Synergistic Effect of Serotoninergic and Cholinergic Nerve Fibers

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 132, No. 12, pp. 624-626, December, 2001
Original article submitted July 31, 2001

The mechanisms of interactions between various compartments of the autonomic nervous system were evaluated by studying sympathetic potentiation of vagal cardioinhibitory action. It was found that this effect is realized through preganglionic serotoninergic nerve fibers making synaptic contacts with intracardiac serotoninergic neurons. Our results indicate that cardiac activity is modulated by the vagus nerve and serotoninergic nerve fibers of the sympathetic nerve acting synergistically.

Key Words: *serotonin; heart; regulation*

Autonomic regulation of internal organs still attracts much attention. Little is known about the mechanisms of synergistic interaction between the sympathetic and parasympathetic nervous systems under normal and pathological conditions.

Previous studies showed that the vagus (VN) and sympathetic nerves produce opposite effects on internal organs. However, the integral effect of these two systems on the organism is often synergistic. Activation of the sympathetic nervous system during physical exercise is accompanied by stimulation of cardiac activity and inhibition of gastrointestinal functions. A decrease in the vagal tone is followed by opposite changes in cardiac and gastrointestinal activity, which is of great biological importance. Stimulation of a sympathetic nerve stimulates or suppresses activity of internal organs [8-10,12,14]. Previous studies showed that weak stimulation of rat sympathetic nerve between the stellate ganglion (SG) and heart inhibits cardiac activity, moderate stimulation does not modulate cardiac functions, while strong stimulation produces a sympathetic effect (increase in heart rate, HR) [9,10].

Stimulation of VN also produced dual changes [1,10]. Stimulation of cervical VN in cats and dogs not only activated, but also inhibited motor functions of the small intestine [5]. The inhibitory effect was abolished after blockade of abdominal nerves and, therefore, resulted from the stimulation of sympathetic fibers in thoracic and subdiaphragmatic VN. These data indicate that the synergistic effect of sympathetic and parasympathetic nervous systems is manifested in the regulation of functions of the same organs. For example, the inhibitory effect of VN on cardiac activity can be augmented by stimulation of the sympathetic nerve [4,13-15]. However, the mechanisms of this phenomenon remain unclear.

Published data show that not only catecholamines and acetylcholine, but also purines [6] and serotonin (5-hydroxytryptamine, 5-HT) are released from sympathetic and parasympathetic nerve endings. These bioactive substances are involved in the mechanisms of synergism between various compartments of the autonomic nervous system. Here we studied the mechanisms underlying synergistic effects of the sympathetic and parasympathetic nervous systems in the regulation of cardiac activity.

MATERIALS AND METHODS

Acute and chronic experiments were performed on 66 rabbits. Right VN was transected 1.5-3 weeks before acute experiments to prevent possible

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0007-4888/01/1326-1147$25.00

stimulation of the parasympathetic nerve with current loops formed during treatment of the sympathetic nerve.

In series I (n=18), the regulation of cardiac activity was studied by recording the impedance cardiogram of contracting myocardium, blood pressure (BP) in the right common carotid artery, and pressure and its first derivative in the left ventricle were reordered with a probe introduced into the left common carotid artery. The animals fixed on a heated table were ventilated using an AID-3 device. After thoracotomy the pericardium was removed, and the heart was washed with warm Ringer solution. Experiments were performed in the surgical stage of narcoses with urethane, hexenal, sodium thiopental, and nembutal (individual or combined treatment). During simultaneous stimulation, SG was stimulated 5-10 sec after the start of VN stimulation, after attaining a stable decrease in HR. VN and SG were stimulated for 40-60 and 10-20 sec, respectively, at 10-20-min intervals. Control stimulations of VN and SG were performed at 1-10-min intervals. SG and VN were stimulated with rectangular pulses (10-20 Hz, 1.5-3.0 msec; current amplitudes 5-15 and 1-7 V, respectively). Stimulation of VN and SG was performed at the level of C_V and first rib, respectively.

In series II, the neurotransmitter mediating the chronotropic effects was identified using dihydroergotoxin (0.1 mg/kg, n=7) and phentolamine (5-10 mg/kg, n=7, individual or combined treatment), rausedyl (2.0-2.5 mg/kg, n=9), lysergic acid (LSD, 0.01-0.03 mg/kg, n=8) blocking 5-HT1 and 5-HT2 receptors, and morphine (0.1-0.2 mg/kg, n=10) blocking 5-HT3 receptors.

The results were analyzed by Student's t test.

RESULTS

In series I we observed sympathetic potentiation of the vagal cardioinhibitory action under conditions of β-adrenoceptors blockade with obsidan (Fig. 1).

