Serotoninergic Nervous System in Intact Heart and Abdominal Organs

A. E. Lychkova

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 138, No. 8, pp. 148-151, August, 2004
Original article submitted December 12, 2003

The participation of serotoninergic nervous system in the synergistic inhibitory effect of different subdivisions of the autonomic nervous system on the heart and their stimulatory effect on smooth muscle organs of the biliary excretion system, stomach, and small intestine were studied on rabbits under normal conditions.

Key Words: *serotoninergic nervous system; heart; biliary excretion system; stomach; small intestine*

The sympathetic and parasympathetic nervous systems can exert synergistic effects on the function of visceral organs. In addition to acetylcholine, epinephrine, and norepinephrine, a certain mediatory role in the potentiation of cardiotropic vagal inhibition observed during stimulation of the stellate cervical ganglion can be played by other biolactive agents such as ATP with its derivatives, 5-hydroxytryptamine (5-HT), and dopamine [1-3].

In addition to parasympathetic nervous system, the serotoninergic system is involved in the stimulation of gastrointestinal motility. 5-HT was found in both the vagus nerve (VN) and sympathetic trunks, which implies participation of this transmitter in the synergic action of various parts of the autonomic nervous system on visceral organs.

Our aim was to study serotoninergic innervation of visceral organs under normal physiological conditions.

MATERIALS AND METHODS

Acute experiments were carried out on Chinchilla rabbits (n=53) under Nembutal anesthesia. Cardiac activity was studied in experiments with electrical stimulation of the left peripheral stump of VN and right stellate ganglion (series I), while function of abdominal smooth muscle organs was studied in experiments with electrical stimulation of the right peripheral stump of VN and left sympathetic trunk (series II-IV). The parameters of electrical pulses were 1.5-15 V amplitude, 2 msec duration, and 10 Hz repetition rate. When studying the mechanisms underlying the synergistic stimulatory effects of sympathetic and parasympathetic nervous systems on electromotor activity (EMA) in abdominal smooth muscle organs, bipolar platinum electrodes with tip diameter 0.3 mm and interelectrode distance 1.5 mm were used. Slow waves (SW) of EMA and fast summational potentials were recorded; the amplitude and frequency of the latter were expressed in mV and number per 100 SW. EMA stimulation was evaluated by the increase in amplitude and frequency of SW and by the rise of amplitude and incidence of summation action potentials.

The $5\text{-HT}_{1,2}$ receptors were blocked with aminazine (0.1-1.0 mg/kg), promethazine (1-2 mg/kg), lysergic acid (0.01-0.03 mg/kg), and sumatriptan (0.5-1.0 mg/kg). Nicotinic cholinergic receptors of autonomic ganglia were blocked with benzohexonium (0.7-1.0 mg/kg). Ganglionic $5\text{-HT}_{3,4}$ receptors were blocked with morphine (0.1-0.2 mg/kg), promedol (1-2 mg/kg), and droperidol (0.5-1.0 mg/kg).

The results were analyzed statistically using Student's t test.

RESULTS

In series I, potentiation of vagal inhibition of cardiac activity after stimulation of the sympathetic nerve

Central Research Institute of Gastroenterology, Moscow

0007-4888/04/1382-0127

under conditions of propranolol blockade of β-adrenoceptors was observed in 70% young rabbits and 80% adult animals (Fig. 1). The degree of the examined synergistic effect of stimulation of VN and stellate ganglion was 7-14% and 10-24% in young and adult rabbits, respectively.

Possible involvement of myocardial 5-$HT_{1,2}$ receptors into potentiation of vagal negative chronotropic effect during stimulation of the stellate ganglion was tested. All preparations (aminazine, promethazine, lysergic acid, and sumatriptan) blocked the examined effect. The most specific blocker lysergic acid was effective in very low doses, which attests to high sensitivity of the examined structures to this agent. Therefore, myocardial 5-$HT_{1,2}$ receptors are involved into sympathetic potentiation of vagal inhibition of cardiac activity.

