International Journal of Advanced Biotechnology and Research (IJBR)
ISSN 0976-2612, Online ISSN 2278–599X,
Vol-8, Issue-3, 2017, pp2332-2339
http://www.bipublication.com

Research Article

Effect of the tryptophan-hydroxylase blocker in the embryonic period on the pumping function of the rat heart in early postnatal ontogenesis

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ABSTRACT

The pumping function of the heart of 14-day-old rats was studied, in the embryonic period of development of which there was a deficiency of serotonin *(5-HT)*, due to the chronic administration of the blockade of serotonin synthesis of *PCPA*. It was revealed that the hearts is of the experimental group of rats at rest, having a reliably high heart rate (451.46 beats per minute), and the shock volume of blood (0.045 ml) pump a larger volume of blood in one minute than in the control. The time for the rapid ejection of blood in experimental and control mice was 0.019 sec and 0.021 sec, respectively ($p < 0.05$), which corresponds to 25.84% and 25.87% of the period of ejection of blood from the left ventricle of the heart ($p > 0.05$). The time of slow blood ejection and the duration of the ejection period are lower in rats of the experimental group than in the control group ($p < 0.05$). The maximum increase in the stroke and minute blood volumes in the rats of the experimental group was observed in response to norepinephrine at a dose of 0.1 μM, in the control group at 1.0 μM.

In 14-day-old rats, in the embryonic period of development, the serotonin synthesis enzyme was blocked, an increase in heart rate, stroke and minute blood volume, and an increase in sensitivity to norepinephrine were found.

Keywords:embryonic ontogeny, tryptophan-hydroxylase, p-chlor-phenyl-alanine, serotonin, heart rate, stroke volume, rat.

INTRODUCTION

The neurotransmitter serotonin (5-HT) has a morpho-functional effect on cells and target organs and its role varies significantly in ontogenesis. In the postnatal period of rats, 5-HT increases the contraction of myocardium at the right atrium and ventricles [18]. It has been proved that the accumulation of serotonin in places of vascular injury leads to the proliferation of endothelium and smooth muscle cells, which is important link in the pathogenesis of arterial and pulmonary hypertension, atherosclerosis [14, 1, 7, 9]. Patients with coronary heart disease showed an increase in serotonin concentration in the blood, an increase in the capture of 5-HT in platelets by a membrane carrier of serotonin[19].

In the embryonic period serotonin acts as a growth factor and plays an important regulating role in the crucial period of embryo development, in particular, development of the cardiovascular system [20]. Cardiac morphogenesis depends on migration, survival and rapid increase in neural crest cells, which are regulated by 5-HT, mainly through 5-HT2B receptors [15, 16]. It was suggested that the pathology of the development of heart defects is caused by a picture of the flow of intracardiac blood [5, 15]. Chronic administration of the neurotoxin pCPA (para-chlorphenylalanine) blocks the tryptophan-hydroxylase enzyme and leads to a decrease in serotonin synthesis [10, 23, 27]. In mutant 5-HT2B receptors in mice, a

disordered arrangement of myocytes in the heart, dilatation of the left ventricle, and a decrease in the diastolic function of the heart are observed [15]. In rats, at 14 days of age, the lowest ventricular myocardial response to 5-HT is observed, which increases with adrenoreceptor blockade [25]. Chronic administration of PCPA in the embryonic period does not cause changes in the myocardial contraction force of the left and right ventricles, increases it in the right atrium, and decreases in the left atrium in 14-day-old rats [17].

It is known that the main indicators of the pumping function of the heart are the stroke volume of blood, the heart rate, the minute volume of blood circulation. The study of the response of the pumping heart function in response to norepinephrine in animals with altered serotonin metabolism in the embryonic period of development will make it possible to evaluate the presence of the relationship of noradrenergic and serotonin effects. Despite the fact that 5-HT belongs to the most important signaling molecules involved in the regulation of brain development, cardiovascular system and a number of other target organs, data on the effect of the 5-HT metabolism disorders in the embryonic period of development on the noradrenergic regulation of the pumping function of the heart in postnatal ontogenesis are practically absent.

Purpose: to study the parameters of the pumping function of the heart (stroke and minute volume of blood and heart rate), the parameters of the phase structure of the cardiac cycle and their response to noradrenaline in 14-day-old rats with chronic tryptophan-hydroxylase blockade in the embryonic period.

