EFFECT OF LIGANDS OF SEROTONIN AND DOPAMINE RECEPTORS ON HEART RATE VARIABILITY IN RATS

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Abstract. A comparative analysis of the effects of serotonin (200 μg/kg), dopamine (60 μg/kg), promethazine (2 mg/kg) and sulpiride (1 mg/kg) administered once intraperitoneally on heart rate variability in male non-linear rats was carried out. Serotonin and dopamine do not change heart rate, but increase the centralization index by 122% ($p < 0.05$), serotonin due to an increase in the power of LF waves by 136% ($p < 0.05$), dopamine due to a downward trend power of HF waves by 51% ($p < 0.1$) compared to the control. Promethazine reduces the power of LF and VLF waves by 64-66% ($p < 0.05$) and the index of centralization ($p < 0.01$), while the proportion of HF waves in the spectrum increases to 75%, which is higher than the control ($p < 0.01$). Sulpiride increases heart rate frequency by 25% ($p < 0.01$) and the index of centralization ($p < 0.001$), reduces the power of HF-waves by 70 % ($p < 0.001$) from the initial state, increases the power of LF-of waves by 336% and VLF-waves by 197% ($p < 0.001$), so the total proportion of LF and VLF waves increases to 85%, which is higher than the control ($p < 0.05$). The results suggest that peripheral serotoninergic and dopaminergic mechanisms have opposite effects on heart rate variability.

Keywords: heart rate variability, serotonin, promethazine, dopamine, sulpiride, rats.

List of Abbreviations

HRV – Heart Rate Variability
HF waves – High Frequency waves
LF waves – Low Frequency waves
VLF waves – Very Low Frequency waves
SI – Stress Index
IC – Index of Centralization

Introduction

Analysis of heart rate variability (HRV) is widely used in medical and biological research to assess the state of the regulatory systems of the body during functional tests, as well as the introduction of pharmacological drugs (Baevsky *et al*., 2002). According to the concept of R.M. Baevsky, the power of high-frequency, or respiratory, waves (HF-waves) is considered as a criterion for the activity of parasympathetic influences and an autonomous regulatory circuit, and the power of low-frequency, or vasomotor, waves (LF-waves), as well as very high-frequency waves (VLF-waves) – criterion for the activity of sympathetic influences and the central circuit of regulation. Participation of others neurotransmitter mechanisms in changes of HRV is not mentioned within the concept of R.M. Baevsky, however, not only sympathetic and parasympathetic mechanisms, but also other neurotransmitter systems are involved in the regulation of visceral functions. It is known that ligands of serotonin and dopamine receptors affect vascular tone and blood pressure (Polakowski *et al*., 2004; Nadeev *et al.*, 2014; Sveshnikov *et al.*, 2016), myocardial contractility (Lychkova, 2012; Laptev *et al.*, 2017), and the activity of neurons in the respiratory and cardiovascular centers (Vernejoul *et al*., 2002; Jordan, 2004; Feuerstein, 2008; Sriranjini *et al*., 2011; Lychkova, 2012; Sévoz-Couche, 2017). Taking into account these data, as well as the results of works on changes in HRV when exposed to monoaminergic systems (Kaya *et al.*, 2004; Kuznetsov *et al.*, 2012), it seems relevant to identify the features of heart rate variability (HRV) under conditions of exposure to serotonin- and dopaminergic receptors. The aim of this work was to analyze and compare changes in heart rate variability (HRV) after administration of agonists and antagonists of serotonin and dopamine receptors in the experiment.

Materials and Methods

The experiment used non-linear male rats 4-5 months of age (n = 48) weighing 220-270 g (vivarium of the Federal State Budgetary Institution Scientific Research Institute for the Study of Leprosy of the Ministry of Health of Russia), kept in a laboratory vivarium of the Astrakhan State University (12-hour light regime, plastic cages with small wood shavings, standard diet - granulated complete feed for laboratory animals (extruded) PK-120 GOST 50258-92 produced by LLC "Laboratorkorm", access to water and feed is free).

