Role of the Rostroventrolateral Medulla in Moxonidine-Induced Changes in Cardiochronotropic Regulation

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The cardiac component of baroreflex and sympathetic tone of the heart were studied in SHR-SP rats receiving moxonidine intragastrically or into the rostroventrolateral medulla. Moxonidine administered intragastrically in a dose of 10 mg/kg had no effect on cardiac sympathetic tone, but reduced the intracardiac rhythm and enhanced baroreflex bradycardia. Local injection of moxonidine into the rostroventrolateral medulla decreased cardiac sympathetic tone, but did not change the amplitude of baroreflex chronotropic responses. Our results indicate that changes in cardiochronotropic regulation after systemic administration of moxonidine are not mediated by the rostroventrolateral zone of the medulla oblongata.

Key Words: *moxonidine; sympathetic tone; baroreflex; rostroventrolateral medulla*

Hypotensive effect of a new preparation moxonidine is realized through I_1-imidazoline receptors in the rostroventrolateral medulla (RVLM) [3,6]. First-generation drugs, whose action is mediated via the central nervous system, interact with α-adrenoceptors in the solitary tract and accentuate the baroreflex response [5,8]. It remains unclear whether moxonidine causes similar changes. This would characterize the selectivity of moxonidine for I_1-imidazoline receptors in RVLM. Here we studied the effect of systemic administration of moxonidine on autonomic cardiochronotropic regulation and evaluated the role of RVLM in this process.

MATERIALS AND METHODS

Experiments were performed on 6-7-month-old spontaneously hypertensive stroke-predisposed male rats (SHR-SP).

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In series I we studied the cardiochronotropic component of baroreflex and sympathetic tone of the heart in awake SHR-SP rats. Moxonidine (10 mg/kg, Farmzashchita) was administered through a gastric tube. Control animals received distilled water (1 ml/kg). In series II cardiochronotropic baroreflex and sympathetic tone of the heart were examined after unilateral injection of 4 nmol moxonidine into RVLM. The rats were intraperitoneally narcotized with 1.5 g/kg urethane. Control animals received 0.5 μl Ringer solution.

Blood pressure (BP) was measured using a catheter inserted into the femoral vein and connected to a SR-01 electromanometer. Test preparations were administered through the catheter to evaluate the cardiochronotropic baroreflex and sympathetic tone of the heart.

Baroreflex was studied by recording heart rate (HR) variability in response to changes in mean BP induced by intravenous injection of nitroprusside and phenylephrine hydrochloride in increasing doses (0.5-25.0 and 0.5-10.0 μg/kg, respectively, Sigma). The mean BP-HR curve was subjected to logarithmic approximation using Graph PadPrizm 3.0 software [7]. The following parameters of baroreflex were estimated: mean BP mode (MBP_{50}), plateau of tachycardia (TC) and bradycardia (BC), total amplitude of the

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reflex response (ΔHR), and amplitudes of sympathetic (ΔTC) and parasympathetic reactions (ΔBC). The absolute maximum of the first derivative of the approximated curve served as the measure of baroreflex sensitivity.

Cardiac sympathetic tone was evaluated as changes in HR (HR_M) after atropine-induced muscarinic cholinoceptor blockade (1 mg/kg, Sigma) compared to the intracardiac rhythm (HR_1) during parasympathetic and sympathetic blockade with atropine and β_1-receptor blocker atenolol (2 mg/kg, Sigma).

Microinjections into RVLM were performed stereotaxically using glass capillaries with pulled narrow tips (diameter 25-30 μ) introduced according to stereotaxic coordinates of this brain area [9]. Proper localization of the capillaries was confirmed by physiological test (hypertensive reactions to 2 nmol L-glutamate, Fluka,) and histological (neutral red spot in RVLM, 0.1 μl 2% solution, Sigma) tests. Cryostat sections of the medulla oblongata were examined (-2.70-3.80 mm from the interauricular line).

The results were analyzed by pairwise and nonpairwise Student's *t* test. The differences were significant at $p<0.05$.

RESULTS

Three hours after intragastric administration of moxonidine MPB and HR decreased by 16±4 and 7±2%, respectively (Table 1).

We observed a shift in the baroreflex curve due to a decrease in MPB_{50} and BC and TC plateaus (Table 2). The total amplitude of reflex chronotropic responses remained unchanged, because of simultaneous inhibition of sympathetic (ΔTC) and activation of parasympathetic responses (ΔBC). Moxonidine had no effect on cardiac sympathetic tone, but decreased HR_1 by 13±3% compared to the control (Table 2).

Thirty minutes after administration of moxonidine into RVLM, MPB and HR decreased by 16±5 and 13±4%, respectively (Table 1). A shift in the baroreflex curve was manifested in a decrease in MPB_{50} and BC and TC plateaus (Fig. 1, *b*). Moxonidine did not change the baroreflex sensitivity and sympathetic and parasympathetic responses, but decreased cardiac sympathetic tone (Table 2).

Our results indicate that RVLM is involved in the regulation of cardiotonic sympathetic, but not vagal baroreflex responses. The activation of cardiac para-

TABLE 1. Effect of Moxonidine on MPB and HR in SHR-SP Rats (*M*±*m*, *n*=7-8)

Parameter		Intragastric treatment		Injection into RVLM	
		control	experiment	control	experiment
MPB, mm Hg	initial	181±4	184±2	186±3	196±4
	after treatment	181±3	155±6*+	191±4	165±8*+
HR, bpm	initial	264±5	265±5	308±5	298±9
	after treatment	262±2	246±6*+	309±7	259±11*+

Note. $p<0.05$: *compared to the baseline level, +compared to the control.