METHODS

Experiments to study the pumping function of the heart were performed in rats aged 14 days, weighing 28-34 g in winter. Conditions for all animals were the same. The permission of the Ethics Committee of the Ministry of Health of the Republic of Tatarstan was obtained for the study. The study was carried out on pregnant female Wistar rats and their offspring at the age of 14 days. Pregnant females, starting from the 11th day of pregnancy for 10 days, were injected intraperitoneally with a blocker of the synthesis of serotonin PCPA (p-chlorphenylalanine; Sigma) at a dose of 100 mcg / kg in the experimental group, and in the control group - physiological saline solution. Changes in the pumping function of the heart were examined after intraperitoneal administration of a pharmacological preparation in the following sequence: norepinephrine with a concentration of 0.1 μM, 1.0 μM, 10.0μM. The volume of the solution enjected for each concentration was 0.2 ml. Each subsequent dose was enjection 20 minutes after the enjection of the previous dose. Experiments to determine myocardial contractility were carried out on the ADL analog-to-digital converter MacLab / 4e, to obtain rheographic signals rheograph 4 RG-2M, made in experimental manufacturing workshops of the AMS of Russia, was used. The results were analyzed using Chart, Claris Works and Igor Pro programs on a Power Macintosh computer. Needle electrodes were attached under the skin. The registration of the differentiated rheogram according to the Kubicek method was carried out at rest (before norepinephrine), after the injection of 1, 2, 3 doses of norepinephrine for 20 minutes for each dose. According to the method, the parameters of the heart rate, stroke and minute blood volume, as well as the parameters of the phase structure of the cardiac cycle are calculated: tu - the period of the injection of blood from the left ventricle of the heart, s; A and c - respectively, the time of rapid and slow injection, c; a% And b% - the time of rapid and slow exile, expressed as a percentage of tu. Static analysis is carried out in accordance with conventional methods of variation statistics. The statistical significance of differences is determined by the Student's t-test.

RESULTS OF RESEARCH AND DISCUSSION

1. Indicators of pumping function of the heart of 14-day-old rats with chronic administration of PCPA in the embryonic period of ontogenesis

It is known that the main indicators of the pumping function of the heart are the stroke volume of blood, the heart rate, the minute volume of blood circulation.Stroke volume of blood (SV, ml) - the amount of blood thrown out

with each contraction of the heart, characterizes the strength and effectiveness of cardiac contractions. In rats of the experimental group, SV is statistically significantly higher in comparison with the control group and is 0.045 ml and 0.042 ml, respectively ($p < 0.05$) (table 1).

Table 1 Indicators of pumping function of 14-day-old rats with chronic tryptophan-hydroxylase blockade in the embryonic period of ontogenesis

Indicators	PCPA	NaCl
Heart rate, beats / min	451,46 ± 6,01*	400,30 ± 15,09*
SV, ml	0,045 ± 0,00047*	0,043 ± 0,001*
MV, ml / min	19,848 ± 0,83	19,095 ± 1,38
a, sec	0,019 ± 0,001*	0,021 ± 0,001*
в, sec	0,055 ± 0,001*	0,062 ± 0,003*
tu, sec	0,073 ± 0,001*	0,082 ± 0,004*
a, %	25,84 ± 0,92	25,87 ± 1,02
в, %	74,16 ± 0,92	74,13 ± 1,02

Note: heart rate - heart rate; SV - shock volume of blood; MV - minute volume of blood circulation; A - is the time of rapid injection of blood; C - time of slow injection of blood; Tu - the period of injection of blood from the left ventricle of the heart; a% - is the time of rapid injection of blood, expressed as a percentage of tu; b% - the time of slow injection, expressed as a percentage of tu; PCPA (experiment) - animals born from females who were injected in the embryonic period with a serotonin synthesis blockterpara-chlor-phenyl-alanine, NaCl (control) - animals born from females who received physiological saline in the embryonic period of development.* - statistically significant differences in the control-experiment ($p < 0.05$).

