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Effects of Blockage of Peripheral Choline, Serotonin, and Dopamine Receptors on Heart Rhythm Variability in Rats under Conditions of Stimulation of Neurotransmitter Systems

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Stimulation of the serotoninergic system (5-hydroxytryptophan, 50 mg/kg; fluoxetine, 3 mg/kg) induced a significant increase in HR and a reduction in the amplitude of all waves of the heart rhythm variability. Stimulation of the dopaminergic system (L-DOPA and amantadine, 20 mg/kg each) resulted in a moderate increase in HR and amplitudes of low-frequency (LF) and very-low-frequency (VLF) waves of the heart rhythm variability. Successive blockade of nicotinic (hexamethonium, 7 mg/kg) and muscarinic cholinergic receptors (atropine, 1 mg/kg) leads to a significant decrease in the variability of cardiointervals (almost to complete levelling) both under control conditions and after stimulation of the neurotransmitter systems. Serotonin receptor blockade (promethazine, 2 mg/kg) did not affect HR, but reduced the amplitude of LF- and VLF-waves. Under conditions of serotoninergic system stimulation, the blockade of serotonin receptors was followed by a significant HR acceleration without changes in heart rhythm variability; blockade of dopamine receptors (sulpiride, 1 mg/kg) induced HR acceleration and increase in the amplitude of LF- and VLF-waves; blockade of dopamine receptors under conditions of dopamine system stimulation was followed by a significant increase in HR and a decrease in the amplitude of all waves of the heart rhythm variability. It can be hypothesized that serotonin- and dopaminergic systems affect the heart rhythm via cardiomyocyte receptors and via modulation of activity of the adrenergic and cholinergic systems. The effects of serotonin- and dopaminergic systems can be considered as synergic in the CNS, and antagonistic at the periphery.

Key Words*: heart rhythm variability; blockade of nicotinic and muscarinic cholinergic receptors; blockade of serotonin $5HT_{1,2}$ receptors and dopamine D_2 receptors; serotoninergic and dopaminergic systems*

The role of the serotoninergic (SS) and dopaminergic (DS) systems in the regulation of visceral functions, in particular, in the functions of the cardiovascular system attracts much attention [2,3,5-14]. There are data that SS can be considered as a component of the autonomic nervous system [6,9]. Various serotonin receptors are presented in the CNS [2] and in endings of autonomic system neurons and cells of internal organs, such as cardiomyocytes and vascular wall cells [6-9,11,12]. Serotonin and agents affecting serotonin uptake can modulate the frequency, amplitude, and velocity of myocardium contractions [5,6,8,13]. The role of dopamine and agonists and antagonists of dopamine receptors in the regulation of cardiac function was addressed in several studies [3,10,14]. SS and DS (monoaminergic systems) can act as either agonists or antagonists of the adrenergic system [2,6]. To better understand the role of these systems, the effects of stimulation (or blockade) of SS and DS should be compared, and the mechanisms of their interaction

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with adrenergic and cholinergic systems at the central and peripheral levels should be analyzed bearing in mind previous data [2,6] and heart rhythm variability (HRV) analysis for evaluation of regulatory influences on chronotropic function of the heart [1,4,5,10].

Here we studied changes in HRV in rats under conditions of stimulation of SS and DS combined with subsequent administration of blockers of nicotinic and muscarinic cholinergic receptors, as well as blockers of serotonin $5HT_{1,2}$ receptors and dopamine D_2 receptors.

MATERIALS AND METHODS

The experiments were performed on outbred male rats (n=76) in accordance to the GOST R-53434-2009 Rules of Good Laboratory Practice, Order No. 199n of the Ministry of Health of the Russian Federation (Approval of the Rules of Good Laboratory Practice), and Directives of the Council of the European Communities 2010/63/EU. The experiments were conducted in the summer period.

