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Effect of different serotonin concentrations on the inotropic function and morphometric parameters of the heart of infant rats

In recent years, studies of serotonin in physiological and pathological processes of the body have widely discussed its role as a link in the pathogenesis of atherosclerosis, arterial hypertension, and coronary heart disease. In the embryonic period, serotonin acts as a growth factor and plays an important regulatory role in the decisive period of embryo development, particularly, in the development of the heart. This research aims to study the influence of serotonin on the temporal parameters of contraction of the myocardium of the right ventricle in the newborn pups with a blockade of serotonin synthesis and membrane transporter in the embryonic period of ontogenesis. Thus, these studies have shown that the response of cardiomyocytes to serotonin is statistically higher in the group with excess serotonin and lower in the group with serotonin deficiency compared to the control group. The article also presents data indicating the change in serotonin concentration, which was created by the blockade of serotonin synthesis and the membrane transporter of serotonin in the embryonic period of ontogenesis, which results in morphological changes in the myocardium in early postnatal ontogenesis.

Keywords: serotonin, myocardium, ontogenesis, heart, fluoxetine, para-chlorophenylalanine, rat, pregnancy.

Introduction

Serotonin or 5-hydroxytryptamine (5-HT) is a neurotransmitter that plays a vital role in humans and animals. Serotonin regulates many biological processes, including the cardiovascular system. It also regulates platelet aggregation. Serotonin is produced and released and secreted into the bloodstream by enterochromaffin cells found in the gastrointestinal tract, then is rapidly absorbed and stored as miniature dense granules in platelets. Serotonin induces its physiological effects through 14 different receptor subtypes. All serotonin receptors, except for type 3, are G-protein-coupled receptors. Three types of serotonin receptors (5-HT1A, 5-HT2, and 5-HT3) are involved in the central mechanisms of regulation of cardiovascular activity. 4 and 2B types of receptors are found in cardiomyocytes, which are involved in the regulation of myocardial contractility and affect the temporary parameters of contraction [1–4].

In humans, an abnormal serotonergic system can lead to health problems such as depression and obsessive-compulsive disorders. To treat such disorders, some drugs have been developed, including selective serotonin reuptake inhibitors (SSRIs) [5, 6].

Parachlorophenylalanine (pCPA) is widely used as an agent to lower serotonin levels. The administration of the serotonin synthesis inhibitor, parachlorophenylalanine, in rats has been found to significantly deplete 5-HT [7].

It can be assumed that a change in the level of serotonin or blockade of its receptors during pregnancy adversely affects a number of cellular processes required for the normal formation of the heart in the fetus.

This research aims to study the effect of serotonin on the contractile function of the right ventricular myocardium in newborn rats with blockade of serotonin and membrane transporter synthesis in the embryonic period of ontogenesis.

The research objectives are as follows:

i) To investigate the effect of blockade of serotonin synthesis and serotonin membrane transporter in the embryonic period of ontogenesis on the time of myocardial contraction in 14-day-old rats.

ii) To study the effect of different concentrations of serotonin on the right ventricular myocardium in 14-day old rats with blockade of the membrane serotonin transporter and blockade of serotonin synthesis in the embryonic period of ontogenesis.

Experimental

The study was approved by the Ethics Committee of the Ministry of Health of the Russian Federation.

The research was carried out in the scientific laboratories of the Department of Normal Physiology and Department of General Pathology of Kazan State Medical University.

Method for determining myocardial contractility. The research object is pregnant female Wistar rats and their offspring at the age of 14 days. Starting from the 11th day of pregnancy and for 10 days in a row, the pregnant female rats were intraperitoneally injected with the following:

Group 1 (control) — saline;

Group 2 — a selective serotonin reuptake inhibitor — antidepressant fluoxetine (Fluoxetine hydrochloride, Sigma, USA) at a dosage of 50 μg/kg;

Group 3 — blocker of serotonin synthesis PCPA (4-Chloro-DL-phenylalanine, Sigma, USA) at a dosage of 100 μg/kg.

As a result, there were 2 experimental groups: i) a group of animals with a blockade of the serotonin transporter, and ii) a group of animals with a blockade of serotonin synthesis.

The research materials are the strips of the myocardium of the right ventricles.

The responses of the temporary characteristics of contraction (duration of contraction) of the right ventricular myocardium strips were evaluated to injections of serotonin (serotonin hydrochloride, Sigma, USA) at successive concentrations of 0.1 mM, 1.0 mM, and 10.0 mM.

