Thus, the results state that modeling of a traumatic brain injury at 70 days of age leads to an increase in heart rate in all examined groups of animals by about 60-65 bpm (P<0.05). However, subsequent regimens of motor activity within 30 days do not equally affect the indices of heart volume. The most favorable regimen of physical activity for mature rats with traumatic brain injury is the performance of dynamic exercises in the form of systematic swimming. Restriction of motor activity and performance of isometric exercises after a traumatic brain injury maintain high levels of heart rate.

Changes in HR in senile rats exposed to different modes of physical activity after a traumatic brain injury

In 180-day-old animals of control group, the heart rate was 397.5±11.5 bpm (Table 3). In the process of natural growth and development of animals, heart rate indicators gradually decreased and by the age of 210 days reached 377.5±15.4 bpm (P<0.05). The difference between the initial values of heart rate at 180 and 210 days of age was 20.0 bpm (P<0.05). Consequently, rats have a natural age-

related decrease in their heart rate in the process of natural vital activity from 180 to 210 days of age.

The UMA rats aged 180 days had their heart rate equal to 399.5±15.3 bpm. On the second day after modeling the traumatic brain injury, heart rate in these animals increased to 510.4±12.6 bpm. This value was 101.9 bpm more than the initial data (P<0.05). During the subsequent maintenance of rats under UMA conditions for 30 days, heart rate remained at a high level. By day 210 of age, heart rate of these animals was 459.7±17.7 bpm. This value is 60.2 bpm more than the initial data (P<0.05). Consequently, in control animals who had a traumatic brain injury at 180 days of age and kept under the UMA conditions until 210 days of age, heart rate remain at a high level. No natural age-related decrease in heart rate is observed in these animals.

In rats of MST group aged 180 days, heart rate was 398.6±14.2 bpm. On the second day after modeling the traumatic brain injury, heart rate was 498.7±11.7 bpm. This value was 100.1 bpm more than the initial data (P<0.05). In the process of dynamic swimming exercises, after a traumatic brain injury, these rats had a significant decrease in their heart rate within 30 days. Enhanced motor mode (MST) by day 210 of age caused an increase in heart rate by 44.9 bpm compared to the initial data (P<0.05). Consequently, in mature animals that underwent traumatic brain injury at the age of 70 days, the subsequent systematic performance of dynamic exercises leads to a significant decrease in heart rate.

At 180 days of age, in rats of LMA group, heart rate was 401.7±16.5 bpm. On the second day after modeling the traumatic brain injury, heart rate was 504.8±11.5 bpm. This value was 103.1 bpm more than the initial data (P<0.05). In the process of daily restriction of physical activity for 30 days in these rats, heart rate increased in comparison with the initial data by 85.2 bpm and amounted to 486.9±18.5 bpm (P<0.05). Thus, in immature rat pups with traumatic brain injury, the subsequent restriction of motor activity (LMA) from 180 to 210 days of age causes a significant increase in heart rate, i.e. the LMA mode inhibits the natural process of slowing down the heart rate.

In animals of IE group aged 180 days of age, heart rate was 404.2±13.6 bpm. On the second day after modeling the traumatic brain injury, heart rate in these animals was 507.9±12.2 bpm. This value was 103.7 bpm more than the initial data (P<0.05). Starting at 180 days of age after suffering a traumatic brain injury, the animals hung upside down on the turntable for the next 30 days (antiorthostasis). The performance of systematically increasing isometric exercises by these animals for 30 days led to a significant increase in heart rate. By 210 days of age, heart rate was 512.7±19.1 bpm, which was 108.5 bpm more than the initial data (P<0.05). Consequently, performing isometric exercises after a traumatic brain injury leads to a significant increase in heart rate.

Thus, the results state that modeling of a traumatic brain injury at 180 days of age leads to an increase in heart rate in all examined groups of animals by about 100 bpm (P<0.05). However, subsequent regimens of motor activity within 30 days differently affect the indices of heart volume. The most favorable regimen of physical activity for rats with traumatic brain injury is the performance of dynamic exercises. Restriction of motor activity and performance of isometric exercises after a traumatic brain injury maintain high levels of heart rate.

Table 1.Changes in HR in immature rats exposed to different modes of physical activity after a traumatic brain injury

Modes of motor activity	n (number of animals)	HR (bpm)		
		day 21 (initial)	day 21 (after trepanation)	day 51 (experiment)
C	10	467.7 ± 15.4	-	435.7 ± 17.5
UMA	9	458.7 ± 17.5	508.9 ± 11.5	467.1 ± 13.7
MST	11	457.4 ± 16.8	509.7 ± 15.8	414.5 ± 12.3
LMA	10	461.2 ± 15.6	512.5 ± 14.6	486.7 ± 12.9
IE	13	460.9 ± 18.7	510.9 ± 15.7	503.6 ± 19.3

Table 2.Changes in HR in mature rats exposed to different modes of physical activity after a traumatic brain injury