Activation of the central neurotransmitter systems was induced by 4-fold administration of substances inducing the synthesis of the corresponding neurotransmitters and agents inhibiting their reuptake [5]. SS was stimulated by combined administration of 5-hydroxytriptophane (50 mg/kg) and fluoxetine (3 mg/kg). DS was stimulated with a combination of L-DOPA and amantadine (20 mg/kg each; all substances were from Sigma). All studied substances were injected intraperitoneally in the morning. Controls received injections of physiological saline (0.1 ml/100 g body weight). For modulation of the peripheral neurotransmitter processes, nicotinic receptor blocker hexamethonium (7 mg/kg) and muscarinic receptor blocker atropine (1 mg/kg) were injected successively with an interval of 10-15 min (experimental series I) [4]. In series II, $5\text{-}HT_{1,2}$ receptor blocker promethazine (2 mg/kg, Sigma) was injected to the animals with stimulated SS and D_2 receptor blocker sulpiride (1 mg/kg, Sigma) was administered to the animals with stimulated DS [2,7]. A half of the control group rats in series II received promethazine or and the other half was treated with sulpiride. All substances were administered intraperitoneally.

ECG was recorded in conscious unrestrained rats using a Varikard instrument and miniature clamp electrodes under local lidocaine anesthesia [4,5]. The analysis of HRV was performed on records including 350 *R-R* intervals using ISKIM6 software (Ramena). HR and stress index (SI) were calculated by formula [5] on the basis of histogram class width 7.8 msec. Spectral analysis of the dynamic series of *R-R* intervals was performed in the ranges of high-frequency (HF; 0.9-3.5 Hz), low-frequency (LF; 0.32-0.90 Hz), and very-low-frequency (VLF; 0.17-0.32 Hz) waves [4,5]. Absolute ($msec^2$) and relative (%) wave powers were calculated for each range. Centralization index (rel. units) was calculated by the formula: IC=(LF+VLF)/HF [1]. HRV parameters were evaluated in each animal initially, 1 h after the last administration of the substances affecting the central neurotransmitter system, 5-10 min after subsequent administration of hexamethonium and atropine, and 20 min after injection of serotonin and dopamine receptor blockers.

Statistical analysis of the results was performed using Student's t test and Statistica 10.0 software. The differences between the means were considered significant at $p<0.05$.

RESULTS

Stimulation of SS was followed by a significant increase in HR (by 30%, to 400-410 bpm under resting conditions, $p<0.001$; Table 1). SI increased by about 9 times ($p<0.001$) due to a decrease in the wave power of HRV spectrum in each range by 84-86% from the initial level ($p<0.001$). DS stimulation was also associated with an increase in HR, but only by 16.4% (to 350-370 bpm; $p<0.001$). Changes in the studied spectral parameters were opposite. The power of HF waves slightly decreased (by 34%), but the power of LF and VLF waves increased by 3.4 and 2 times, respectively ($p<0.05$). Centralization index increased by more than 2 times ($p<0.01$), and LF and VLF waves became prevalent in the spectrum (up to 43 and 35% of the total power, respectively). Thus, SS stimulation induced a total decrease in variability in all HRV spectrum ranges. DS stimulation was associated with specific changes in HRV spectrum (potentiation of VLF and particularly LF wave ranges) accompanied by an increase in HR.

In animals with SS stimulation, in contrast to controls, administration of hexamethonium did not change HR (390-420 bpm). However, rigidity of the heart rhythm tended to increase with decreasing wave power (by 3 times in the HF range, by 9 times in the LF range, and by 11 times in the VLF range, $p<0.01$-0.001) in comparison with the level after SS stimulation. Waves powers in the LF and VLF ranges decreased to 0.1 $msec^2$ and lower. Atropine administration did not increase HR after SS stimulation and even slightly reduced tachycardia (to 380-390 bpm), but heart rhythm became more rigid due to reduced variability in the LF and VLF ranges practically to 0 (Table 1). Slight tendency to increase in wave power was observed in HF range, and thus, the contribution of HF to the spectrum increased up to 80-85%.

