Mechanism of Vagal Inhibition of Small Intestine Contraction

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The mechanism of inhibition of small intestine contraction in response to weak stimulation of the peripheral end of the vagus nerve cut at the cervical level was studied in experiments on anesthetized dogs. This inhibition can be blocked with arfonade or hexamethonium, atropine, and rausedyl, as well as by combined, but not individual administration of propranolol and dihydroergotoxine. We assume that inhibition is triggered by the release of catecholamines from sympathetic postganglionic terminals in response to activation of their muscarinic receptors induced by acetylcholine released from parasympathetic terminals during excitation.

Key Words: *small intestine; contractions; vagus; regulation*

It is widely known that the vagus nerve can not only stimulate, but also inhibit motility of the gastrointestinal tract (GIT) [6,9,12,13]. However, the mechanism of this phenomenon is not clear and is the matter of controversy. It was hypothesized that vagal inhibition of the motility of the small intestine and stomach can be realized via sympathetic fibers of the vagosympathicus [1]. Other researchers believe that this phenomenon is realized via antidromic activation of high-threshold fibers of the inhibitory intestine-intestinal pathways [9]. There are data indicating that vagal inhibition of intestinal contractions is mediated via intramural efferent adrenergic neurons that form synapses with preganglionic parasympathetic vagal fibers [4]. In that paper, vagal stimulation with pulses of a moderate amplitude (5-10 V, 15-30 Hz, 1-2 msec) applied against the background of atropine blockade did not increase, but even inhibited intestinal contractions. The inhibitory effect was abolished by ganglioblockers, rausedyl, and combined, but not individual administration of propranolol and dihydroergotoxine. The inhibition of intestinal motility was also observed during (0.5-2.5 V) weak vagal stimulation without application of pharmacological preparations, which was interpreted as the effect of the same population of intramural adrenergic neurons [4].

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Thus, current view on the mechanism of vagal inhibition of GIT activity is the matter of vigorous controversy. Our aim was to study the mechanisms of this effect. This is the way to understanding the regulation of digestive organs and the development of a concept of functional structure of the autonomic nervous system.

MATERIALS AND METHODS

The study was carried out on 52 outbred dogs (body weight 7-15 kg) during surgery stage of narcosis (sodium thiopental, 45-60 mg/kg, and urethane, 1.5 g/kg intramuscularly).

Contractions of the small intestine, blood pressure, and respiration were recorded using external high-sensitive electrical EMT-35 transducers, UBP2-03 amplifiers, and an N3020-5 plotter. Arterial pressure transducer was connected via a polyethylene tube to a cannula inserted into the left common carotid artery. The tube and transducer were filled with physiological saline. The respiration transducer was connected with a balloon placed under the diaphragm. The intestinal transducer was connected with a balloon placed in the median portion of the small intestine. The volume of the balloons was 50-70 ml. Balloons and tubes were filled with warm (38°C) distilled water. The peripheral end of the right vagus nerve was stimulated on the neck using an ESL-2 stimulator.

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Body core temperature was maintained at a constant level. Different subdivisions of the autonomic nervous system were blocked with intravenous benzohexonium (5 mg/kg), dihydroergotoxin (0.1-1.0 mg/kg) or intramuscular rausedyl (1 mg/kg) injected 1-3 times during the experiment. Contractions of the small intestine were inhibited by weak stimulation of the vagus nerve with trains of pulses (0.5-2.5 V, 10-15 Hz, 0.5-1.0 msec, and train duration 0.5-2.0 min).

