Balance of Activity of Sympathetic, Parasympathetic, and Serotoninergic Divisions of the Autonomic Nervous System in Rabbits

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We studied the balance of activity of sympathetic, parasympathetic, and serotoninergic divisions of the autonomic nervous system in the regulation of the heart function in rabbits. High activities of the sympathetic and parasympathetic system are associated with antagonistic interactions between them. Moderation of activity of these systems could be accompanied by activation of the serotoninergic system. Physiological sympathectomy and parasympathectomy lead to hyperfunction of the serotoninergic system and pathology.

Key Words: *activity of sympathetic, parasympathetic system and serotoninergic system; pathology*

Similar effects of different compartment of the autonomic nervous system on the functions of visceral organs are observed during weak stimulation of the vagus and sympathetic nerves [4]. They can result from activation of adrenoceptors in nervous terminals and cardiomyocytes with modulation of ganglionic excitability [9] and involvement of serotoninergic structures [2,7] in addition to acetylcholine and catecholamines [5,8].

Aging is accompanied by moderation of activity of the sympathetic [6] and parasympathetic [3] nervous systems. Our aim was to reveal the role of age-related alterations in changes in the balance between subdivisions of the autonomic nervous system.

MATERIALS AND METHODS

The experiments were carried out on nembutal-narcotized (40 mg/kg) rabbits of two age groups: 4-5 months (<3 kg) and 6-12 months (3-6 kg). In the study of the vagosympathetic balance in heart control, we recorded blood pressure in the right carotid artery and myocardial impedance of anterior wall of the left ventricle [1].

Cardiac parameters were recorded using an UBP-2-03 biopotential amplifier, an EMT-35 pressure transducer, and an H327-5 recorder.

The peripheral stump of the vagus nerve was stimulated with voltage pulses (1-7 V amplitude, 2 msec pulse duration, 10 Hz repetition rate). The peripheral stump of the sympathetic trunk was stimulated at the level of 4-5 cervical vertebrae, and the stellate ganglion was pulsed at the level of the first rib (5-15 V amplitude, 2 msec pulse duration, 10 Hz repetition rate).

Testing of the transmitter nature of the examined effects was performed using sympatholytic rausedyl in low (1 mg/kg), medium (1.5 mg/kg), and high (2.0-2.5 mg/kg) doses, β-adrenoceptor blocker Inderal or propranolol (0.5-5.0 mg/kg), presynaptic sympatholytic bretylium tosylate (10-20 mg/kg), and serotonin receptor blockers of ganglionic (morphine and droperidol) and peripheral (lysergic acid, sumatriptan, and spiperone) action.

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RESULTS

In 16 experiments on rabbits stimulation of the vagus nerve and stellate ganglion were conducted after careful preparation of the nerves for evaluation of their functional potency.

In 4-5-month rabbits, stimulation of the stellate ganglion produced positive chrono- and inotropic effects: HR increased from 231.3±6.0 to 268±11.3 bpm (p<0.02). When stimulation of the stellate ganglion was added to vagal stimulation, the negative chronotropic effect of vagal stimulation decreased in group 1 rats from 186.2±12.0 to 218.7±14.1 bpm. Therefore, functional activity of the sympathetic nervous system in young rabbits prevents the appearance of synergic effects of two major branches of the autonomic nervous system.

The codirected inhibitory influence of the subdivisions of the autonomic nervous system in young rabbits were observed only under the blockade of β-adrenoceptors by Inderal or propranolol. These drugs decreased the baseline HR to 170.8±5.8 bpm, while stellate stimulation exerted virtually no effect on HR, which remained 170.8±6.2 bpm. Addition of stellate ganglion stimulation to vagal stimulation under conditions of β-adrenoceptor blockade potentiated the stimulatory vagal effects and produced an additional drop in HR by 7-11%.