The pre-anesthetized with urethane (800 mg/kg) hearts of rats were removed. The 2–3 mm long and 0.8–1 mm in a diameter strip were prepared from the myocardium of the right ventricle. The specimens were fixed vertically with one end to the force transducer and the other one to the point of support. Each specimen was immersed in a separate reservoir with a working solution, 25 ml in volume, injected at a temperature of 28 °C. The working solution composition for 400 ml. distilled water (gr.) is as follows: NaCl — 3.2, KCl — 0.12, $CaCl_2$ — 0.12, $MgCl_2$ — 0.05, $NaHPO_4$ — 0.07, cevitamic acid — 0.02, glucose — 0.8. The indicators were recorded using Chart 4.0. and Acq Knowledge 4.1. software. The signals were processed using the Elf program (developed by A.V. Zakharov).

In this experiment, the rate of myocardial contraction was determined. Since the obtained results of experiments with isolated (in vitro) cardiac muscle fibers inextricably link force with speed [8]. The rate of separation of the myosin head was identified as a key parameter affecting contractility, since it determines the time during which myosin binds to actin in the state of force creation [9]. The rate of attachment of myosin to actin, the frequency of cycles, the amount of time during which myosin attaches to actin, and the total number of myosin heads in the active state are all determinants of the development of parameters such as force (F), contraction time (T max), and relaxation time (T min) [10, 11].

These parameters are important since the discovery of many mutations in cardiomyopathy and a new generation of chemical compounds that change the "motor" kinetics of myosin and chemomechanical processes can produce different effects on the force and rate of contraction [12–14].

Thus, in our experiment, to determine myocardial contractility, parameters such as contraction time were calculated.

The reaction of the duration of contraction was calculated as a percentage of the initial value (initial parameters of the contraction time), i.e., before the introduction of the first concentration (0.1 mmol/l) of serotonin. The statistics were processed with the definition of M, m and δ; the significance of differences has been calculated using the Student's t-test with the differences considered significant at $p<0.05$.

Morphological studies. The preparation was fixed in the 10 % neutral formalin as per Lilly's. According to the generally accepted technique [15], after appropriate processing in the alcohols of increasing concentration, it was treated in xylene and embedded in paraffin. Leica SM 2000 R was utilized to make paraffin sections with a thickness of 4–5 μm. The resulting preparations were stained with hematoxylin and eosin, as well as picrofuxin as per Van Gieson's. The Zeiss AG Axioscope was used for microscopic examination.

S.B. Stefanov's morphometric grid of the random step was used for conducting a quantitative analysis [16]. The areas of blood vessels, connective tissue, adipose tissue, perivascular edema, interstitial edema, necrosis and myocardial muscle tissue were determined. The grid was applied directly to the micropreparation, and the number of its intersections falling on each of the studied structures was calculated at the low magnification (eyepiece ×7, lens — ×10). The position of the grid along the histological section was arbitrarily changed several times, each time repeating the count. The total number of grid intersections per slice obtained as a result of the calculation was taken as 100 %. Afterwards, the number of grid intersections

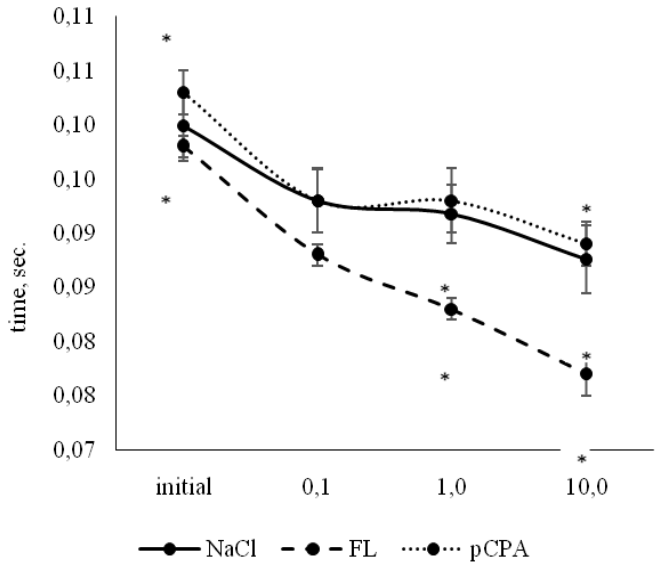
falling separately on each of the studied structures was converted into percentages accordingly. The obtained data were processed statistically with the calculation of the Student's criterion and the P value (reliability of differences).