Possible participation of intracardiac ganglia in synergistic performance of different subdivisions of the autonomic nervous system was examined under conditions of benzohexonium blockade. In this case, stimulation of VN produced a negative chronotropic effect: the heart rate (HR) decreased by 20.7% from 132.0±5.8 to 104.6±9.1 min^{-1} ($p<0.05$). Stimulation of the stellate ganglion did not modify this effect (HR was 104.7±8.9 min^{-1}). Thus, benzohexonium in low doses completely eliminated the examined inhibitory phenomenon, which attested to the involvement of nicotinic cholinergic structures of the intramural ganglia.

Administration of morphine and promedol blocked the examined effect, which attested to the involvement of 5-$HT_{3,4}$ receptors into realization of the studied phenomenon.

The preganglionic serotoninergic fibers take part in synergic effect of cholinergic and serotoninergic neurons. They relay excitation to intramural neurons, which have nicotinic cholinergic receptors and 5-$HT_{3,4}$ receptors on their surface. These neurons transmit excitation to the myocardium via 5-$HT_{1,2}$ receptors.

In series II, stimulation of peripheral end of the right VN activated SW in all portions of the stomach. By contrast, stimulation of the peripheral end of the sympathetic trunk on the neck without blockade of α- and β-adrenoceptors produced a weak inhibitory effect on gastric EMA. Stimulation of the sympathetic trunk potentiated the vagal-activated SW by 64, 54, and 86% in the gastric fundus, antrum, and pylorus, respectively.

Sumatriptan abolished potentiation of vagal-activated EMA in various portions of the stomach by sympathetic influences. In this case, stimulation of VN increased the frequency and amplitude of SW in the fundus by 68% ($p<0.01$) and 20%, respectively. These values remained virtually the same after stimulation of the sympathetic trunk. Similar results were obtained in the antrum and pylorus.

Potentiation of vagal stimulation of EMA in various portions of the stomach by sympathetic influences was also eliminated by droperidol. In the antrum of droperidol-treated rabbits, vagal stimulation increased the frequency and amplitude of SW from 4.2±0.4 to 6.5±0.6 min^{-1} (55%, $p<0.05$) and from 0.12±0.03 to 0.14±0.03 (13%), respectively. Under these conditions stimulation of the sympathetic trunk did not change the frequency and amplitude of SW in this region. Similar results were obtained in the fundus and pylorus.

Potentiation of vagus-induced motility of various divisions of the stomach by sympathetic stimulation is mediated via preganglionic serotoninergic fibers projecting to serotoninergic intramural neurons, which relay excitation to 5-$HT_{1,2}$ receptors in the effector tissues.

All divisions of the stomach responded similarly by increasing vagus-induced EMA in response to supplementary sympathetic stimulation. Potentiation was most pronounced in the pylorus and was minor in the antrum. Different degree of the examined phenomenon can be explained by different content of 5-HT and acetylcholine in gastric subdivisions.

In series III carried out on the duodenum (DD) and biliary excretion system, vagal stimulation activated EMA in DD: frequency and amplitude of SW increased to 17.2±1.8 min^{-1} (32.3%, $p<0.05$) and 0.28± 0.03 mV (17%), respectively. Moreover, this stimulation evoked fast summational potentials with incidence of 0.64±0.09. Supplementary stimulation of sympathetic trunk produced a further increase in DD motility: the frequency of SW increased to 27.0±2.0 min^{-1} (57%, $p<0.05$), although the amplitude of SW did not change (Fig. 3).