In animals subjected to DS stimulation followed by administration of hexamethonium, HR decreased

TABLE 1. Dynamics of Changes in HRV Parameters in Outbred Rats Subjected to SS and DS Stimulation and Subsequent Administration of Hexamethonium and Atropine (*M*±*m*)

Parameter	Group	Initial value	During stimulation	After hexamethonium injection	After atropine injection
HR, bpm	Control	321.5±6.6	301.5±7.5	370.8±7.2^{ooo}	409.7±27.7^{***ooo}
	SS stimulation	308.7±7.3	403.8±7.6^{***+++}	393.8±15.8	381.3±20.1
	DS stimulation	309.6±5.3	360.5±11.7^{***+++}	322.0±15.8^{+}	456.5±9.4^{***ooo}
SI, rel. units	Control	30.2±5.8	36.3±9.4	94.9±16.7^{oo}	199.4±57.5^{***ooo}
	SS stimulation	27.7±3.7	246.5±32.9^{***+++}	272.0±50.5^{***++}	314.3±65.0***
	DS stimulation	37.7±6.3	50.5±8.7	97.2±20.7^{***o}	212.2±57.9^{***ooo}
HF, msec^2	Control	6.7±0.8	7.9±1.5	2.1±0.7^{**o}	0.6±0.2^{***o}
	SS stimulation	8,0±1.2	1.1±0.2^{***+++}	0.3±0.1^{***o+}	0.6±0.2***
	DS stimulation	6.8±1.5	4.5±0.8^{+}	0.7±0.1^{*o}	0.5±0.1^{*oo}
LF, msec^2	Control	6.6±0.9	5.2±2.7	0.4±0.1	0.2±0,1
	SS stimulation	5.7±0.8	0.9±0.3***	0.10±0.04^{***+}	0.08±0.02***
	DS stimulation	4.3±0.7	14.6±4.2*	0.7±0.2	0.6±0.2
VLF, msec^2	Control	5.9±0.9	2.9±0.8	0.4±0.2**	0.2±0.1**
	SS stimulation	4.9±0.6	0.8±0.3^{***+}	0.07±0.02^{***o}	0.03±0.01^{***o}
	DS stimulation	3.2±0.5	6.3±1.2^{*+}	0.30±0.07^{**oo}	0.2±0.1^{**oo}
Centralization index, rel. units	Control	2.3±0.4	1.0±0.2	0.6±0.2*	0.6±0.1*
	SS stimulation	1.8±0.2	1.3±0,3	0.7±0.2**	0.2±0.04^{***o}
	DS stimulation	1.9±0.2	4.1±0.7^{**+++}	1.4±0.4^{o}	0.6±0.2^{**o}
HF%	Control	38.8±4.4	64.3±7.4**	70.0±7.9**	64.9±4.9**
	SS stimulation	42.6±4.1	39.0±4.0	61.4±6.9*	85.5±3.0$^{***ooo++}$
	DS stimulation	40.5±2.9	25.8±2.5^{***+++}	46.0±6.3^{oo+}	65.7±7.0^{***ooo}
LF%	Control	31.0±2.9	30.7±4.2	12.3±2.2**	13.5±2.3**
	SS stimulation	29.9±2.4	32.5±2.7	19.6±3.1*	10.2±2.3^{***oo}
	DS stimulation	33.4±3.6	43.4±4.4^{+}	37.2±6.9^{+++}	23.0±4.8^{o}
VLF%	Control	30.2±3.4	18.8±4.7	17.7±6.7	21.6±3.7
	SS stimulation	28.7±2.4	28.6±3.1	19.0±5.8	4.3±0.8$^{***oo+++}$
	DS stimulation	29.3±3.1	35.8±3.1^{++}	19.2±3.3^{ooo}	11.3±3.0^{**ooo+}

Note. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$ in comparison with the initial level; $^{o}p<0.05$, $^{oo}p<0.01$, $^{ooo}p<0.001$ in comparison with the levels before SS and DS stimulation (in the control, during physiological saline administration); $^{+}p<0.05$, $^{++}p<0.01$, $^{+++}p<0.001$ in comparison with the corresponding control.