Results

In the control group of 14-day-old rats, the initial values of the duration of contraction are 0.100 sec. At the minimum concentration of serotonin, time of myocardial contraction decreases by 0.007 (7 %) sec. compared to the initial parameters and amounts 0.093 sec. ($p<0.05$). At concentrations of 0.1 mM and 10.0 mM, the duration of contraction is 0.092 sec. and 0.088 sec., respectively. For the last two concentrations of serotonin, there is a decrease in the time of contraction by 0.008 sec. (8 %) and 0.012 sec. (12 %) compared to the initial values ($p<0.05$).

In the first experimental group of 14-day-old animals, the initial parameters of the contraction time are 0.098 sec. 5-HT reduces the contraction time in the concentration of 0.1 mM by 0.088 sec. and for the last two concentrations at 0.083 sec. and 0.077 sec. The myocardial contraction time is reduced in a concentration of 0.1 mM by 0.010 sec. (10 %) ($p<0.05$), at a concentration of 1.0 mM for 0.015 sec. (15 %) ($p<0.05$) and at a concentration of 10.0 mM for 0.21 sec. (21 %) ($p<0.05$) compared with the initial parameters. The time of myocardial contraction in the maximum concentration of serotonin compared to the minimum concentration is reduced by 0.011 sec. (11 %); compared with a concentration of 1.0 mM for 0.006 sec. (6 %) ($p<0.05$). At a concentration of 1.0 mM, the myocardial contraction time is 0.005 sec. lower compared to a concentration of 0.1 mM. (5 %) ($p<0.05$).

In the second experimental group of young rats, the initial parameters of the contraction time are 0.103 sec. At a concentration of 0.1 mM and 1.0 mM, the myocardial contraction time is the same and reaches 0.093 sec. For the highest concentration of serotonin, the time is 0.089 sec. At concentrations of 0.1 mM and 1.0 mM, the myocardial contraction time decreases by 0.010 sec. (10 %) and in a concentration of 10.0 mM for 0.014 sec. (14 %) ($p<0.05$) compared to the initial values. At the maximum concentration of 5-HT, there is a statistically significant decrease in the myocardial contraction time compared to concentrations of 0.1 mM and 1.0 mM by 0.004 sec. (4 %) ($p<0.05$) (Fig. 1).



* — Statistically significant differences compared to the initial data (* $p<0.05$).
NaCl — saline; FL — fluoxetine; pCPA — para-chlorophenylalanine

Figure 1. Effect of serotonin on the time of myocardial contraction in 14-day-old infant rats

It was found that the histological picture of the myocardium in both experimental groups differs from the control group. At the same time, the detected changes in these groups are almost identical. Thus, changes in the circulatory microvasculature are dominant. The total area of blood vessels increases up to 6.59±0.30 % in the first group and up to 6.44±0.27 % in the second one (Tab. 1). The vessels are full-blooded with their lumen expanded and perivascular edema observed (Fig. 1). The edema's area is 6.48±0.46 % and

7.04±0.85 %, respectively. There is a sporadic release of blood cells outside the vascular bed (Fig. 2). In the lymphatic vessels one could observe the phenomena of lymphostasis (Fig. 3). Along the area of 9.62±1.15 % in the 1-group and 10.20±1.22 % in the 2-group, there is a pronounced interstitial edema with discomplexation of muscle fibers (Fig. 4). In the stroma of the myocardium, some small focal lymph histiocytic infiltrates are detected (Fig. 5). In some observations, micronecrosis of cardiomyocytes is detected, occupying an area of 2.46±0.10 % and 3.00±0.19 % (Fig. 6).

Table 1

Areas of the structural components of the myocardium (%, M±m)

Variant	Blood vessels	Connective tissue	Adipose tissue	Perivascular edema	Interstitial edema	Necrosis	Muscle tissue
Control group	3.31±0.17	10.24±1.09	1.45±0.17	1.29±0.09	3.54±0.21	–	80.17±4.86
I experimental group	6.59±0.30	11.05±1.48	4.57±0.75	6.48±0.46	9.62±1.15	2.46±0.10	59.23±3.14
II experimental group	6.44±0.27	10.31±1.13	5.50±0.82	7.04±0.85	10.20±1.22	3.00±0.19	57.51±2.94