Modes of motor activity	n (number of animals)	HR (bpm)		
		day 70 (initial)	day 70 (after trepanation)	day 100 (experiment)
C	9	415.7 ± 11.7	-	405.7 ± 11.5
UMA	11	417.3 ± 12.5	479.7 ± 10.3	438.7 ± 11.8
MST	10	419.6 ± 15.8	480.2 ± 11.6	393.9 ± 13.1
LMA	12	416.9 ± 13.7	478.5 ± 12.3	470.3 ± 15.5
IE	9	418.4 ± 14.2	482.6 ± 11.8	492.6 ± 16.4

Table 3.Changes in HR in senile rats exposed to different modes of physical activity after a traumatic brain injury

Modes of motor activity	n (number of animals)	HR (bpm)		
		day 180 (initial)	day 180 (after trepanation)	day 210 (experiment)
C	-	397.5 ± 11.5	-	377.5 ± 15.4
UMA	10	399.5 ± 15.3	501.4 ± 12.6	459.7 ± 17.7
MST	12	398.6 ± 14.2	498.7 ± 11.7	443.5 ± 12.9
LMA	9	401.7 ± 16.5	504.8 ± 11.5	486.9 ± 18.5
IE	11	404.2 ± 13.6	507.9 ± 12.2	512.7 ± 19.1

On the second day after modeling an open TBI, rats of all age groups show a pronounced increase in heart rate. We believe this is due to the combined damage of both frontal lobes and the brain stem by increasing edema, which reveals an increased activity of the dopaminergic system and a tendency to an increase in the activity of the peripheral (adrenaline) link of the sympathetic system. In case of damage to the two main central regulatory structures of the sympathetic nervous system (frontal lobes and brainstem), the response to TBI proceeds mainly in the peripheral type with an increase in adrenaline levels and a decrease in the norepinephrine / epinephrine ratio (NE/EP) [15]. The regulation of the central link of the sympathetic system is carried out through the interaction of the frontal lobes with the noradrenergic pontine center (A5 and A6 nuclei). The peripheral link of the sympathetic system also has its own central regulatory center located in the medulla oblongata (adrenergic C1 nuclei) and under the inhibitory control of the locus coeruleus (LC) [16]. We can assume that such an arrangement of the regulatory center determines its greater safety in case of injury due to

the more rare primary damage to the medulla oblongata or its incompatibility with life. Therefore, in surviving animals with trunk injuries, damage to the central link is more likely, and, therefore, the response to trauma through activation of the peripheral link of the sympathetic system, as was noted in the examined sample of animals.

Thus, the results obtained indicate that, after a traumatic brain injury, the most favorable mode of physical activity for immature rat pups is the performance of dynamic exercises in the form of systematic swimming. In our opinion, this fact is explained as follows. Against the background of natural processes occurring in the developing organism of rat pups, dynamic muscle training, at earlier stages of postnatal development, causes significant changes in the heart itself and the mechanisms of its regulation. First, myocardial hypertrophy is developing at a significant rate. Secondly, muscle training, organized at earlier stages of postnatal development, significantly alters the sympathetic and parasympathetic influences, as well as their ratio in the regulation of the pumping function of the heart. Muscle training also contributes to the faster maturation of intracardiac regulatory mechanisms.

Limited physical activity and isometric exercises after a traumatic brain injury maintain the heart rate at an increased level in all age groups of animals, and also significantly restrain the natural age-related decrease in the heart rate of immature animals. It is likely that with isometric loading, a minimal change in muscle length occurs, and at the same time its tone increases. Muscle tension for a longer period of time in comparison with dynamic exercises causes a compression of the vessels (arteries) of the muscles, thus, their resistance increases. In this case, only certain muscle groups are involved, and external work is not performed. The oxygen demand during this exercise is proportional to the mass of the muscles involved and is usually moderate. However, these needs cannot be met by increasing blood flow, as local vasodilation is limited by mechanical compression of the resistive vessels by the isometrically contracting muscle, and therefore blood flow in the working muscle may actually decrease. Muscle perfusion is maintained by an increase in blood pressure, which is mediated by a reflex arc originating in the contracting muscle, which leads to an increase in systemic vascular resistance even with moderate exercise. Along with this, there can be a decrease in stroke volume and the development of an excessive reaction from the heart rate to isometric load.

Thus, in contrast to isotonic exercise, isometric exercise poses increased demands on the systolic function of the heart in the form of a significant increase in pressure load. In our opinion, when the animal is fixed upside down on the turntable, an increase in cerebral edema occurs, which aggravates the traumatic damage to the trunk and frontal lobes of the brain.

CONCLUSION

On the first day after modeling an open traumatic brain injury, rats of all age groups show a pronounced increase in heart rate. At the same time, the slightest heart rate response to brain injury is observed in immature animals. Systematic dynamic exercises contribute to a significant decrease in heart rate of mature and pre-senile animals, after modeling a traumatic brain injury. Immature animals show more pronounced bradycardia of training. Restriction of motor activity and performance of isometric exercises after a traumatic brain injury maintain high levels of heart rate in all age groups of animals and significantly restrain the natural age-related decrease in heart rate of immature animals.

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