by 10% ($p<0.1$), but SI increased by ~2 times ($p<0.05$) due to reduction in the HF (by 85%, $p<0.05$), LF, and VLF wave powers (by 95%, $p<0.01$). Absolute wave power in each range was 1 msec^2 and lower, the lowest levels were typical of VLF waves (Table 1). Centralization index decreased by ~3 times ($p<0.05$). Subsequent administration of atropine induced a significant increase in HR (by 42%, $p<0.001$) and further increase in heart rhythm rigidity ($p<0.001$). The power of HRV waves tended to decrease in all ranges, but the absolute values remained at the level of 0.2-0.8 msec^2, and centralization index was <1 (Table 1).

After blockade of nicotinic and muscarinic cholinergic receptors, the differences in HRV parameters between the control and treatment groups practically disappeared. High HR and low power of HRV waves were revealed in all animals. The power of LF and VLF waves were minimum in the animals subjected to SS stimulation and maximum in rats with activated DS. Thus, successive blockade of nicotinic and muscarinic cholinergic receptors led to a significant decrease (up to disappearance) of HR variability. This effect was observed under the conditions of reduced (after SS stimulation) and enhanced (after DS stimulation) power of HRV waves. Thus, under conditions of altered monoamine metabolism at the central and peripheral levels [8,10,15], cholinergic system determined variability of cardiac intervals at

all ranges of HRV via nicotinic and muscarinic cholinergic receptors. These data are in line with previous reports [4,13]. The role of autonomic ganglia in transmission of information from the central regulation contour (catecholaminergic structures of the brain) to the heart was most pronounced during DS stimulation, because administration of nicotinic receptor blocker completely prevented enhancement of LF and VLF waves induced by L-DOPA and amantadine.

The administration of serotonin receptor blocker to the control group rats did not affect HR and power of HF waves, but slightly reduced the power of LF and VLF waves, centralization index, and led to prevalence of HF waves in the HRV spectrum ($p<0.05$; Table 2). Injection of serotonin receptor blocker to rats with stimulated SS was followed by a significant HR deceleration from 400 to 290-310 bpm (by 27%, $p<0.001$), and a slight decrease in SI, but the wave powers remained at the same low level as in animals with stimulated SS.

Administration of serotonin receptor blocker induced a significant increase in HR (by 31.5%, $p<0.001$), slight reduction in HF wave power, and pronounced increase in the intensity of LF and VLF waves (by 2.2 times, $p<0.05$ and by 3 times, $p<0.001$, respectively; Table 2) in control group rats. Centralization index increased by 8.4 times ($p<0.001$), which led to the prevalence of LF and VLF waves in the HRV

TABLE 2. Dynamics of Changes in HRV Parameters in Outbred Rats Subjected to SS and DS Stimulation after Blockade of Serotonin and Dopamine Receptors (*M*±*m*)

Parameter	Group	During stimulation (before blocker administration)	After blockade of serotonin receptors	After blockade of dopamine receptors
HR, bpm	Control	302.5±6.70	307.8±20.2	397.2±22.9***
	SS stimulation	403.8±7.60	293.3±15.9***	—
	DS stimulation	360.5±11.7^{++}	—	415.6±16.8
SI, rel. units	Control	34.3±4.20	33.6±3.6	30.7±4.50
	SS stimulation	246.5±32.9^{+++}	145.3±45.2^{+}	—
	DS stimulation	50.8±7.50	—	130.7±39.8^{+}
HF, msec^2	Control	10.4±2.80	10.9±1.8	2.5±0.4
	SS stimulation	1.1±0.2^{+++}	1.0±0.4^{+++}	—
	DS stimulation	4.3±0.8^{+}	—	0.8±0.2^{++}
LF, msec^2	Control	5,3±1,7	1.1±0.2	11.8±2.4*
	SS stimulation	0.9±0.3^{++}	0.5±0.2	—
	DS stimulation	12.6±3.8	—	2.5±0.8^{++}
VLF, msec^2	Control	3.0±0.6	1.3±0.2	9.2±1.5***
	SS stimulation	0.8±0.3^{++}	0.6±0.3	—
	DS stimulation	6.0±1.2	—	1.8±0.6^{+++}
Centralization index, rel. units	Control	0.8±0.2	0.3±0.1	6.7±1.2***
	SS stimulation	1.3±0.3	1.7±0.9	—
	DS stimulation	4.9±0.7^{+++}	—	6.8±2.3
HF%	Control	55.6±5.7	80.3±3.6*	14.7±5.7***
	SS stimulation	53.0±4.0	51.8±9.8^{+}	—
	DS stimulation	23.9±2.5^{+++}	—	19.4±4.6
LF%	Control	28.3±3.8	8.5±1.7**	45.2±9.4
	SS stimulation	25.5±2.7	20.6±4.0^{+}	—
	DS stimulation	44.6±4.1^{+}	—	42.8±7.0
VLF%	Control	16.0±3.0	11.2±2.2	40.0±10.1**
	SS stimulation	21.6±3.1	27.6±10.9	—
	DS stimulation	32.5±3.5^{++}	—	37.8±8.0