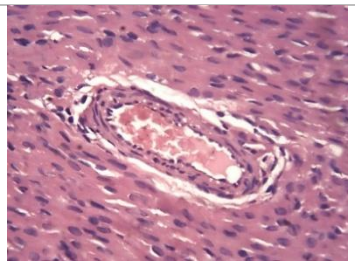


Figure 1. Vascular congestion and perivascular edema

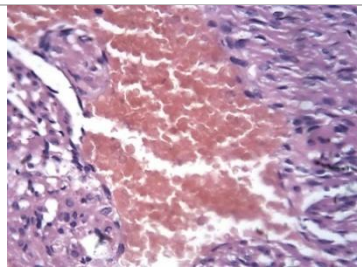


Figure 2. Outflow of blood corpuscles outside the vascular bed

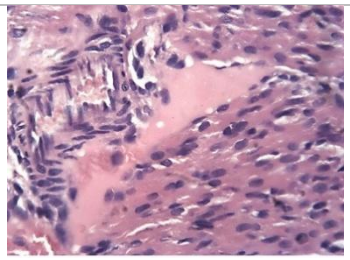


Figure 3. Lymphostasis

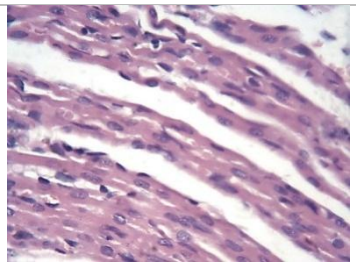


Figure 4. Interstitial edema with muscle fiber discomplex

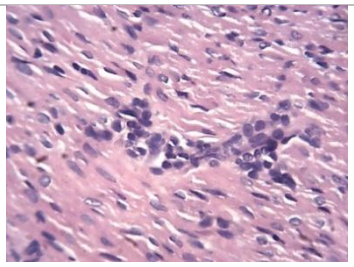


Figure 5. Focal lymphohistiocytic infiltrate

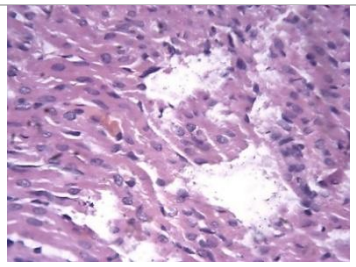


Figure 6. Foci of micronecrosis in the myocardium

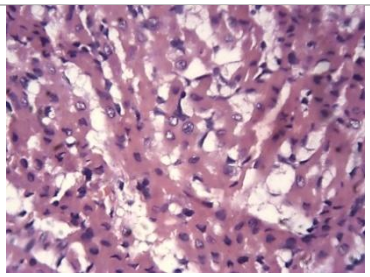


Figure 7. Areas of adipose tissue between muscle fibers

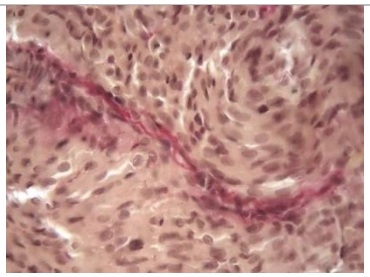


Figure 8. Connective tissue fibers in the myocardial stroma

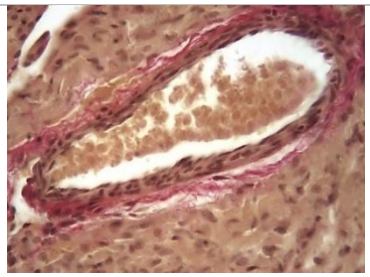


Figure 9. Connective tissue fibers in the myocardial stroma

There are sporadic extensive areas of adipose tissue between the muscle fibers (4.57±0.75 % and 5.50±0.82 %) (Fig. 7). Meanwhile, the volume of connective tissue does not differ from the control one (11.05±1.48 % and 10.31±1.13 %). The Van Gieson's staining reveals its fibers in the stroma of the organ (Fig. 8). Some minor sclerosis of the vascular walls can only be noted in some cases (Fig. 9).

Discussion

In the experimental group with blockade of the serotonin transporter, the shortest significant time of myocardial contraction has been found in comparison with other groups. This might be due to the blockade of serotonin transporter in the embryonic period, as a result of which there could be an increase in 5-HT in this group of animals. The largest number of serotonin receptors is activated, which possibly has led to a rapid contraction of the myocardium.

In the early postnatal period of rats, the adrenergic innervation of the heart is immature. It becomes important to maintain the inotropic function due to other non-adrenergic mechanisms, in particular serotonin ones [17].