The heart rate in the rats of the experimental group was 451.46 beats / min, which is higher than in the control group, in which the heart rate was 400.30 beats per minute ($p < 0.05$). The minute volume of blood in rats that were exposed to the *PCPA* in the embryonic period is significantly higher compared to the control and is 19.8 ml.Then, we analyze the parameters of the phase structure of the cardiac cycle. The time of rapid injection of blood (a, sec) in experimental and control mice is 0.019 sec and 0.021 sec, respectively ($p < 0.05$), which corresponds to 25.84% and 25.87% of the period of blood ejection from the left ventricle of the heart. The time of a slow ejection of blood (c, sec) is also lower in rats in the experimental group than in the control group and is 0.055 sec and 0.061 sec, respectively ($p < 0.05$). The time of rapid and slow ejection of blood is part of the duration of the expulsion of blood from the left ventricle of the heart (tu, sec). In rats of the experimental group, this value is 0.073 sec, which is 0.009 sec less compared to the control ($p < 0.05$).

2. Effect of norepinephrine on cardiac pumping parameters

Norepinephrine at a concentration of 0.1 μM statistically significantly increases the stroke volume of blood in 14-day-old rats of the experimental and control groups to 0.049 ml and 0.056 ml, respectively ($p < 0.05$) (Fig. 1). The maximum reaction of SV in the control group is achieved by norepinephrine 1.0 μM, and in the experiment - at norepinephrine in a concentration of 0.1 μM.

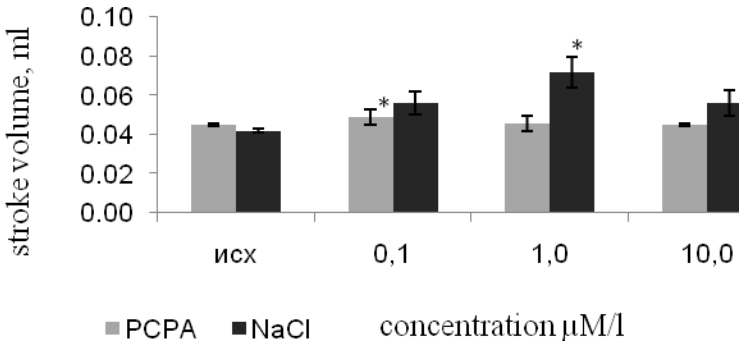

Fig. 1. Effect of norepinephrine on the stroke volume of 14-day-old rat with chronic tryptophan-hydroxylase blockade in the embryonic period of ontogenesis

Note: on the abscissa - the concentrations of noradrenaline (0.1 μM, 1.0 μM, 10.0 μM); On the ordinate axis - the shock volume of blood, ml; PCPA are animals born from females who were injected in the embryonic period with a serotonin synthesis blockterpara-chlor-phenyl-alanine (experiment), NaCl-animals born from females that received physiological saline (control) in the embryonic period of development.

* - statistically significant differences in comparison with the control indicators (* - $p < 0.05$).

With the injection of norepinephrine with increasing stroke volume, the minute volume of circulation increases, which reaches 20.1 ml / min and 22.7 ml / min, respectively. A further increase in the concentration of the pharmacological preparation in the experimental group of rats leads to a decrease in the pumping function of the heart to the initial values. In rats of the control group, the maximum value of SV and MV is achieved at a concentration of norepinephrine at a dose of 1.0 μM: 0.072 ml and 27.4 ml / m ($p < 0.05$). The subsequent increase in norepinephrine also reduces the pumping function of the rat heart. Thus, we assert that the higher stroke volume of the cardiac circulation of the rat heart, observed in the embryonic period, in which the serotonin deficiency was observed by the chronic enjection of the serotonin synthesis blocker, is reduced and is unable to provide the required level of minute volume of blood circulation in comparison with control values.The parameters of the phase structure of the cardiac cycle when norepinephrine is enjected are characterized by the fact that the time of rapid and slow ejection does not undergo significant changes, and the duration of the period of blood ejection from the left ventricle of the heart of both groups of rats does not change significantly ($p < 0.05$) (Fig.2)