In most rabbits of the elder group, stimulation of the stellate ganglion produced no positive ino- or chronotropic effects: HR was 218.4±12.3 bpm before and during stimulation. Vagal stimulation produced a negative chronotropic effect (HR decreased to 174.0±6.7 bpm, 20.3%, p<0.05). The supplementary stellate ganglion stimulation potentiated the negative chronotropic effect: HR decreased to 153.4±5.7 bpm(11.8%, p<0.05).

Therefore, in elder rabbits the phenomenon of codirected inhibitory influence of both branches of the autonomic nervous system was revealed under conditions of initially low functional activity of the sympathetic nervous system. In younger rabbits, this phenomenon was observed only under conditions of β-adrenoceptor blockade in cardiomyocytes.

Injections of benzohexonium, promedol, and morphine completely blocked the examined phenomenon (Fig. 1). Therefore, it is mediated via ganglionic structures carrying nicotinic cholinoceptors, 5-$HT_{3,4}$-, and 5-$HT_{1,2}$ receptors (Fig. 2).

In young rabbits with high functional activity of the sympathetic and parasympathetic systems, activity of the serotoninergic system was low, and it was revealed only during blockade of β-adrenoceptors. Probably, this activity played a role of a "functional reserve". In elder rabbits, whose sympathetic tone was markedly lower and who demonstrated signs of decreased parasympathetic activity, activity of the serotoninergic system increased, and it produced a synergistic effect on the heart.

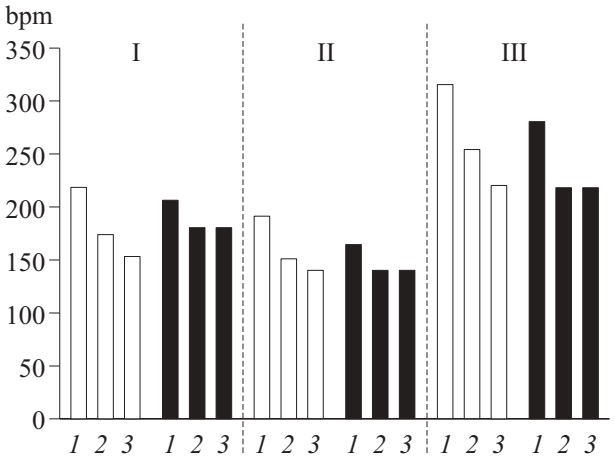

Fig. 1. HR before stimulation (*1*), during vagal stimulation (*2*), during combined stimulation of vagus nerve and stellate ganglion (*3*) before (light bars) and after (dark bars) application of nicotinic cholinoceptor blocker (I) and 5-$HT_{3,4}$-blockers promedol (II) and morphine (III).

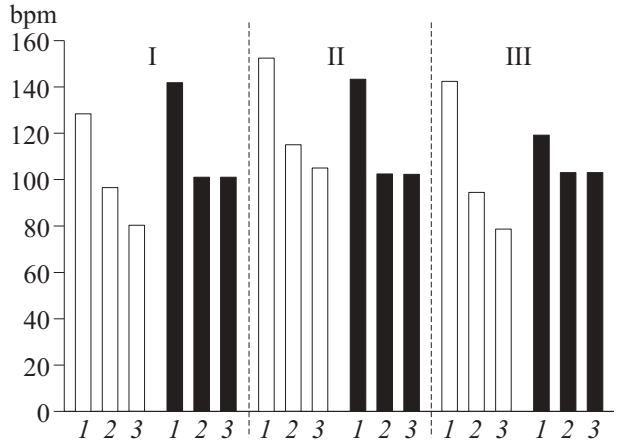

Fig. 2. HR before stimulation (*1*), during vagal stimulation (*2*), during combined stimulation of vagus nerve and stellate ganglion (*3*) before (light bars) and after (dark bars) application of aminazine (I), lysergic acid (II), and sumatriptan (III).

These findings confirm an important role of the serotoninergic system in the regulation of cardiac activity in aging organism. This point is further corroborated by the experiments with successive pharmacological blockade of the sympathetic and parasympathetic systems with various doses of rausedyl (reserpine).