The experiments were performed in accordance with the National Standard of the Russian Federation GOST R-53434-2009 "Principles of Good Laboratory Practice", Order of the Ministry of Health of the Russian Federation No. 199n dated April 1, 2016 "On Approval of the Rules of Good Laboratory Practice" and the European Convention Directive 2010/63/EU of 22 September 2010, that is confirmed with ethical committee of the Astrakhan state university (Report ¹10 from 10.06.2021). Studies were carried out in the morning (from 8 to 13 hours).

Serotonin at a dose of 200 μg/kg was used to stimulate serotonin receptors, and promethazine, an antagonist of 5-$HT_{1,2}$ receptors, at a dose of 2 mg/kg was used for blockade (Lychkova, 2012; Nadeev *et al.*, 2014). Stimulation of dopamine receptors was induced by administration of dopamine at a dose of 60 μg/kg, blockade by sulpiride, a selective D_2 receptor antagonist, at a dose of 1 mg/kg (Katzung *et al.*, 2012). All preparations were obtained from Sigma (Germany). The preparations were dissolved in water for injection and administered intraperitoneally once in a volume of 0.1 ml per 100 g of body weight. Animals of the control group received a single injection of saline from the same calculation.

ECG was recorded in awake unfixed rats using the "Varicard" hardware-software complex (Ramena, Russia) using miniature clamp electrodes under local anesthesia with lidocaine (0.05 ml of a 0.5% solution intradermally) (Kuryanova *et al.*, 2016). In each individual, an ECG was recorded in the initial state (before the administration of the drug). After obtaining an ECG in a state of calm wakefulness, the recording was suspended and an injection was made. In accordance with the distribution by groups, rats received: group 1 (Control) - saline, group 2 (Serotonin) – serotonin (200 μg/kg), group 3 (Promethazine) – promethazine (2 mg/kg), group 4 (Dopamine) – dopamine (60 μg / kg), group 5 (Sulpiride) – sulpiride (1 mg / kg). Then, ECG recording was resumed and continued for 20–30 min after drug injection, when, according to (Katzung *et al.*, 2012), their peripheral effects will develop.

Data processing was carried out using the ISKIM6 computer program (Ramena, Russia) (Kuryanova *et al.*, 2016). For analysis, continuous stationary series of 350 R-R intervals were taken from records made 15-20 minutes after drug administration. Heart rate frequency (bpm), mode (Mo, ms), variation range (ΔX, ms), mode amplitude (AMo, %) were determined. stress index (rel. units) considering the histogram class width of 7.8 ms: SI = (AMo /2 x x ΔX x Mo) x (50/7.8) x 1000 (Baevsky *et al.*, 2002; Kuryanova *et al.*, 2016). HRV spectral analysis was performed in the following ranges: HF (0.9–3.5 Hz), LF (0.32–0.9 Hz), VLF (0.15–0.32 Hz) (Kuryanova *et al.*, 2016). The absolute (ms^2) and relative (%) wave power in each band was calculated, the index of centralization (rel. units): IC = (LF+VLF) / HF (Baevsky *et al.*, 2002).

The results were statistically processed in the Statistica 10.0 program using the nonparametric Mann-Whitney U test. The revealed differences were confirmed by the results of analysis of variance (ANOVA, Statistica 10.0). The table shows the average values and their errors (M ± m). Differences between the means were considered significant at $p < 0.05$.

Results

According to the data obtained (Table 1), the administration of serotonin was accompanied by a trend towards an increase in LF waves, the power of which increased by 136% ($p < 0.05$), and the proportion in the spectrum increased by almost 2 times ($p < 0.01$) compared to with control (Fig. 1). In this regard, IC increased to 2 rel. units or 122% of control ($p < 0.05$) (Table 1).

