MECHANISM OF STIMULATION OF DUODENAL CONTRACTIONS BY THE GREATER SPLANCHNIC NERVE

V. M. Smirnov, V. A. Klevtsov,
N. A. Smirnova, and A. É. Lychkova

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The splanchnic nerves can exert not only an inhibitory, but also a stimulating action on motor activity of the gastrointestinal tract [1, 2, 9, 11, 15]. Some workers [11] consider that stimulation of intestinal peristalsis of arising in response to stimulation of a sympathetic nerve by reserpine, is the result of excitation of cholinergic fibers of the vagus nerve running in the mesentery. According to the authors of [15], intestinal contractions are stimulated by those sympathetic nerve fibers which directly innervate muscles. We know that adrenalin and noradrenalin can increase the firing rate of neurons of the myenteric (Auerbach's) plexus, evidently through their action on the α-adrenoreceptors of the postsynaptic membrane, for the stimulating effect is blocked by phentolamine and is unchanged by propranolol [5]. Excitation of these neurons may perhaps also lead to strengthening of intestinal contractions. The view that intestinal movements can be enhanced by sympathetic action through α-adrenoreceptors is confirmed by experimental results [8] showing that two types of α-adrenoreceptors — excitatory and inhibitory — evidently exist in the membranes of intestinal smooth muscle cells. However, this view differs significantly from the other two just mentioned. Different authors thus hold very contradictory opinions on the mechanisms of the excitatory effect of the sympathetic nerve. Knowledge of these mechanisms is essential, however, for a deeper understanding of the mechanisms of regulation of the functions of the small intestine and the functional organization of the peripheral part of the autonomic nervous system, and also for the improvement of diagnosis and pharmacotherapy of diseases of the gastrointestinal tract.

The aim of this investigation was to study the phenomenon described above.

EXPERIMENTAL METHOD

Experiments were carried out on 34 mongrel dogs of both sexes weighing 6-12 kg, in the surgical stage of anesthesia with hexobarbital (70-100 mg/kg) or thiopental sodium (150 mg/kg), with subsequent addition of urethane (1.5-2 g/kg) intramuscularly. In half of the experiments the hydrostatic pressure in the intestinal lumen was recorded by an up-to-date version of the balloon-graphic method, and in the other half the impedance of the intestinal wall was measured by means of an RG4-0.1 rheograph, UBP2-03 biopotentials amplifier, and N3020-5 automatic ink-writer. In the experiments the peripheral segment of the divided right greater splanchnic nerve was stimulated by means of an ÉFL-2 stimulator, not in the abdomen (as was done by other workers [1, 2, 9, 11]), where it contains a large number of parasympathetic fibers [3], but in the chest, where this nerve is "purely" sympathetic. Another nine experiments on nine dogs were performed under chronic conditions after (2-4 weeks) preliminary division of the right vagus nerve in the region of the neck, followed by degeneration (in one animal both nerves were divided), which was an additional guarantee that a purely sympathetic nerve was obtained on the right.

To stimulate the greater splanchnic nerve the thorax was opened through a skin incision followed by blunt dissection of the muscles in the 9th-10th right intercostal space (artificial respiration with a Type-297 apparatus was used in the experiments). Different segments and branches of the autonomic nervous system were blocked surgically (vagotomy) and pharmacologically: with bretylium tosylate (20 mg/kg), benzohexonium, dicoline (dimethiodide of 2-diethylaminoethyl ester of pipecolic acid), dimecoline (dimecolonium), and trimetaphan

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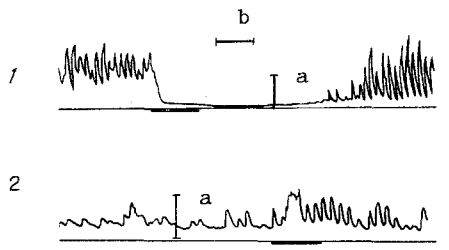

Fig. 1. Inhibition of contractions of duodenum during weak stimulation of peripheral end of divided greater splanchnic nerve in chest (1) and potentiation of contractions during stimulation of average intensity (2) without the use of drugs. a) Scale 30 mm Hg, b) time marker, 30 sec. Hydrostatic pressure in duodenal lumen recorded.

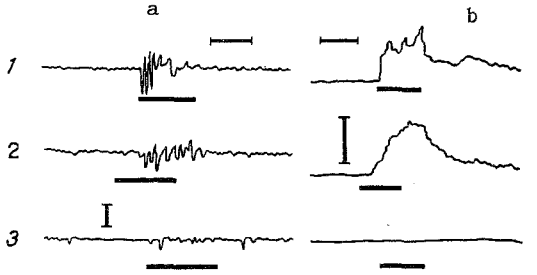

Fig. 2. Potentiation of motor activity of duodenum during stimulation of the greater splanchnic nerve preceded by administration of bretylium (1a, b), bretylium + benzohexonium (2a, b), and blocking of stimulatory effects of atropine (3a) and promethazine (3b). Scale 10 Ω, time marker, 30 sec. Impedance of muscular wall of duodenum recorded.

camsylate (5-40 mg/kg of each) — separately or together — atropine (0.5-1 mg/kg), and promethazine (5-10 mg/kg). All drugs were injected intravenously.