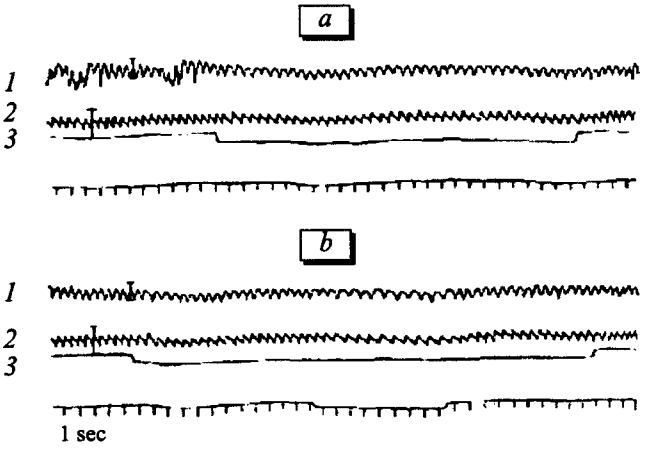

Fig. 1. Potentiation of vagus-induced negative chronotropic effect by sympathetic stimulation. *a*) Control chronotropic effect of vagal stimulation; *b*) potentiation of vagal action by electrical stimulation of stellate ganglion under the conditions of pharmacological blockade of β-adrenoceptors. *1*) impedance of the anterior wall of left ventricle in the heart; *2*) arterial pressure; *3*) zero line with the time mark indicating the period of vagal stimulation.

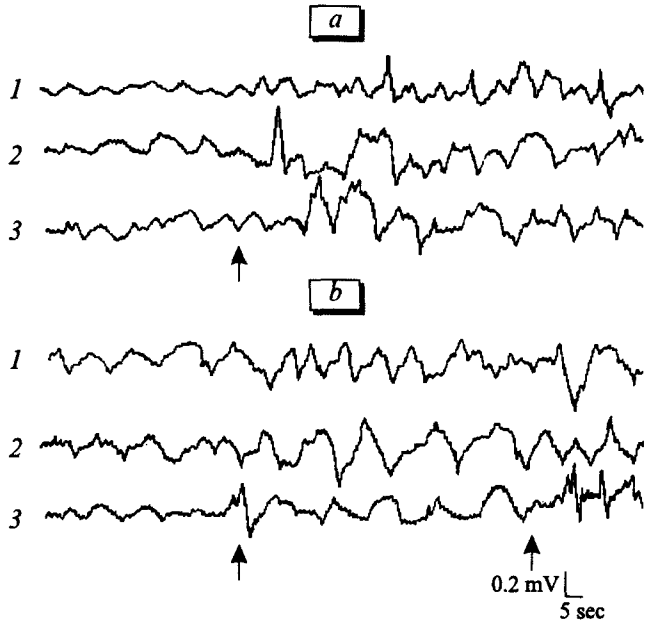

Fig. 2. Vagus-induced electromotor activity (*a*) in gastric fundus (*1*), antrum (*2*), and pylorys (*3*) and its potentiation by stimulation of sympathetic trunk (*b*). Here and in Fig. 3: the left arrow marks the onset of vagal stimulation, and the right arrow indicates the onset of supplementary stimulation of sympathetic trunk.

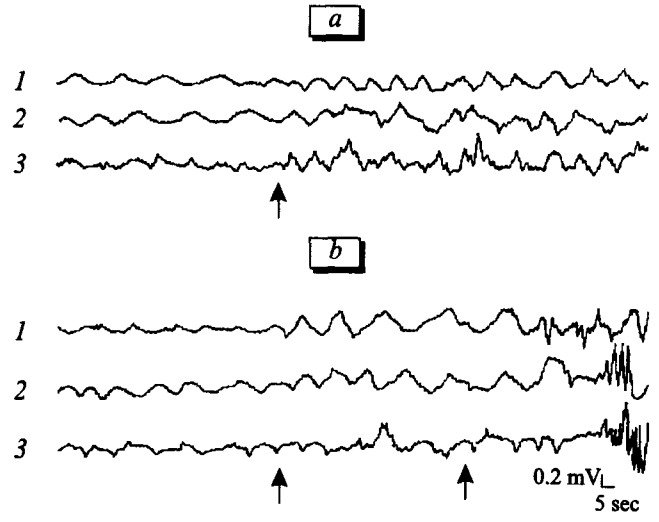

Fig. 3. Vagus-induced electromotor activity (*a*) in gallbladder (*1*), Oddi's sphincter (*2*), and duodenum (*3*), and its potentiation by stimulation of sympathetic trunk (*b*).

Vagal stimulation increased frequency of SW in gallbladder to 21.0±1.5 min^{-1} (30%, $p<0.05$), but produced no effect on SW amplitude. Supplementary stimulation of the sympathetic trunk increased the frequency of SW to 33.0±1.6 min^{-1} (57%, $p<0.01$).