Table 1

Indicators of heart rate variability in rats after administration of agonists and antagonists of serotonin and dopamine receptors, M ± m

Parameters of HRV	Groups	Initial state	Experimental state
HRF, beats/min	Control	313.9 ± 4.9	317.8 ± 9.0
	Serotonin	303.3 ± 8.8	319.9 ± 17.7
	Prometazine	335.0 ± 23.2	300.5 ± 17.1
	Dopamine	320.7 ± 9.2	312.8 ± 9.9
	Sulpiride	314.3 ± 6.1	397.2 ± 22.8 **, ###, &&&,^^
Mo, ms	Control	191.8 ± 2.9	191.3 ± 5.4
	Serotonin	200.3 ± 5.7	192.8 ± 10.5
	Prometazine	183.5 ± 10.6	201.7 ± 9.9
	Dopamine	186.8 ± 5.7	193.8 ± 6.1
	Sulpiride	190.6 ± 3.2	148.7 ± 9.7 **, ###
Stress Index, rel. units	Control	29.6 ± 3.7	30.8 ± 6.1
	Serotonin	44.5 ± 6.8	44.3 ± 6.5
	Prometazine	34.9 ± 7.6	46.5 ± 6.0
	Dopamine	36.7 ± 7.0	42.7 ± 6.5
	Sulpiride	26.1 ± 2.6	31.9 ± 4.5
HF, ms^2	Control	7.1 ± 1.1	8.1 ± 2.3
	Serotonin	5.8 ± 1.4	5.4 ± 1.2
	Prometazine	7.1 ± 1.4	7.3 ± 1.2
	Dopamine	5.9 ± 1.1	4.0 ± 0.8
	Sulpiride	8.4 ± 0.8	2.5 ± 0.4 ***, ^^
LF, ms^2	Control	4.4 ± 1.1	2.5 ± 0.6
	Serotonin	3.3 ± 1.3	5.9 ± 1.5 #
	Prometazine	3.6 ± 1.3	0.9 ± 0.2 +
	Dopamine	3.7 ± 0.5	3.9 ± 1.3
	Sulpiride	4.8 ± 1.5	10.9 ± 2.5 *, ###, ^^
VLF, ms^2	Control	3.6 ± 0.8	3.3 ± 0.6
	Serotonin	4.4 ± 1.9	3.3 ± 0.8
	Prometazine	4.7 ± 1.4	1.1 ± 0.2 *, #
	Dopamine	3.6 ± 0.7	3.5 ± 0.9
	Sulpiride	3.2 ± 1.1	9.8 ± 1.6 **, ###, &&, ^^^
Index of Centralization, rel. units	Control	1.1 ± 0.1	0.9 ± 0.1
	Serotonin	1.4 ± 0.3	2.0 ± 0.4 #
	Prometazine	1.1 ± 0.4	0.3 ± 0.1 ##, ++
	Dopamine	1.5 ± 0.2	2.0 ± 0.5 #
	Sulpiride	0.9 ± 0.3	9.1 ± 1.5 ***, ###, &&&, ^^^

The significant differences were calculated by Mann-Whitney U-test.

*, **, *** – $p < 0.05$, $p < 0.01$, $p < 0.001$ – compared with the initial state in each group;

#, ##, ### – $p < 0.05$, $p < 0.01$, $p < 0.001$ – compared to Control group;

+, ++, +++ – $p < 0.05$, $p < 0.01$, $p < 0.001$ – compared with the Serotonin group;

&&, &&& – $p < 0.01$, $p < 0.001$ – compared with the Dopamine group;

^^, ^^^ – $p < 0.01$, $p < 0.001$ – compared with the Promethazine group.

Number of animals in groups: Control (12), Serotonin (12), Promethazine (6), Dopamine (12), Sulpiride (6).