The 5-HT_4 receptor signaling is similar beta-adrenergic receptors, and induces inotropic effects through a pathway involving cAMP and PKA-mediated phosphorylation of proteins that leads to an increase in Ca^{2+}. It has been shown that the 5-HT_{2B} serotonin receptor is critically important during embryogenesis, since knockout of this gene in rats causes heart defects and embryonic lethality, which makes further analysis of other types of embryonic cells and tissues difficult. The 5-HT_{2B} receptor modulates many secondary signals (mitogenic and morphogenetic cascades). The 5-HT_{2B} receptor activates Ras and kinases regulated by extracellular signals and mitogen-activated protein kinase via $G_{\alpha q}$ and $G_{\beta\gamma}$. The activation of this mechanism leads to 5-HT-induced cell proliferation [1, 2, 17].

In the experimental group with blockade of serotonin synthesis, the smallest reduction in contraction time is observed compared to other groups. This may be due to the interference of the full formation of the necessary serotonin in the embryonic period, which may cause structural rearrangements of calcium channels, as well as their insufficient formation. The relationship between the level of 5-HT in the embryonic period of ontogenesis and the functioning of Ca^{2+} channels of the membrane of cardiomyocytes and sarcoplasmic reticulum in newborn rats has been established [18].

In the histological studies of the right ventricle of the heart, it was found that a change in the concentration of serotonin in prenatal ontogenesis resulted in some morphological changes in the myocardium in the experimental animals compared to the control group. The excess or deficiency of serotonin in prenatal ontogenesis may have led to impaired function of serotonin receptors. In the experiments aimed at cultivating mouse embryos, those antagonists with a high affinity for the 5-HT_{2B}, such as ritanserin, caused morphological abnormalities in the heart (disorderly arrangement of myocytes, dilatation of the left ventricle, decreased diastolic function). During the formation of the heart, they lead to abnormal organization of the sarcomeres of the subepicardial layer and to the absence of myocardial trabeculosis [19]. Such morphological changes in the right ventricular myocardium in the experimental groups might have affected the normal contraction of cardiomyocytes in the postnatal ontogenesis. It should be noted that cardiac changes undergo significant morphological changes at the level of cardiomyocytes.

Conclusion

The heart begins to function at an early stage of development under the action of changing mechanical stimuli in the womb, the greatest growth and reorganization of cells. The given research shows that the blockade of the transporter and synthesis of serotonin in prenatal ontogenesis results in a shift in the inotropic function of cardiomyocytes in early postnatal ontogenesis, which is due to a change in the time of contraction by increasing concentrations of serotonin in the experimental groups versus the control group as well as morphological defects in the heart in the experimental groups.

The cardiovascular effects of serotonin are complex, and its contribution to the physiological and pathological processes of the myocardium remains insufficiently understood.

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References

1 Berger M. The expanded biology of serotonin / M. Berger, J. Gray, B. Roth // Annual review of medicine. — 2009. — No. 60. — P. 355–366. https://doi.org/10.1146/annurev.med.60.042307.110802

2 McCorvy J.D. Structure and function of serotonin G protein-coupled receptors / J.D. McCorvy, B.L. Roth // Pharmacology & Therapeutics. — 2015. — No. 150. — P. 129–142. https://doi.org/10.1016/j.pharmthera.2015.01.009

3 Sharp T. Central 5-HT receptors and their function; present and future / T. Sharp, N. Barnes // Neuropharmacology. — 2020. — Vol. 6, No. 177. — P. 108–155. https://doi.org/10.1016/j.neuropharm.2020.108155

4 Redpath G. Serotonin: an overlooked regulator of endocytosis and endosomal sorting? / G. Redpath, N. Deo // Biol Open. — 2022. — Vol. 11, No. 1. — P. 1–13. https://doi.org/10.1242/bio.059057

5 Vemacor A. Selective serotonin reuptake inhibitor use of antidepressants in the first trimester of pregnancy and the risk of specific congenital anomalies: a study based on European registries / A. Vemacor, K. Casson, E. Garne, M. Bakker, M.S. Addor, L. Arriola // Eur J Epidemiol. — 2015. — No. 30. — P. 1187–1198. https://doi.org/10.1007/s10654–015–0065-y

6 Edinoff A. Selective Serotonin Reuptake Inhibitors and Adverse Effects: A Narrative Review / A.N. Edinoff, H.A. Akuly, T.A. Hanna, C.O. Ochoa, S.J. Patti, Y.A. Ghaffar, O. Viswanath, I. Urits, A.G. Boyer, E.M. Cornett, A.M. Kaye // Neurol Int. — 2021. — Vol. 13, No. 3. — P. 387–401. https://doi.org/10.3390/neurolint13030038