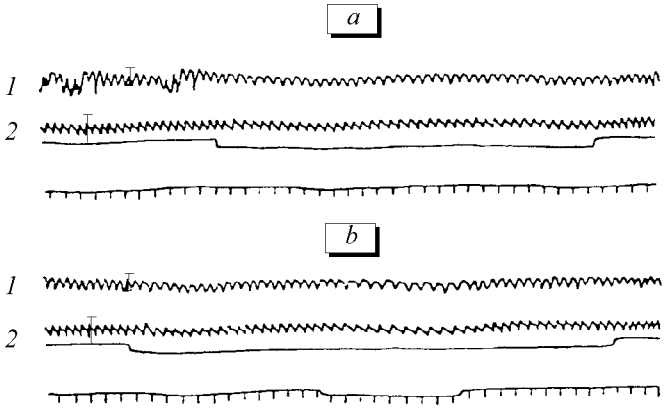

Fig. 1. Negative chronotropic effect of vagal stimulation (*a*); potentiation of vagal cardioinhibitory action during simultaneous stimulation of the stellate ganglion and left vagus nerve (*b*). *1*) impedance cardiogram; *2*) blood pressure.

During sympathetic potentiation of the vagal negative chronotropic action systolic, diastolic, and pulse BP did not differ from those observed during VN stimulation (Table 1).

Thus, BP remained practically unchanged during sympathetic potentiation of the vagal negative chronotropic effect.

We recorded impedance cardiogram and its waves in the myocardium of the left ventricle anterior wall to evaluate changes in myocardial contractility during various phases of the cardiac cycle.

Parameters of impedance cardiogram reflecting the strength of cardiac contractions changed insignificantly (Table 1).

Individual and combined treatment with dihydroergotoxin and phentolamine did not block these changes. Our results contradict published data on the role of α-adrenoceptors in this phenomenon [1] probably due to species- and age-related differences between experimental animals (previous studies were performed on newborn dogs).

Pretreatment with high doses of rausedyl depleting catecholamine stores and attenuating the sympathetic effect abolished potentiation of the vagal cardio-

TABLE 1. Changes in BP (mm Hg) and Amplitude of Impedance Cardiogram Waves (Ω) of the Left Ventricle Anterior Wall during VN and SG Stimulation ($M \pm m$)

Parameter		Baseline level	VN stimulation	
			without SG stimulation	+SG stimulation
BP	systolic	78.0±76.0	75.0±6.5	72.0±5.2
	diastolic	44.0±4.5	38.0±4.0	37.0±3.4
	pulse	34.0±3.8	37.0±4.5	35.0±4.1
Waves	αβ	5.1±0.6	6.1±0.7	5.3±0.7
	βγ	7.4±0.6	8.3±0.7	8.3±0.7
	βE	11.3±1.0	11.1±1.0	11.8±0.7

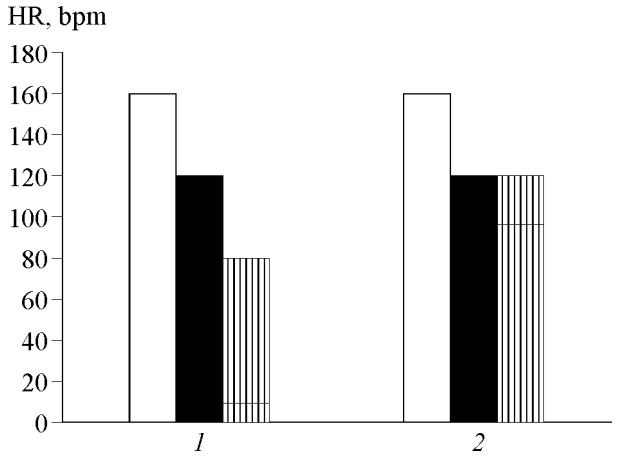

Fig. 2. HR in rabbits before (light bars) and after vagal stimulation (dark bars) and during simultaneous stimulation of the stellate ganglion and vagus nerve (hatched bars). *1*) potentiation of vagal cardioinhibitory action, *2*) treatment with lysergic acid (blockade of the inhibitory effect).

inhibitory action. This was probably related to antiserotonin and other activities of rausedyl. 5-HT administered into the left ventricle and coronary vessels in doses of 3-6 and 0.2-0.6 mg/kg, respectively, caused bradycardia and hypotension. This reaction was observed 2-3 sec after treatment with 5-HT [8]. 5-HT decreases HR in cats and dogs [2,7]. The effects of 5-HT on the heart are probably realized through specific receptors.

LSD blocked sympathetic potentiation of vagal cardioinhibitory action (Fig. 2). It should be emphasized that in our experiments LSD was used in low doses. This indicates high sensitivity of the studied structures to LSD.

Morphine abolished sympathetic potentiation of vagal cardioinhibitory action, which indicates that 5-HT3 receptors play an important role in the realization of this phenomenon.

Our results indicate that potentiation of vagal cardioinhibitory action during SG stimulation involves preganglionic serotoninergic fibers making synaptic contacts with intramural serotoninergic neurons. Therefore, serotoninergic and cholinergic nerve fibers synergistically modulate cardiac activity.

Thus, serotoninergic structures are involved in sympathetic potentiation of vagal cardioinhibitory action. These results are consistent with published data that dog thoracic sympathetic pathway includes serotoninergic nerve fibers stimulating contractions of the gastrointestinal tract [3].

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