Injection of reserpine in low and medium doses gradually decreased the content of catecholamines in sympathetic terminals in young rabbits. In rabbits preliminary treated with reserpine, the baseline HR was 138.8±11.4 bpm and remained unchanged

during stimulation of the stellate ganglion. Vagal stimulation decreased HR to 100.5±5.2 bpm (27.6%, $p<0.05$), and the supplementary stellate stimulation potentiated vagal negative chronotropic effect by further decreasing HR to 89.7±4.6 bpm (10.7%, $p<0.05$).

The data of this series showed that in young rabbits pharmacological blockade of the sympathetic system or block of β-adrenoceptors activated the serotoninergic system, but the influence of this system was not profound (7-14%).

The high doses of reserpine led to bradycardia (HR=113.0±4.3 bpm). As in the previous series of experiments, stimulation of the stellate ganglion produced no effect on the baseline HR. Addition of sympathetic stimulation to the vagal one resulted in a negative chronotropic effect: HR decreased to 95.3±2.4 bpm (15.6%, $p<0.05$). Further supplementary stimulation of the stellate ganglion had no effect on HR.

This series of experiments showed that high doses of rausedyl prevented the development of the examined phenomenon, which can be related to catecholamine depletion not only in the labile pool (which is caused by low and medium doses of rausedyl), but also in their stable pool. In addition, rausedyl could decrease the content of serotonin in the corresponding nerve terminals.

Rausedyl treatment is a peculiar model of aging: low and medium doses of this agent reversibly deplete the labile pool of catecholamines, but preserve functional activity of the parasympathetic and serotoninergic systems. The smaller the store of catecholamines in the labile pool of the sympathetic system, the greater is functional activity of serotoninergic system.

By inhibiting the release of catecholamines from the labile and stable pools of sympathetic nervous system and by moderation of serotonin release from serotoninergic terminals, high doses of rausedyl disturb the balance between the branches of the autonomic system resulting in predominance of the parasympathetic system. Analysis of changes in vagal chronotropic effect during gradual increase of rausedyl dose revealed not only proportional inhibition of the sympathetic and then serotoninergic systems, but also a certain decrease in parasympathetic activity. Injection of high doses of rausedyl led to gradual degradation of the regulatory potency of the autonomic nervous system and death of experimental animals.

Individual activation of serotoninergic system provoked the development of cardiac pathology in the form of myocardial dystrophy or myocarditis

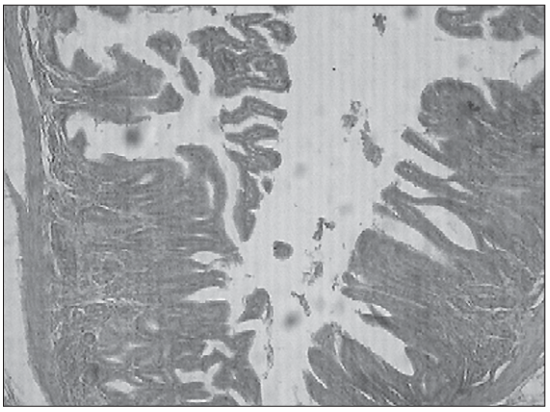

Fig. 3. Loosening of myocardial muscle fibers by hydropic fluid during hyperserotoninemia. Staining with hematoxylin and eosin, ×140.

(Fig. 3). Overstimulation of serotoninergic nerve fibers in the sympathetic trunk under conditions of β-adrenoceptor blockade resulted in loosening of myocardial muscle fibers by hydropic fluid, which disturbed the contractile function of the myocardium and led to myocardial dystrophy (Fig. 3).

Thus, young animals demonstrated predominance of sympathetic and parasympathetic activities. In aging animals, activity of the sympathetic system gradually decreased, while activity of the serotoninergic system relatively increases. Overstimulation of the serotoninergic system leads to pathology, specifically to myocardial dystrophy.

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