7 Theron J.J. The effect of a serotonin inhibitor on the serotonin content and ultra-structure of rat atria and ventricles with special reference to atrial granules / J.J. Theron, R. Biagio, A.C. Meyer, S. Boekkooi, J.C. Seegers // Life Sciences. — 1978. — Vol. 23, No. 2. — P. 111–119. https://doi.org/10.1016/0024–3205(78)90258–8

8 Muir W. Myocardial Contractility: Historical and Contemporary Considerations / W. Muir, R. Hamlin // Front Physiol. — 2020. — Vol. 11, No. 222. — P. 20–31. https://doi.org/10.3389/fphys

9 Liu C. Controlling load-dependent kinetics of β -cardiac myosin at the single-molecule level / C. Liu, M. Kawana, D. Song, K.M. Ruppel, J.A. Spudich // Nat. Struct. Mol. Biol. — 2018. — No. 25. — P. 505–514. https://doi.org/10.1038/s41594-018-0069-x

10 Greenberg M.J. Inherent force-dependent properties of β -cardiac myosin contribute to the force-velocity relationship of cardiac muscle / M.J. Greenberg, H. Shuman, E.M. Ostap // Biophys. J. — 2014. — Vol. 107, No. 12. — P. 1041–1044. https://doi.org/10.1016/j.bpj.2014.11.005

11 Sweeney H.L. Muscle contraction / H.L. Sweeney, D.W. Hammers // Cold SpringHarb. Perspect. Biol. — 2018. — Vol. 10, No. 2. — P. 232–238. https://doi.org/10.1101/cshperspect.a023200

12 Tardiff J.C. Targets for therapy in sarcomeric cardiomyopathies / J.C. Tardiff, L. Carrier, D.M. Bers, C. Poggesi, C. Ferrantini, R. Coppini, L.S. Maier, H. Ashrafian, S. Huke, J. van der Valden // Cardiovasc. Res. — 2015. — No. 105. — P. 457–470. https://doi.org/10.1093/cvr/cvv023

13 Malik F.I. Cardiac myosin activation: a potential therapeutic approach for systolic heart failure / F.I. Malik, J.J. Hartman, K.A. Elias, B.P. Morgan, H. Rodriguez, K. Brejc, et al. // Science — 2011. — Vol. 331, No. 6023. — P. 1439–1443. https://doi.org/10.1126/science.1200113

14 MacLeod K.T. Recent advances in understanding cardiac contractility in health and disease / K.T. MacLeod // Browse Faculty Reviews. — 2016. — No. 5. — P. 1–13. https://doi.org/10.12688/f1000research.8661

15 Саркисов Д.С. Микроскопическая техника: руководство для врачей и лаборантов / Д.С. Саркисов, Ю.Л. Перов. — М.: Медицина, 1996. — 544 с.

16 Стефанов С.Б. Морфометрическая сетка случайного шага как средство ускоренного измерения элементов морфогенеза / С.Б. Стефанов // Цитология. — 1974. — № 6. — С. 785–787.

17 Ахметзянов В.Ф. Возрастные особенности инотропного влияния серотонина на миокард крысы / В.Ф. Ахметзянов, А.Ф. Якупова, Р.Р. Нигматуллина // Казан. мед. журн. — 2010. — Т. 91, № 4. — С. 467–471.

18 Недорезова Р.С. Влияние блокаторов Ca^{2+}- каналов дантролена и метоксиверапамила на инотропную функцию миокарда крысят с измененным уровнем серотонина / Р.С. Недорезова, Т.В. Гарипов, Р.Р. Нигматуллина // Ученые записки Казан. гос. акад. ветеринарной медицины им. Н.Э. Баумана. — 2019. — Т. 240, № 4. — С. 123–127. https://doi.org/10.31588/2413–4201–1883–240–4-123–128.