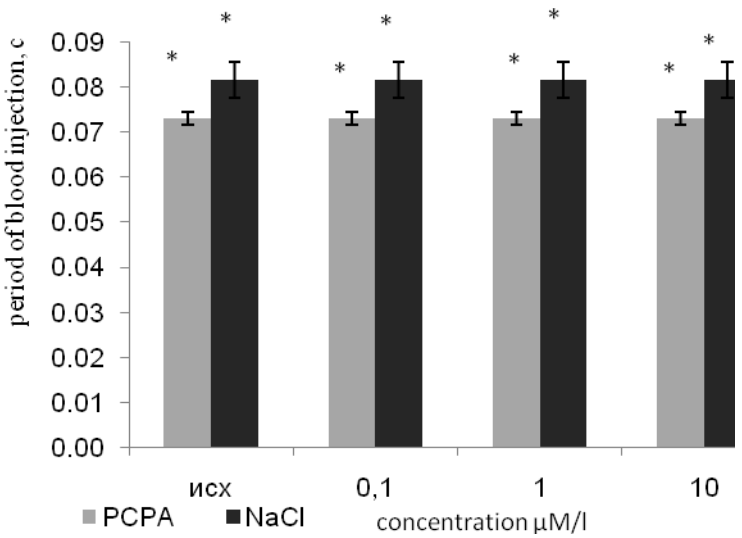

Fig. 2. Change in the duration of the ejection period when norepinephrine is injected in 14-day-old rats with chronic tryptophan-hydroxylase blockade in the embryonic ontogeny period

Note: on the abscissa - the concentrations of noradrenaline (0.1 μM, 1.0 μM, 10.0 μM); along the ordinate - the duration of the period of enjection of blood, sec; PCPA are animals born from females who were injected in the embryonic period with a serotonin synthesis blockterpara-chlor-phenyl-alanine (experiment), NaCl-animals born from females that received physiological saline (control) in the embryonic period of development. * - statistically significant differences in comparison with the control indicators (* - $p < 0.05$).

DISCUSSION

In this article, we present the results obtained in experiments *in vivo* on the effect of pharmacological blockade of tryptophan hydroxylase in the embryonic period on cardiac function in early postnatal ontogenesis of rats.Tryptophan-hydroxylase is the rate-limiting enzyme of the first stage serotonin biosynthesis, i.e. is a marker of serotonin synthesis. This enzyme is found in various tissues: in the pineal gland, serotonergic neurons of the rathe nuclei, the axons of which are projected into all regions of the brain, in enterochromaffine cells and in neurons of the muscular plexuses of the

gastrointestinal tract [12, 13]. Two isoforms of tryptophan-hydroxylase were detected: neuronal (tph2) and peripheral (tph1) [24]. Serotonin was discovered almost 70 years ago in the blood as a vasoconstrictor of large vessels [21]. Subsequently, it was revealed that in the gastrointestinal tract it stimulates motility [4], in the CNS is a neurotransmitter [2]. Serotonin was detected during the early development of the brain, which indicates its involvement in proliferation, migration and differentiation of neurons [11]. More than 95% of peripheral serotonin synthesized in the gastrointestinal tract [6] upon activation of tph1, is stored in platelets and takes part in blood clotting and maintenance of homeostasis. In the heart, serotonin can cause arrhythmia [8] and valve hyperplasia [22]. Serotonin regulates the development of the cardiovascular system [26]. The knockout 5-HT2 receptor showed that it is involved in the morphogenesis of the heart [15, 16]. However, the mechanisms of the effect of the chronic blockade of the main enzyme of serotonin synthesis of tryptophan-hydroxylase in embryogenesis on heart rate and stroke volume in the early postnatal period have not yet been disclosed. In our study, the blockade of tryptophan-hydroxylase was performed begining from the 10th day of embryonic development. This is due to the fact that in the embryonic period of ontogenesis of mice up to 10 days of age, the source of serotonin for the developing organism is the mother [26]. Our studies show that in rats, in the embryonic period of which a chronic pharmacological blockade of both isoforms of tryptophan-hydroxylase was carried out, higher values of heart rate, stroke volume and minute blood volume are observed. The heart of 20-week-old mice knocked out by the gene tph1 is increased in size by 26% compared to the wild type of mice [3]. The heart rate, changed by pulse fluctuations of arterial pressure, in knockout mice is higher, in comparison with the wild type. The dilated heart of knockout mice works almost normally under resting conditions, but is practically incapable of adapting to stressful situations [3]. We injected rats with norepinephrine to assess the sensitivity and reactivity of stroke volume. We found a higher sensitivity of the inotropic function of the heart of 14-day-old experimental rats to norepinephrine compared to control animals. It was found that in experimental mice the maximal reaction of the stroke volume of the blood is observed on norepinephrine in a concentration of 0.1 μM, and when the concentration is increased to 1.0 μM and 10 μM, its significant decrease occurs, while in animals the control is observed Dose-dependent increase in the positive reaction of stroke volume of blood to noradrenaline.

