Serotoninergic Nervous System of the Heart and Abdominal Organs during Functional Load and Pathology

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We studied the involvement of serotoninergic system into postprandial motility of the stomach and small intestine and into the development of experimental myocarditis and stomach ulcer. Gradual increase in activity of this system was observed under pathological conditions.

Key Words: *serotoninergic nervous system; myocarditis; experimental stomach ulcer; postprandial motility*

Apart from the parasympathetic nervous system, the serotoninergic system is also involved in the stimulation of gastrointestinal motility [3,7,8]. Serotonin (5-hydroxytryptamine, 5-HT) was found in the vagus and sympathetic trunks. Membrane of 5-HT-containing enterochromaffin cell carries 5-HT_3 and 5-HT_4 receptors [6]. These data attest to the involvement of 5-HT into activation of postprandial motility of the stomach and small intestine.

In some cases, changes in the balance between sympathetic and parasympathetic activities promote the development of myocarditis and ulceration in the stomach and duodenum [1,2,4,5]. These effects could be related to changes in the balance of neurotransmitters.

Here we studied serotoninergic innervation of visceral organs during functional load and under pathological conditions.

MATERIALS AND METHODS

Acute and chronic experiments were carried out on 32 Chinchilla rabbits (3.5-4.0 kg) and 12 Wistar rats (250-350 g) narcotized with Nembutal. For evaluation of cardiac function, the peripheral end of the left vagus nerve and right stellate ganglion were stimulated with electrical pulses (rate 10 Hz, amplitude 1.5-15.0 V, pulse duration 2 msec). In experiments on the stomach, small intestine (series I), and jejunum (series II) we used bipolar platinum electrodes (diameter 0.3 mm and interelectrode distance 1.5 mm). Slow waves of electromotor activity (EMA) and fast summational potentials were recorded, and their amplitude and frequency (the number of fast potentials per 100 slow waves) were determined. The degree of EMA stimulation was assessed by the increase in the amplitude and frequency of slow waves and summation action potentials.

Activation of postprandial motility was established after standard test feeding. Pharmacological analysis was carried out using blocker of nicotinic cholinergic receptors of autonomic ganglia benzohexonium (0.7-1.0 mg/kg), blocker of 5-$HT_{3,4}$ receptor in autonomic ganglia droperidol (0.5-1.0 mg/kg), peripheral 5-HT_2 receptor blocker spiperone (0.5-1.0 mg/kg), and 5-$HT_{1,2}$ receptor blocker sumatriptan (imigran, 0.5-1.0 mg/kg). The drugs were injected intravenously.

Myocarditis (experimental series III) was modeled on Chinchilla rabbits after preliminary right-sided vagotomy. Blood pressure in the right carotid artery, ECG, and myocardial impedance were measured during individual or combined stimulation of the vagus and/or right stellate ganglion.

Experimental stomach ulcer (series IV) was produced by the method of Okabe.

For elucidation of the transmitter mechanism of ulceration 5-HT receptor blocker sumatriptan was injected 30 min before induction of ulcer or blocker of

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ganglionic 5-HT receptor droperidol during ulcer modeling.

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

RESULTS

In series I, EMA of the stomach and duodenum increased during feeding. Benzohexonium inhibited postprandial motility in the stomach and duodenum by 21% and 7%, respectively (Table 1). Since benzohexonium did not completely blocked postprandial motility, the latter is mediated via not only nicotinic receptors of intramural ganglia, but also ganglionic receptors of different mediator profile.

Droperidol injected 20 min after test feeding completely eliminated postprandial motility. It decreased the frequency of slow EMA waves in the stomach and duodenum (Table 1) and reduces the frequency of fast potentials to 0.14 per 100 slow waves *vs.* 0.57 during fasting ($p<0.05$).

TABLE 1. Effect of 5-HT Antagonists on EMA in Stomach and Duodenum (*M*±*m*)

Experimental conditions (*n*=6)	Frequency of slow waves of EMA, min^{-1}	
	stomach	duodenum
Fasting background	6.3±1.0	36.9±1.3
Benzohexonium	> for 50%	> for 22%
Droperidol	3.8±0.9*	29.0±3.1*
Sumatriptan	3.9±0.8*	30.0±1.6*
Spiperone	3.9±1.1*	29.5±1.2*

Note. *$p<0.05$ compared to the corresponding value of fasting background.

TABLE 2. Effect of Experimental Stomach Ulcer on Frequency and Amplitude of Slow EMA Waves (*M*±*m*)

Index	Baseline	Experimental ulcer of stomach
Antrum of stomach		
frequency, min^{-1}	4.0±0.5	14.0±0.5*
amplitude, mV	0.35±0.05	1.1±0.1*
Fundus of stomach		
frequency, min^{-1}	4.7±0.3	17.5±0.5*
amplitude, mV	0.12±0.02	0.35±0.06*
Duodenum		
frequency, min^{-1}	28.5±0.7	27.5±0.5
amplitude, mV	0.22±0.02	0.25±0.03

Note. *$p<0.05$ compared to baseline.

Sumatriptan or spiperone injected after test feeding also inhibited postprandial motility and decreased the frequency of slow EMA waves in the stomach and duodenum (Table 1). These data showed that 5-HT_2 receptors in smooth muscles of the stomach and duodenum play a more important role in activation of postprandial motility in comparison with 5-HT_1 receptors.

Thus, in addition to parasympathetic fibers, neurons of autonomic ganglia carrying nicotinic and 5-$HT_{3,4}$-receptors on the membrane are involved in the stimulation of postprandial motility. Serotoninergic neurons transmit excitation to 5-$HT_{1,2}$ receptors of the effector cells, where 5-HT_1 receptors play the leading role among all 5-HT receptors. Therefore, serotoninergic neurons exert a stimulatory effect synergistic to vagal influences.