19 Choi D.S. 5-HT2B receptor-mediated serotonin morphogenetic functions in mouse cranial neural crest and myocardiac cells / D.S. Choi, S. Ward, N. Messaddeq, J.M. Launay, L. Maroteaux // Development. — 1997. — Vol, 124, No. 9. — P. 1745–55. https://doi.org/10.1242/dev.124.9.1745

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Серотониннің түрлі концентрацияларының егеуқұйрық күшіктерінің жүрегінің инотропты қызметіне және морфометриялық көрсеткіштеріне әсері

Соңғы жылдары ағзаның физиологиялық және патологиялық үрдістеріне серотониннің әсерін зерттеу жұмыстарында оның атеросклероздың, артериялық гипертензияның және жүректің ишемиялық ауруының патогенезі ретіндегі рөлі кеңінен талқылануда. Дамудың эмбрионалды кезеңінде серотонин өсу факторы ретінде әрекет ете отырып, эмбрион дамуының шешуші кезеңінде, атап айтқанда, жүректің дамуында маңызды реттеуші рөл атқарады. Біздің зерттеуіміздің мақсаты онтогенездің эмбрионалдық кезеңінде серотонин синтезінің және мембраналық тасымалдаушысының блокадасы жасалынған жаңа туған егеуқұйрық күшіктерінің оң жақ қарынша миокардының жиырылуының

уақыт көрсеткіштеріне серотониннің әсерін зерттеу. Зерттеу нәтижесінде, бақылау тобымен салыстырғанда серотонин мөлшері жоғары болған эксперименттік топта серотонинге кардиомиоциттердің реакциясы статистикалық жоғары және серотонин тапшылығы бар топта төмен екендігі анықталды. Сонымен қатар, онтогенездің эмбрионалды кезеңінде серотонин синтезі мен мембраналық тасымалдаушысының тежеуі арқылы серотонин концентрациясының өзгеруі жасалынған эксперименттік топ жануарларында онтогенездің ерте постналды кезеңінде миокардтың морфологиялық өзгерістері байқалған.

Кілт сөздер: серотонин, миокард, онтогенез, жүрек, флуоксетин, пара-хлорфенилаланин, егеуқұйрық, жүктілік.

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Влияние разных концентраций серотонина на инотропную функцию и морфометрические показатели сердца крысят

За последние годы в исследованиях серотонина в физиологических и патологических процессах организма широко обсуждают его роль как звена в патогенезе атеросклероза, артериальной гипертензии, ишемической болезни сердца. В эмбриональном периоде серотонин выступает в качестве фактора роста и играет важную регулирующую роль в решающий период развития эмбриона, в частности, развития сердца. Целью нашего исследования явилось изучение влияния серотонина на временные параметры сокращения миокарда правого желудочка у новорожденных крысят с блокадой синтеза серотонина и мембранного переносчика в эмбриональном периоде онтогенеза. Наши исследования показали, что реакция кардиомиоцитов на серотонин статистически выше в группе с избытком серотонина и ниже в группе с дефицитом серотонина по сравнению с группой контроля. В настоящей работе приведены данные, свидетельствующие о том, что изменение концентрации серотонина, которое создавалось блокадой синтеза серотонина и мембранного переносчика серотонина в эмбриональном периоде онтогенеза, приводит к морфологическим изменениям миокарда в раннем постнатальном онтогенезе.

Ключевые слова: серотонин, миокард, онтогенез, сердце, флуоксетин, пара-хлорфенилаланин, крыса, беременность.

References

1 Berger, M., Gray, J., & Roth, B. (2009). The expanded biology of serotonin. *Annual review of medicine, 60;* 355–366. https://doi.org/10.1146/annurev.med.60.042307.110802

2 McCorvy, J.D., & Roth, B.L. (2015). Structure and function of serotonin G protein-coupled receptors. *Pharmacology & Therapeutics, 150;* 129–142. https://doi.org/10.1016/j.pharmthera.2015.01.009

3 Sharp, T., & Barnes, N. (2020). Central 5-HT receptors and their function; present and future. *Neuropharmacology, 6, 177;* 108–155. https://doi.org/10.1016/j.neuropharm.2020.108155

4 Redpath, G., & Deo, N. (2022) Serotonin: an overlooked regulator of endocytosis and endosomal sorting? *Biol Open, 11, 1;* 1–13. https://doi.org/10.1242/bio.059057

5 Vemacor, A., Casson, K., Garne, E., Bakker, M., Addor, M.S., & Arriola, L. (2015). Selective serotonin reuptake inhibitor use of antidepressants in the first trimester of pregnancy and the risk of specific congenital anomalies: a study based on European registries. *Eur J Epidemiol., 30;* 1187–1198. https://doi.org/10.1007/s10654-015-0065-y

6 Edinoff, A.N., Akuly H.A., Hanna T.A., Ochoa C.O., Patti S.J., Ghaffar Y.A., Kaye, A.D., Viswanath, O., Urits, I., Boyer, A.G., Cornett, E.M., & Kaye, A.M. (2021). Selective Serotonin Reuptake Inhibitors and Adverse Effects: A Narrative Review. *Neurol Int., 13, 3;* 387–401. https://doi.org/10.3390/neurolint13030038