RESULTS

In control series (10 dogs), weak stimulation of the peripheral end of the right vagus nerve (0.5-2.5 V, 10-35 Hz, 0.3-1.0 msec) evoked not only stimulatory, but sometimes inhibitory reactions (20 of 94 cases, 21%) i.e. weakening of intestinal contractions (Fig. 1, *a*). In one-third cases the intestine did not respond to vagal stimulation, which is thought to reflect a balance between stimulatory and inhibitory vagal influences. Indeed, weaker stimulation caused neither inhibition nor activation of intestine contractions, while moderate and strong stimulation (5-15 V) always enhanced intestinal motility, which indicates that stimulatory effect of the vagus nerve prevailed over its inhibitory effect. Control experiments also showed higher excitability of inhibitory processes compared to stimulatory. The stimulatory effect is mediated via intramural cholinergic neurons, which form synaptic connections with vagal preganglionic parasympathetic fibers. The next experiments identified neurons and receptors involved in the realization of the inhibitory effect.

In series II (11 dogs) we studied the role of nicotinic receptors of vegetative ganglia in the inhibitory effect produced by weak vagal stimulation. In intact animals moderate vagal stimulation usually stimulated intestinal contractions, while weak stimulation induced both inhibitory and stimulatory effects in the same dog. Intestinal pressure decreased from 15 to 10 mm Hg during inhibition. As a whole, the inhibitory effect in this series was documented in 36 of 144 cases (25%).

Injection of ganglioblocker to the same dogs prevented the development of both stimulatory and inhibitory effects even under longer (then usual) vagal stimulation (Fig. 1, *a*). These data indicate that both inhibition and stimulation of intestinal contractions induced by weak vagal stimulation are mediated via preganglionic cholinergic fibers that form synapses with nicotinic acetylcholine receptors on intramural intestinal neurons. It is suggested that these neurons are cholinergic, because their blockade with hexamethonium abolishes not only the inhibitory, but also the stimulatory effect evoked by excitation of cholinergic neurons of the parasympathetic nervous system.

To increase the incidence of inhibitory reactions in response to weak vagal stimulation, in the next series we used atropine, a blocker of muscarinic receptors, because activation of these receptors is known to stimulate intestinal contractions. The results were paradoxical. Atropine abolished not only the stimulatory, but also the inhibitory reactions to weak vagal stimulation.

These results corroborated our hypothesis that both the stimulatory and inhibitory responses to weak vagal stimulation are mediated via cholinergic neurons. These data also indicate that the examined inhib-