Stimulation of the peripheral end of the right VN elevated activity of the muscles in Oddi's sphincter by increasing SW amplitude, SW frequency and incidence of fast potentials to 0.26±0.04 mV (30%), 22.9±2.4 min^{-1} (76%, $p<0.05$), and 0.87±0.12 (74%, $p<0.05$), respectively. Supplementary stimulation of the sympathetic trunk potentiated this vagal effect: SW frequency and incidence of fast potentials increased to 27.9±2.5 min^{-1} (22%, $p<0.05$) and by 13%, respectively.

Stimulation of the peripheral end of VN activated motility of Oddi's sphincter, gallbladder, and DD. Supplementary stimulation of the sympathetic trunk potentiated vagal stimulatory influence on biliary excretion tracts and DD. Less pronounced potentiation in the gallbladder compared to that in Oddi's sphincter can be explained by antiphase activity of these organs in the organism. In cases when the degree of synergism in different subdivisions of the autonomic nervous system was pronounced, and this synergism was revealed in all organs of the biliary excretion system and DD, this effect was considered as initial manifestation of biliary dyskinesia.

Droperidol completely prevented the development of the examined effect in DD, gallbladder, and Oddi's sphincter. Therefore, 5-$HT_{3,4}$ receptors of intramural ganglia participate in the vagosympathetic synergism.

Addition of stimulation of the sympathetic trunk to vagal stimulation in sumatriptan-treated rabbits had no effect on SW frequency in DD. In the gallbladder, sumatriptan also prevented the synergistic effect, decreased SW frequency in Oddi's sphincter to 15.5±3.5 min^{-1} or to 18.0±3.0 min^{-1} during vagal stimulation. Thus, sumatriptan completely blocked the examined effect in Oddi's sphincter.

Therefore, the examined synergistic effect is mediated via ganglionic serotoninergic neurons transmitting excitation to 5-$HT_{1,2}$ receptors in DD, gallbladder, and Oddi's sphincter.

Our data demonstrate positive lateromedial gradient of serotoninergic innervation of the biliary excretion tracts: the discussed serotoninergic synergism was observed in the gallbladder, Oddi's sphincter, and the adjacent part of DD in 20, 40, and 53%, respectively.

In series IV, stimulation of the sympathetic trunk potentiated the effect of cervical vagal stimulation on the jejunum, which enhanced EMA in response to vagal influences. Sympathetic stimulation increased SW frequency to 18.6±1.3 min^{-1} (7%), but did not change SW amplitude.

This effect was prevented by droperidol. In this case, supplementary sympathetic stimulation produced no effect on EMA parameters in the jejunum under conditions of vagal stimulation: SW frequency and amplitude were 14.8±1.1 min^{-1} and 0.25±0.03 mV, respectively. Therefore, the intramural cells carrying surface 5-$HT_{3,4}$ receptors participate in the examined effect.

By contrast, sumatriptan induced fast summational potentials and increased SW amplitude in the jejunum.

Thus, similarly to other examined organs, the jejunum demonstrated potentiation of vagal-induced motility by sympathetic stimulation. However, sumatriptan did not eliminated vagosympathetic synergism in the jejunum, and even potentiated it. In the jejunum, the examined synergism is mediated via serotoninergic systems carrying 5-$HT_{3,4}$ receptors on the cell membranes, for instance, enterochromaffin cells.

The degree of synergism between the major subdivisions of the autonomic nervous system decreases in the distal direction from the stomach to jejunum and attains maximum in the gastric pylorus and DD.

Comparison of the degree of the examined synergism in the heart and gastro-intestinal tract revealed positive craniocaudal gradient of serotoninergic innervation of visceral organs.

REFERENCES

1. G. Burnstock, *Trends Pharmacol. Sci.*, **22**, No. 4, 182-188 (2001).
2. I. Hatip-Al-Khatib and F. Bolukbasi-Hatip, *Pharmacology*, **66**, No. 1, 19-25 (2002).
3. A. Moran, C. Velasco, M. L. Martin, and L. San Roman, *Eur. J. Pharmacol.*, **252**, No. 2, 161-166 (1994).