TABLE 2. Effect of Moxonidine on Baroreflex and Cardiac Sympathetic Tone in SHR-SP Rats (*M*±7*m*, *n*=8)

Parameter	Intragastric treatment		Injection into RVLM	
	control	experiment	control	experiment
MPB_{50}, mm Hg	177±3	156±7*	191±5	143±5*
BC plateau, bpm	224±8	182±10*	301±11	223±8*
TC plateau, bpm	365±13	296±13*	364±13	304±10*
ΔHR, bpm	141±11	114±12	64±9	81±4
ΔBC, bpm	-42±4	-64±6*	-25±6	-29±3
ΔTC, bpm	99±11	50±8*	39±5	52±3
BRS_{max}	-1.01±0.14	-0.84±0.06	-1.14±0.21	-1.03±0.07
HR_1, bpm	300±2	262±6*	262±7	253±6
HR_M, bpm	348±5	307±8*	347±11	316±8*
ST, bpm	47±4	43±5	86±7	63±6*

Note. BRS_{max}: maximum baroreflex sensitivity. ST: sympathetic tone. *$p<0.05$ compared to the control.

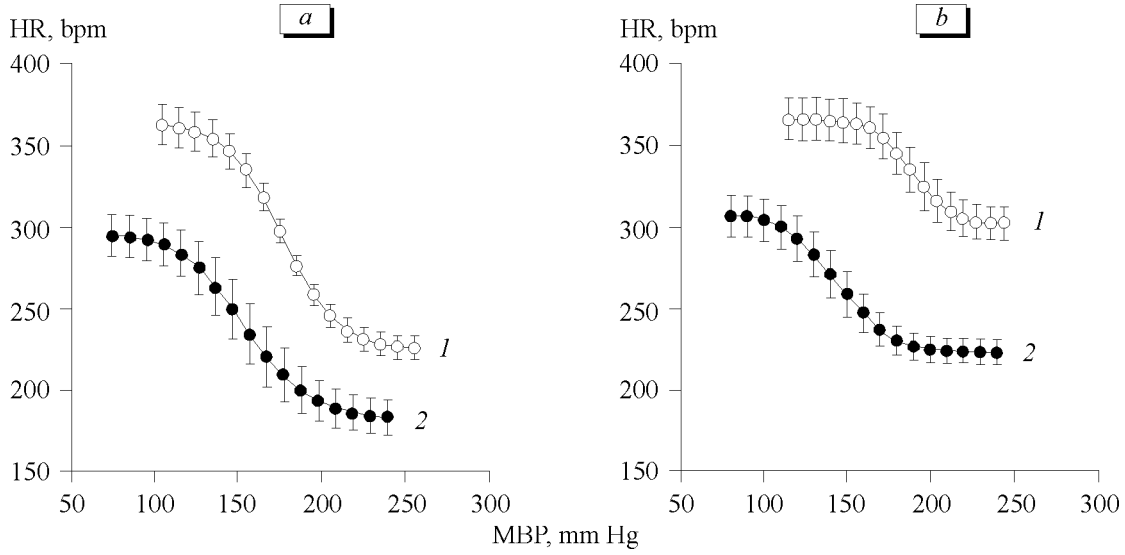

Fig. 1. Baroreflex curves reflecting the dependence of HR on mean blood pressure (MPB) in SHR-SP rats receiving moxonidine intragastrically (*a*) or into the rostroventrolateral medulla (*b*). Baroreflex parameters are shown in Table 2. *1*) control and *2*) moxonidine.

sympathetic reflex responses after intragastric administration of moxonidine is probably realized via nuclei of the solitary tract, whose α_2-adrenoceptors mediate the effects of first-generation preparations with central activity [5,8]. Previous studies showed that intracerebroventricular injection of rilmenidine, but not clonidine, reduces reflex TC in rabbits (similarly to intragastric administration of moxonidine) [4]. Rilmenidine possesses high selectivity for I_1-imidazoline receptors. It was hypothesized that the effects of this preparation are realized via I_1-imidazoline receptors, but not via α_2-adrenoceptors. However, in our experiments administration of moxonidine into RVLM did not inhibit sympathetic reflex responses of the heart. Hence this area of the medulla oblongata is not involved in the realization of moxonidine-induced changes.

It should be emphasized that HR_1 decreased after intragastric administration of moxonidine. This can be explained by decreased plasma catecholamine concentration and indirect deceleration of diastolic pacemaker depolarization. Previous studies showed that catecholamines affect the rate of diastolic depolarization and shift the curve reflecting activation of hyperpolarization-dependent channels towards more positive voltage [1]. Intragastric and central administration of moxonidine into RVLM produced similar changes in the amplitude of hypotensive reactions. However, HR_1 did not decrease after moxonidine injection into RVLM (as differentiated from intragastric treatment). Therefore, this effect of moxonidine is associated with its peripheral activity. Published data show that systemic administration of moxonidine inhibits the sympathetic system not only via central, but also via peripheral adrenergic endings and adrenal medulla [2,10]. The moxonidine-induced decrease in plasma catecholamine level and reduction of HR_1 are probably mediated by peripheral mechanisms.

Our results indicate that changes in cardiochronotropic regulation after intragastric administration of moxonidine to SHR-SP rats are not realized via RVLM.

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