In series II carried out on fasting rats, jejunal EMA was characterized by patterns comprising 4-8 waves in a group. After feeding jejunal EMA was grouped in the patterns of 4-10 waves, and the repetition rate of these trains increased by 16% in comparison with the baseline.

Sumatriptan decreased the frequency of waves within patterns by 14% and in 30% cases triggered spike activity (65.0±0.5 per 100 slow waves). Increased spike activity was probably determined by contractions of smooth muscles indicating stimulation of postprandial motility in the jejunum. Sumatriptan had no effect on activation of 5-HT-containing enterochromaffin cells, the source of 5-HT during activation of postprandial motility. Therefore, neurotransmitter 5-HT is not involved in the regulation of postprandial motility of the jejunum. However, participation of serotoninergic enterochromaffin cells in jejunal postprandial motility cannot be excluded. Therefore, 5-HT that activates EMA in jejunum during feeding is released by serotoninergic enterochromaffin cells rather than serotoninergic nerve terminals.

In chronic experiments, the quantitative study of serotoninergic effects, which are synergistic to cholinergic effects in the control of postprandial motility in the stomach, duodenum, and jejunum, revealed craniocaudal gradient of serotoninergic regulation of postprandial motility (stomach 50%, duodenum 22%, and jejunum 15%). Moreover, in the jejunum 5-HT is mobilized not from nerve terminals, but from enterochromaffin cells.

In series III carried out on rabbits, stimulation of the stellate ganglion against the background of vagal stimulation potentiated vagal inhibition of cardiac activity: the heart rate (HR) decreased from 170.8±5.8 min^{-1} (individual vagal stimulation) to 150.4±5.6 min^{-1} (combined vagal and stellate stimulation, $p<0.05$). The degree of inhibitory effect was 7-24%.

Fifteen minutes after reproduction of this effect visually observed surface of the myocardium lost structural organization and looked "polished" in 5 rabbits (42%) of the elder group and in 5 rabbits (16%) of the younger group. Systolic pressure decreased from 135.0±5.2 to 78.4±3.0 mm Hg, and diastolic pressure dropped from 74.0±6.0 to 47.0±4.7 mm Hg. The amplitude of *R* wave in ECG decreased by 12.0±0.1%, wave *T* flattened by 5.00±0.22%, and *QT* interval increased by 9.0±0.1%. The very first minutes of myocarditis development were accompanied by a dramatic drop in acetylcholine and norepinephrine levels and by an increase in 5-HT concentration.

Blockade of 5-$HT_{3,4}$ receptors of autonomic ganglia with morphine or promedol or blockade of 5-$HT_{1,2}$ receptors in the myocardium increased excitability of cholinergic myocardial structures, but at the same time, it eliminated the phenomenon of potentiation of cardiotropic vagal inhibition by sympathetic nerve and prevented the development of myocarditis.

With intact 5-HT-reactive structures 42% experimental animals died during the first hour of myocarditis (*vs.* 16% in experiments with blockade of these structures). The development of myocarditis during simultaneous stimulation of the sympathetic and parasympathetic systems probably results from the prevalence of serotoninergic nerve terminals in comparison with those in adreno- and cholinergic terminals. 5-HT receptor blockade in autonomic ganglia or in the peripheral efferent terminals produced a cardioprotective effect.

The development of "serotoninergic" myocarditis provoked by combined stimulation of the vagus and sympathetic trunk resulting in pronounced activation of serotoninergic fibers is characterized by moderation of activity of the sympathetic and parasympathetic systems and activation of serotoninergic system. During this process, the content of acetylcholine decreased by 48.0 and 43.7% in the atria and ventricles, respectively; atrial and ventricular levels of norepinephrine decreased by 12.5 and 30.8%, respectively. At the same time, the content of 5-HT increased by 46.1 and 25.3% in the atria and ventricles, respectively. Therefore, the development of pathology (specifically, myocarditis) is characterized by an increase in serotoninergic activity.

In series IV (experimental stomach ulcer) application of acetoacetic acid to the boundary between the antrum and fundus sharply increased EMA in these regions (Table 2) and triggered spike activity (0.76 spikes per 100 slow waves). In the duodenus application of acetoacetic acid slightly decreased the frequency of slow waves, increased their amplitude (Table 2), and elicited spike activity (0.76 spikes per 100 slow waves).

One hour after inducing gastric ulcer "nociceptive" EMA gradually decreased. In the following 4 days, gastric EMA remained slightly enhanced, while EMA in the duodenum returned to normal. However, on ulcer day 5, gastric EMA increased again.

The development of experimental gastric ulcer was accompanied by a pronounced increase in 5-HT-mediated EMA by 272 and 350% in the fundus and antrum, respectively. By contrast, in the duodenum only minor increase in EMA (4-13%) was observed, which attested to pronounced activation of the ascending and descending serotoninergic pathways in the stomach. Preliminary injection of sumatriptan completely eliminated both ascending and descending activation of EMA in the antrum and fundus during experimental ulcer. The increase in gastric EMA during experimental ulcer and increased motility of the antrum during feeding determined 2.7-3.5-fold stimulation of 5-HT-mediated motility in experimental ulcer and only 50% increase during feeding.

The data obtained in all experimental series with myocarditis and isolated stimulation of the serotoninergic systems in experimental gastric ulcer suggest that under pathological conditions activity of the serotoninergic systems increases against the background of inhibition of cholinergic and adrenergic structures.

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