7 Theron, J.J., Biagio, R., Meyer, A.C., Boekkooi, S., & Seegers, J.C. (1978). The effect of a serotonin inhibitor on the serotonin content and ultra-structure of rat atria and ventricles with special reference to atrial granules. *Life Sciences, 23, 2;* 111–119. https://doi.org/10.1016/0024-3205(78)90258-8

8 Muir, W., & Hamlin, R. (2020). Myocardial Contractility: Historical and Contemporary Considerations. *Front Physiol., 11, 222;* 20–31. https://doi.org/10.3389/fphys.2020.00222

9 Liu, C., Kawana, M., Song, D., Ruppel, K.M., & Spudich, J.A. (2018). Controlling load-dependent kinetics of β-cardiac myosin at the single-molecule level. *Nat. Struct. Mol. Biol., 25;* 505–514. https://doi.org/10.1038/s41594-018-0069-x

10 Greenberg, M.J., Shuman, H., & Ostap, E.M. (2014). Inherent force-dependent properties of β-cardiac myosin contribute to the force-velocity relationship of cardiac muscle. *Biophys. J., 107, 12;* 1041–1044. https://doi.org/10.1016/j.bpj.2014.11.005

11 Sweeney, H.L., & Hammers, D.W. (2018). Muscle contraction. *Cold Spring Harb. Perspect. Biol., 10, 2;* 232–238. https://doi.org/10.1101/cshperspect.a023200

12 Tardiff, J.C., Carrier, L., Bers, D.M., Poggesi, C., Ferrantini, C., Coppini, R., Maier, L.S., Ashrafian, H., Huke, S., & van der Velden, J. (2015). Targets for therapy in sarcomeric cardiomyopathies. *Cardiovasc. Res., 105;* 457–470. https://doi.org/10.1093/cvr/cvv023

13 Malik, F.I., Hartman, J.J., Elias, K.A., Morgan, B.P., Rodriguez, H., Brejc, K., et al. (2011). Cardiac myosin activation: a potential therapeutic approach for systolic heart failure. *Science, 331;* 1439–1443. https://doi.org/10.1126/science.1200113

14 MacLeod, K.T. (2016). Recent advances in understanding cardiac contractility in health and disease. *Browse Faculty Reviews, 5;* 1–13. https://doi.org/10.12688/f1000research.8661

15 Sarkisov, D.S., & Perov, Yu.L. (1996). Mikroskopicheskaia tekhnika: rukovodstvo dlia vrachei i laborantov *[Microscopic technique: a guide for physicians and laboratory technicians]*. Moscow: Meditsina, 544 [in Russian].

16 Stefanov, S.B. (1974). Morfometricheskaia setka sluchainogo shaga kak sredstvo uskorennogo izmereniia elementov morfogeneza [Morphometric grid of random step as a means of accelerated measurement of elements of morphogenesis]. *Tsitologiia — Cytology, 6;* 785–787 [in Russian].

17 Akhmetzianov, V.F., Yakupova, A.F., & Nigmatullina, R.R. (2010). Vozrastnye osobennosti inotropnogo vliianiia serotonina na miokard krysy [Age-related features of inotropic effect of serotonin on rat myocardium]. *Kazanskii meditsinskii zhurnal — Kazan Medical Journal, 91, 4;* 467–471 [in Russian].

18 Nedorezova, R.S., Garipov, T.V., & Nigmatullina, R.R. (2019). Vliianie blokatorov Ca^{2+}-kanalov dantrolena i metoksiverapamila na inotropnuiu funktsiiu miokarda krysiat s izmenennym urovnem serotonina [Influence of dantrolene and methoxiverapamil channels Ca^{2+}-channels on the rating myocardial function of rats with changed serotonin level]. *Uchenye zapiski Kazanskoi gosudarstvennoi akademii veterinarnoi meditsiny imeni N.E. Baumana — Kazan State Academy of Veterinary Medicine named after N.E. Bauman, 240, 4;* 123–127 [in Russian]. https://doi.org/10.31588/2413-4201-1883-240-4-123-128

19 Choi, D.S., Ward, S., Messaddeq, N., Launay, J.M., & Maroteaux, L. (1997). 5-HT2B receptor-mediated serotonin morphogenetic functions in mouse cranial neural crest and myocardiac cells. *Development, 124, 9;* 1745–1755. https://doi.org/10.1242/dev.124.9.1745