The model of development in conditions of blockade of both isoforms of tryptophan-hydroxylase, which is carried out in our study, is important for understanding the relationship between the development of the nervous and cardiovascular systems in the embryonic period of ontogenesis. In our study, we created a serotonin deficiency by chronic administration of PCPA at a dose of 100 mg / kg for 9-10 days, i.e. the enzyme tryptophan-hydroxylase was blocked. It was established that a triple injection of PCPA at 150 mg / kg, total 450 mg / kg led to a 10-fold decrease in the serotonin concentration in mouse blood plasma [27]. In another study, a single injection of PCPA at a dose of 300 mg / kg reduced the concentration of serotonin in the hypothalamus of mice by 5.6 times in three days [10].

Based on the data obtained, it was found that the higher stroke volume of blood in 14-day-old rats, in the embryonic period of which there was a deficiency of central and peripheral serotonin by the chronic administration of the tryptophan-hydroxylase blocker, under the conditions of increasing norepinephrine pharmacological load, decreases and is unable to provide the required level of minute Volume of blood circulation in comparison with control values.

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Table 1 Indicators of pumping function of 14-day-old rats with chronic tryptophan-hydroxylase blockade in the embryonic period of ontogenesis

Indicators	PCPA	NaCl
Heart rate, beats / min	451,46 ± 6,01*	400,30 ± 15,09*
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MV, ml / min	19,848 ± 0,83	19,095 ± 1,38
a, sec	0,019 ± 0,001*	0,021 ± 0,001*
в, sec	0,055 ± 0,001*	0,062 ± 0,003*
tu, sec	0,073 ± 0,001*	0,082 ± 0,004*
a, %	25,84 ± 0,92	25,87 ± 1,02
в, %	74,16 ± 0,92	74,13 ± 1,02

Note: heart rate - heart rate; SV - shock volume of blood; MV - minute volume of blood circulation; A - is the time of rapid injection of blood; C - time of slow injection of blood; Tu - the period of injection of blood from the left ventricle of the heart; a% - is the time of rapid injection of blood, expressed as a percentage of tu; b% - the time of slow injection, expressed as a percentage of tu; PCPA (experiment) - animals born from females who were injected in the embryonic period with a serotonin synthesis blockterpara-chlor-phenyl-alanine, NaCl (control) - animals born from females who received physiological saline in the embryonic period of development.
* - statistically significant differences in the control-experiment ($p < 0.05$).

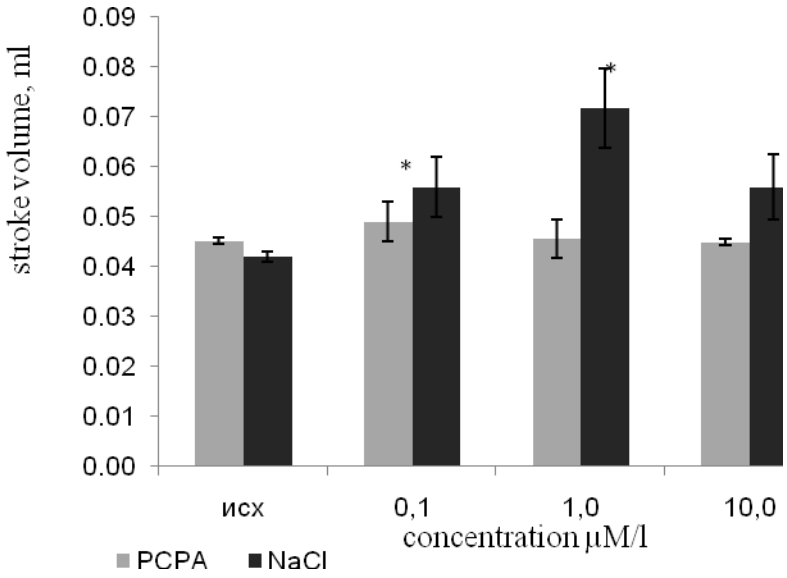

Fig. 1. Effect of norepinephrine on the stroke volume of 14-day-old rat with chronic tryptophan-hydroxylase blockade in the embryonic period of ontogenesis

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