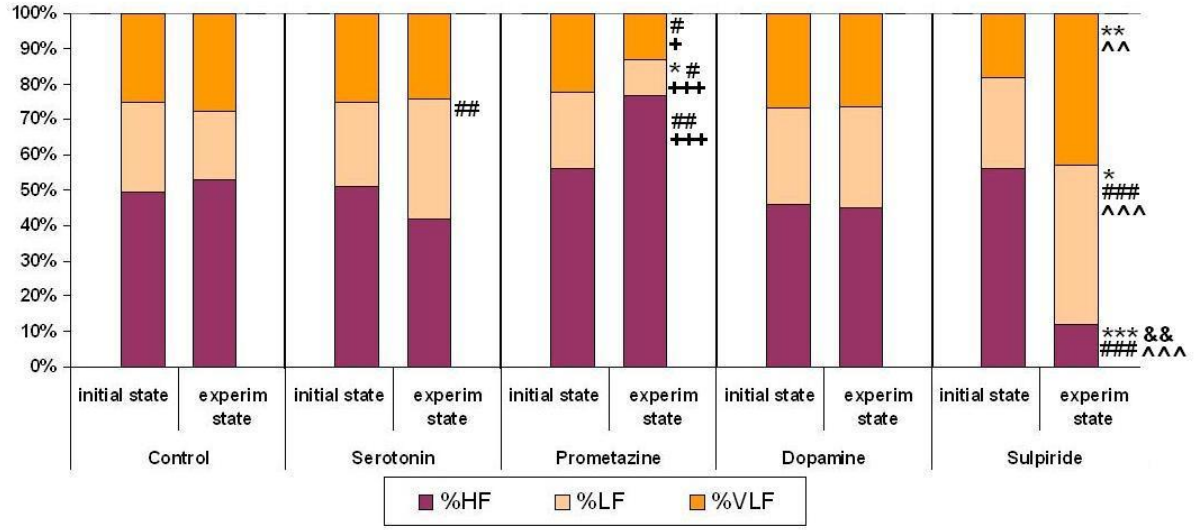

Fig. 1. Change in the ratio of spectral components of heart rate variability in rats after administration of agonists and antagonists of serotonin and dopamine receptors

Note: *, **, *** – $p < 0.05$, $p < 0.01$, $p < 0.001$ – compared with the initial state in each group;

#, ##, ### – $p < 0.05$, $p < 0.01$, $p < 0.001$ – compared to Control group;

+, ++, +++ – $p < 0.05$, $p < 0.01$, $p < 0.001$ – compared with the Serotonin group;

&&, &&& – $p < 0.01$, $p < 0.001$ – compared with the Dopamine group;

^^, ^^^ – $p < 0.01$, $p < 0.001$ – compared with the Promethazine group.

Number of animals in groups: Control (12), Serotonin (12), Promethazine (6), Dopamine (12), Sulpiride (6)

Thus, after the administration of serotonin, there was an increase in the power of LF waves associated with the regulation of vascular tone, which is interpreted as an increase in the centralization of heart rhythm control, according to (Baevsky *et al.*, 2002).

The introduction of promethazine led to a decrease in the absolute power of low-frequency waves, especially VLF (by 66%, $p < 0.05$) (Table 1), as well as the share of LF% and VLF% in the spectrum to 10-12% ($p < 0.05$) in comparison of baseline and control (Fig. 1). At the same time, the proportion of HF waves increased to 75% or more, which is almost 23% more than the control ($p < 0.01$). The weakening of the power of slow waves caused a decrease in IC to a minimum value of 0.3 rel. units ($p < 0.05$) (Table 1). After the introduction of promethazine, the smallest values of the absolute and relative powers of LF waves were recorded among all series of the experiment. Differences between the Serotonin and Promethazine groups are most significant in HF% (by 34.4%, $p < 0.001$) and LF% (by 23.3%, $p < < 0.001$) (Fig. 1), as well as in the IC value, which in the presence of promethazine 85% lower than with serotonin ($p < 0.01$) (Table 1). In general, after the introduction of serotonin and promethazine, changes in the power of LF waves and IC are clearly opposite and significant.

Dopamine administration did not change heart rate and most of the parameters of rhythm variability. But the IC in this series exceeded the control level by 122% ($p < 0.05$) due to a trend towards a decrease in the power of HF waves by 51% ($p < 0.1$) compared to the control (Table 1). After the introduction of sulpiride, specific for D_2-type receptors, there was a sharp increase in heart rate (by 26.5%, $p < 0.01$) with a corresponding decrease in Mo cardiointervals ($p < 0.01$) (Table 1). The power of HF waves decreased by 70% ($p < 0.001$), while the powers of LF and VLF waves increased (by 128%,