Note. *$p<0.05$, **$p<0.01$, ***$p<0.001$ in comparison with the levels before administration of the corresponding blockers; $^{+}p<0.05$, $^{++}p<0.01$, $^{+++}p<0.001$ in comparison with the corresponding control.

spectrum (up to 85% from the total power; $p<0.01$). Rats subjected to DS stimulation and injected with dopamine receptor blocker sulpiride demonstrated additional increase in HR by 15% (up to 450 bpm; $p<0.1$) and SI. Variability of cardiointervals was reduced for all frequency ranges: by 80% for HF, 70% for LF ($p<0.1$), and 38% for VLF in comparison with the levels during DSR activation. Thus, heart rhythm became very strained and centralization index remained at the high level similar to that observed after DS stimulation.

Comparison of the results showed certain antagonism in the effects of blockers of serotonin and dopamine receptors. In control rats, administration of serotonin receptor blocker did not affect HR, but slightly weaken LF and VLF waves, which can be considered as a sign of attenuation of sympathoadrenal innervation [1]. On the contrary, injection of dopamine receptor blocker was followed by potentiation of sympathoadrenal influences, which manifested in tachycardia and increased power of LF and VLF waves [1]. Promethazine administration against the background of SS stimulation led to a significant deceleration of HR, which promoted a decrease in SI. On the contrary, sulpiride injection against the background of DS stimulation increased HR and SI, but attenuated all HRV waves, which can be considered as the excessive enhancement of sympathoadrenal influences on the heart rhythm [1]. Thus, the blockers of peripheral serotonin and dopamine receptors have opposite effects on HR and HRV under normal conditions and after stimulation of the corresponding neurotransmitter systems.

These and previous results [1,9,13] suggest that pronounced decrease in HR and the power of all HRV waves during SS stimulation reflect generalized activation of the serotoninergic and adrenergic influences. The development of this "hypersympathization" of heart rhythm can be related to an increase in the concentrations of serotonin and catecholamines in the blood [13,15], direct effects of serotonin on cardiomyocytes via various types of 5-HT receptors [7,9,13], enlarged catecholamine depots due to uptake of serotonin and norepinephrine by sympathetic terminals [8,9], and inhibitory effects of serotonin on acetylcholine release from cholinergic terminals in the myocardium [6,7]. Moreover, stable BP decrease observed under conditions of high blood serotonin concentrations significantly contributed to the changes in HR and HRV [9,12]. The increase in LF and VLF wave power and moderate tachycardia after administration of L-DOPA and amantadine can be considered as signs of moderate activation of central catecholaminergic mechanisms [1]. This suggestion is in line with previous results [5,10] and the data on the role of DS in the regulation of hemodynamic center in the brain [14]. Stimulation of SS induces excessive, and stimulation of DS — moderate activation of sympathetic influences on the heart rhythm.