EXPERIMENTAL RESULTS

Stimulation of the peripheral end of the divided greater splanchnic nerve, with average intensity (10 V, 20-30 Hz, 2 msec) evoked inhibitory (Fig. 1, 1) responses of the duodenum in 10 of the 19 dogs and stimulating responses (Fig. 1, 2) in nine dogs, i.e., excitatory and inhibitory responses were observed equally often. Meanwhile weak stimulation (0.5-3 V, 10 Hz, 0.1-0.5 msec) as a rule evoked inhibition in 10 other animals (eight experiments), and evoked strengthening of intestinal contractions much less frequently (two experiments). In 83 cases inhibitory responses to stimulation of average intensity were observed 28 times, excitatory responses 30 times, and in 25 tests the intestine did not respond at all, evidence of an equal degree of activity of excitatory and inhibitory mechanisms. With weak stimulation (37 cases) the corresponding frequency was 25, 4, and 8 times. Good intestinal peristalsis promoted the development of inhibitory responses, weak peristalsis promoted stimulating responses of the duodenum.

Blockade of the sympathetic nervous system by bretylium, which prevents catecholamine (CA) release, not only did not prevent, but actually facilitated the development of an excitatory effect (Fig. 2, 1, a, b), which became apparent during stimulation of the splanchnic nerve of average intensity in 15 of the 19 dogs. The hydrostatic pressure in the lumen of the intestine during its contractions increased from 9.8 ± 4.6 to 28.4 ± 6.9 mm Hg (by 189%) and the impedance increased from 3.3 ± 0.6 to 11.5 ± 2.6 Ω (by 248%, Fig. 2, 1, a, b), and

the frequency of intestinal contractions was virtually unchanged at 6-8/min. In 13 experiments of the next series stimulation of the splanchnic nerve after administration of bretylium and after blocking of nicotinic acetylcholine receptors of the autonomic ganglia by benzohexonium, dicoline, dimecoline, or trimetaphan (injected together or separately) was accompanied by the same stimulating effect as without the use of the ganglion blockers (Fig. 2, 2, a, b). The reliability of nicotinic acetylcholine receptor blockade was tested relative to disappearance of the stimulating effect of the vagus nerve on intestinal activity, which usually appears in response to vagus nerve stimulation before injection of ganglion blockers. The results of these and previous experiments are evidence that the stimulating effect of the splanchnic nerve is noncholinergic and nonadrenergic, for it was not abolished by reliable blockade of cholinergic and adrenergic mechanisms, namely by bilateral vagotomy followed by administration of bretylium and ganglion blockers.

On the basis of data in the literature according to which the intramural nervous apparatus of the intestine contains serotoninergic neurons [7, 10, 14], that serotonin stimulates motor activity in the gastrointestinal tract [7, 14], and that stimulation of mesenteric and visceral nerves increases serotonin secretion into the perfusion fluid of the intestine by 1.5-3 times [4, 13], we postulated that in the present experiments stimulation of the splanchnic nerve stimulates intestinal activity also through the intervention of serotonin. Direct proof of the action of such a mechanism was obtained in experiments with blockers of serotoninergic receptors [7, 12]. These experiments showed that splanchnic nerve stimulation accompanied by bilateral vagotomy, after preliminary administration of benzohexonium or its analogs and bretylium, potentiated intestinal contractions, whereas the same stimulation after additional injection of atropine, a blocker of muscarinic serotoninergic receptors of autonomic ganglia (10 dogs from previous experiments) was not accompanied by any change in intestinal activity (Fig. 2, 3, a). In the next series of experiments the excitatory effect of the splanchnic nerve was abolished also by promethazine — a blocker of D-serotoninergic receptors of smooth muscle — irrespective of whether promethazine was given after combined or separate administration of bretylium and benzohexonium, or without the use of any other drugs whatsoever (Fig. 2, 3, b).

In the last stage of the investigations (four animals) our conclusion was confirmed by the fact that serotonin was found in the greater splanchnic nerve, in its thoracic portion, and its concentration determined by the method in [6] was 3.19 ± 0.006 μg/g tissue.

We thus showed for the first time that the greater splanchnic nerve in its thoracic portion contains noncholinergic and nonadrenergic nerve fibers with a powerful stimulating effect on contraction of the musculature of the small intestine. According to data obtained by the methods used, their mediator is serotonin. These fibers are preganglionic and they are connected synaptically with serotoninergic neurons of the intramural nervous apparatus of the intestine. We also showed that drugs such as atropine and promethazine, so widely used in clinical practice, besides their known mechanisms of action also possess another property: they abolish the excitatory influence of the greater splanchnic nerve on intestinal movements, and this must be taken into account in clinical practice.

These results may provide a deeper understanding of the mechanisms of regulation of the functions of individual viscera and of the functional organization of the autonomic nervous system as a whole, and they will also lead to improvements in the diagnosis and pharmacotherapy of intestinal diseases.

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