$p < 0.05$ and 206%, $p < 0.01$, respectively). The share of HF in the spectrum fell to 10-12% ($p < 0.001$), and the LF- and VLF-waves became dominant, the share of which in total reached 85% ($p < 0.05$, $p < 0.01$) (Fig. 1). The change in the ratio of the spectrum components caused a multiple increase in IC (by 10.1 times, $p < 0.001$). That is, after the introduction of sulpiride, the highest values of heart rate, LF and VLF, IC wave powers and the lowest HF wave power among all experimental groups were noted. These differences were significant in comparison with the initial state and the control series: the power of HF waves was 69% lower, and the powers of LF and VLF waves were 336% and 197% higher than the control values ($p < 0.001$) (Table 1). Differences between the Dopamine and Sulpiride groups were traced only in heart rate ($p < 0.001$), absolute power VLF (by 180%, $p < 0.01$), HF% (by 41.8, $p < 0.01$), and IC, which is 4.5 times higher against the background of sulpiride than against the background of dopamine ($p < 0.001$). It is important to note that the antagonism of the effects of dopamine and sulpiride in relation to HRV parameters is not observed, the differences between the series are determined by significant shifts after the administration of sulpiride, while against the background of dopamine, the indicators are close to control. At the same time, changes in HRV against the background of sulpiride are clearly opposite to the changes recorded after the administration of promethazine.

Discussion

Turning to the discussion, we note that serotonin caused a noticeable trend towards an increase in LF waves and an increase in their share in the HRV spectrum. These heart rate waves, according to (Baevsky *et al.*, 2002), are associated with fluctuations in blood pressure. This effect of serotonin is consistent with the data on its effect on vascular tone through the subtypes of 5-HT_1- and 5-HT_2 receptors on smooth vascular myocytes and endothelial cells (Nadeev *et al.*, 2014; Sveshnikov *et al.*, 2016). A direct effect of serotonin on the myocardium is not excluded, taking into account the localization of 5-HT_4 receptors on atrial cardiomyocytes (Lychkova, 2012; Nadeev *et al.*, 2014). Thus, the introduction of serotonin contributes to an increase in the variability of cardio intervals in the LF range, enhances the conjugation of the heart rhythm with blood pressure fluctuations.

Promethazine, used in the work as an antagonist of 5-$HT_{1,2}$ receptors, caused the opposite effect, reducing the power of LF and VLF waves, as a result, their shares in the spectrum decreased so much that HF waves began to account for 75% of the power of the spectrum, although the absolute the power of the latter has not changed much. That is, the rearrangement of the wave structure of the spectrum was determined by a drop in the power of low-frequency oscillations, especially LF waves. We believe that the administration of promethazine led to a limitation of serotonergic effects on vascular tone, taking into account the data (Lychkova, 2012; Nadeev *et al.*, 2014; Sveshnikov *et al.*, 2016). In addition, promethazine is able to block α_2-adrenergic receptors (Katzung *et al.*, 2012), which, in turn, could reduce adrenergic effects on blood vessels. Blocking of presynaptic 5-HT_2 receptors (Lychkova, 2012) and α_2-adrenergic receptors (Katzung *et al.*, 2012), through which serotonin and noradrenaline inhibit the release of acetylcholine from cholinergic terminals, could contribute to the rapid development of HRV changes. The removal of this block could potentiate cholinergic influences, which contributed to the maintenance of heart rate variability at the frequency of respiratory oscillations (HF waves). That is, the administration of promethazine led to changes in HRV, which can be regarded as the result of a weakening of the conjugation of the heart rhythm with fluctuations in blood pressure and the activity of the vasomotor center, while increasing the role of the autonomic circuit in the regulation of the heart rhythm according to Baevsky *et al* (2002). Taken together, the changes in HRV after the administration of serotonin and promethazine give reason to believe that serotonergic mechanisms, through a direct effect on vascular tone, as well as pre-synaptic modulation of the level of cholinergic and adrenergic influences, are involved

in the formation of LF waves and are important for the presence of these waves in the HRV spectrum.

In turn, the introduction of dopamine almost did not change HRV, only contributed to the weakening of the variability of cardio intervals in the HF range, which led to an increase in the centralization of heart rhythm control. Fluctuations in the duration of cardiac cycles at frequencies in the HF band are considered to be respiratory waves, which usually account for up to 50% of the total spectrum power during quiet wakefulness (Kuznetsov *et al.*, 2012; Kuryanova *et al.*, 2016). A possible cause of changes in HRV after administration of dopamine could be a slight decrease in the overall activity of the autonomic nervous system, since there are data on the ability of dopamine to inhibit the transmission of information in autonomic nodes via D_1 and D_2 receptors (Vernejoul *et al.*, 2002).