The blockade of autonomic nervous system ganglia with hexamethonium and following atropine administration did not affect HRV changes induced by SS stimulation. HR remained high and wave power (particularly LF and VLF waves) remained low. We believe that the humoral pathway of regulation plays an important role in the alteration of HRV during SS activation. Fluoxetine administration increased the concentration of serotonin and catecholamines in the blood [13,15] allowing local effects of serotonin on cardiomyocytes and autonomic nervous system terminals via various types of 5-HT receptors [6-9,11]. After DS activation, the increase in HR and power of low frequency HRV waves was attenuated by the blockade of nicotinic receptors of the autonomic nervous system ganglia. These data indicate the crucial role of the sympathetic regulation in the changes of HRV during the activation of monoaminergic systems by L-DOPA and amantadine. The experiments with hexamethonium and atropine showed that the transmission of signals via nicotinic and muscarinic cholinergic receptors during the activation of monoaminergic systems and enhanced monoamine metabolism determines the forming of lower and higher variability of cardiac intervals at all wave frequencies of HRV, which corresponds to previous data [4,13]. The administration of the blocker of nicotinic receptors allowed to show that the specific changes in HRV during DS stimulation are mostly mediated by autonomic nervous system ganglia. Generalized alterations of HRV during SS stimulation might be determined by humoral and neuronal, local and systemic mechanisms of regulation.

Administration of serotonin receptor blocker immediately attenuated tachycardia induced by SS stimulation. Thus, the increase in HR under these conditions is mediated by the effects of serotonin via 5-HT receptors, which are blocked by promethazine. These receptors can be localized on pacemaker cells [7,8], as well as cholinergic and adrenergic nerve terminals in the myocardium [6,9]. Stability of low frequency HRV waves after serotonin receptor blocker administration also reflects the involvement of other types of 5-HT receptors and adrenergic mechanisms of forming of heart rhythm rigidity during SS activation. The absence of pronounced effects of serotonin receptor blocker on HRV in control animals can be explained by the fact that under normal conditions serotonin modulates the effects of catecholamines and their release from the terminals and that the effects of serotonin depend on its level in the area of 5-HT receptors [6,7,9,11].

In contrast to serotonin receptor blockade, administration of dopamine receptor blocker induced a

significant increase in HR and power of LF and VLF waves of HRV. Under the conditions of DS stimulation, sulpiride promoted further increase in HR and rigidity of the heart rhythm, and significantly reduced the power of LF, VLF, and even HF waves. Probably, blockade of D_2 receptors by sulpiride potentiated an enhancement in adrenergic innervation by the inhibitory effects of dopamine on norepinephrine release from the sympathetic terminals [2,6] and enhancement of dopamine effects on the myocardium via other types of D receptors [3]. The activation of catecholamine-mediated mechanisms by the administration of L-DOPA and amantadine is followed by a severe rise in sympathoadrenal influence. Thus, all specific changes in HRV transform into non-specific pronounced rigidity. Altogether, we observed antagonism of blockers of serotonin and dopamine receptor. Blockade of serotonin receptors promotes moderate attenuation of sympathoadrenal regulation, while blockers of dopamine receptors potentiate it, which manifested in excessive influence of sympathetic system on the heart rhythm under conditions of DS stimulation.

Therefore, the observed changes in HR and HRV indicate that SS induces excessive activation of sympathoadrenal regulation via humoral and neural mechanisms. DS stimulation is followed by moderate activation of the sympathetic effects on the chronotropic heart function. Cholinergic mechanisms maintain the certain level of variability of cardiointervals at all HRV frequencies. Opposite effects on adrenergic influences were observed after administration of blockers of peripheral receptors of serotonin (mild suppression) and dopamine (potentiation). Bearing in mind published data, we hypothesize that serotoninergic and dopaminergic mechanisms of heart rhythm regulation are mediated via receptor systems in cardiomyocytes and via modulation of adrenergic (probably, cholinergic) mechanisms at the level of autonomic nervous system ganglia, synaptic terminals, and signal cascades in myocardial cells. Central serotoninergic and dopaminergic systems similarly affect the heart rhythm, but have opposite effects at the peripheral level.

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