Sulpiride, on the contrary, induced a sharp increase in heart rate, a significant drop in HF power, and a significant increase in the absolute and relative power of LF and VLF waves; in total, these waves began to account for up to 85% of the total power of the spectrum. Such changes, according to the concept of R.M. Baevsky (2002) are regarded as signs of a sharp increase in sympathoadrenal influences and centralization of heart rhythm control. The obtained results are consistent with the facts about the ability of dopamine to reduce vascular resistance via D_2 receptors on vascular smooth myocytes (Polakovski *et al.*, 2004), and to inhibit the release of norepinephrine from sympathetic terminals via presynaptic D_2 receptors (Kaya *et al.*, 2003). Sulpiride, blocking D_2 receptors, potentiates the growth of vascular resistance and enhances sympathoadrenal effects on the heart and blood vessels. The increase in blood pressure and the flow of signals from baroreceptors, apparently, resulted in an increase in the conjugation of the heart rhythm with the activity of the vasomotor center and suprasegmental structures, which manifested itself in an increase in the power of the LF and VLF waves of the HRV spectrum. It is important to note that there is no pronounced antagonism in the effects of dopamine and sulpiride on HRV, dopamine almost does not change HRV, and the administration of sulpiride affects the wave power of the entire spectrum of HRV. In general, the features of HRV after the administration of dopamine and sulpiride indicate that dopaminergic mechanisms affect HRV indirectly through modulation of the activity of the adrenergic regulation channel, which is reflected mainly in the power of the waves of the low-frequency range of the HRV spectrum. However, the role of dopaminergic mechanisms in the formation of HRV under normal conditions, apparently, is not decisive, it manifests itself in extreme conditions or the introduction of specific drugs.

It should also be noted that the introduction of both serotonin and dopamine changes HR and HRV mainly in the form of trends, but serotonin has a more pronounced and definite effect on the variability of cardio intervals in the LF range. The reason for the weak severity of effects, apparently, is the rapid metabolism of exogenous monoamines. After the introduction of antagonists of serotonin and dopamine receptors, changes in HRV are very significant and clearly multidirectional. Promethazine potentiates a slight decrease in heart rate, a weakening of the conjugation of the heart rhythm with the activity of the vasomotor center, an increase in the role of the autonomic circuit and cholinergic influences in the formation of HRV. Sulpiride, on the contrary, potentiates tachycardia, increases the conjugation of the heart rhythm with the activity of the vasomotor center and the suprasegmental level of regulation, and increases the role of sympathoadrenal mechanisms in the formation of HRV. Changes in HRV with the introduction of antagonists of 5-$HT_{1,2}$ receptors and D_2 receptors are persistent, pronounced and characterized by very distinct antagonism, which can be explained by the specificity of binding only to certain receptor subtypes and a longer period of action of synthetic drugs in the body.

Conclusion

So, the results of studies with the introduction of agonists and especially antagonists of serotonin and dopamine receptors indicate that

peripheral serotonin- and dopaminergic mechanisms are capable of causing multidirectional changes in HRV. We believe that serotonin- and dopaminergic mechanisms are involved in changes in HRV parameters through presynaptic modulation of the activity of the cholinergic and adrenergic channels of heart rhythm regulation, respectively. But serotonin, carrying out 5-$HT_{1,2}$-mediated regulation of vascular tone, contributes to the formation of LF-waves of the HRV spectrum.

The data presented in the work are important for understanding the mechanisms of formation of variability of cardiointervals and the role of serotonin- and dopaminergic mechanisms of regulation in this process, since HRV analysis methods are used in medical practice. This information is important in connection with the creation and use of drugs that affect the metabolism of serotonin and dopamine in the body. To form a more complete picture of the effects of agonists and antagonists of serotonin and dopamine receptors, it makes sense to analyze their effects not only in a state of calm wakefulness, but in conditions of other functional states and in combination with other drugs, which will be the subject of further research.

Conflict of interest statement:
Nothing declared.

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