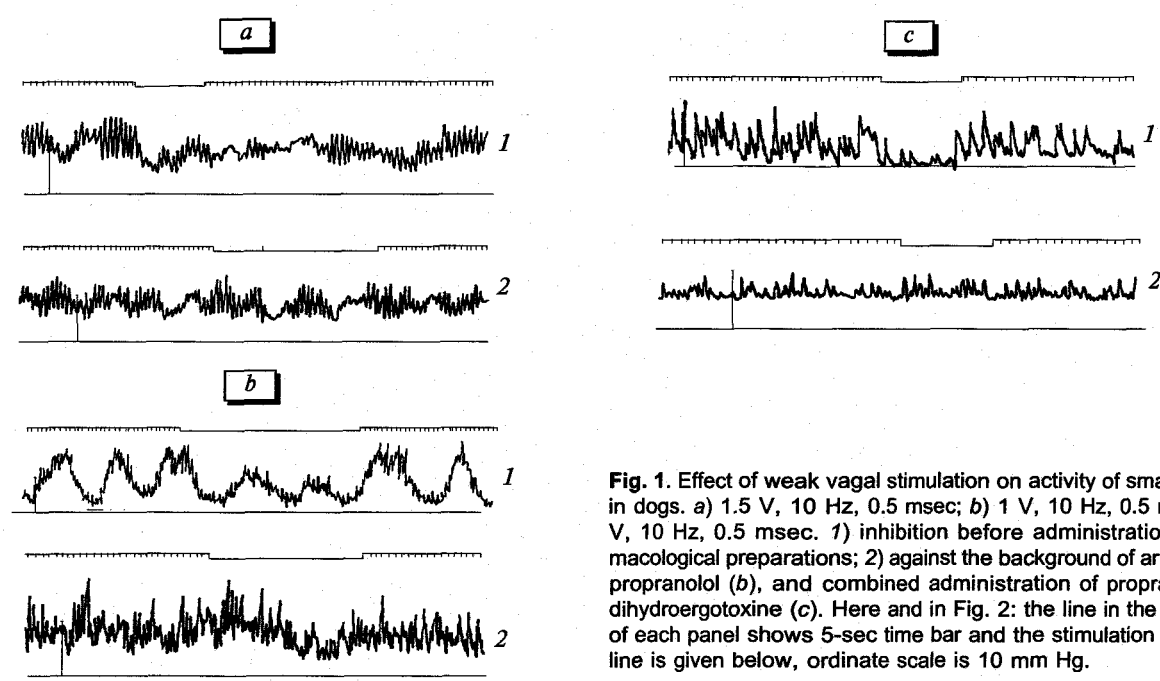

Fig. 1. Effect of weak vagal stimulation on activity of small intestine in dogs. *a*) 1.5 V, 10 Hz, 0.5 msec; *b*) 1 V, 10 Hz, 0.5 msec; *c*) 2 V, 10 Hz, 0.5 msec. *1*) inhibition before administration of pharmacological preparations; *2*) against the background of arfonade (*a*), propranolol (*b*), and combined administration of propranolol and dihydroergotoxine (*c*). Here and in Fig. 2: the line in the upper part of each panel shows 5-sec time bar and the stimulation ticks. Zero line is given below, ordinate scale is 10 mm Hg.

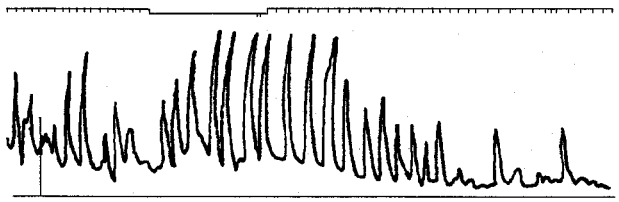

Fig. 2. Enhancement of contraction of canine small intestine induced by electrical stimulation of the vagus nerve of moderate intensity (5 V, 29 Hz, and 0.5 msec) applied after injection of rausedyl.

itory mechanism is triggered via muscarinic receptors in some inhibitory structures.

Published data and our findings substantiate the hypothesis that the examined inhibitory phenomenon is mediated via activation of muscarinic receptors on terminals of sympathetic postganglionic fibers of the extraorgan origin. Many investigators showed availability of muscarinic receptors in these terminals [2, 10,11,14].

Our hypothesis was supported in the next experimental series on 10 dogs injected once or twice with rausedyl (1 mg/kg) 20 and 10 h prior to vagal stimulation. Weak vagal stimulation applied 10 h after single injection of rausedyl evoked the inhibitory reaction only in 5 of 100 tests (5% *vs.* 24-26% without rausedyl). Vagal stimulation applied 10 h after the second injection of rausedyl produced no inhibitory effect. In the same experiments, vagal stimulation of moderate intensity resulted in usual or even higher increase of intestinal contractions. For example, in experiments with stimulation parameters 5 V, 20 Hz, and 0.5 msec (Fig. 2) intestinal pressure rose from 22 to 37 mm Hg. These data indicate that inhibition of intestine motility caused by weak vagal stimulation is mediated via catecholamines released from sympathetic terminals triggered in response to activation of their muscarinic receptors. This hypothesis is confirmed by the fact that the inhibitory effect is blocked not only by rausedyl, but also by muscarinic acetylcholine receptor blocker atropine and arfonade, a blocker of muscarinic receptors in autonomic ganglia.

In the last experimental series performed on 14 dogs we studied the role of α- and β-adrenoceptors in the development of inhibitory effect. In these experiments, control weak vagal stimulation (for example, 1 V, 10 Hz, and 0.5 msec, Fig. 1, *b*) often inhibited contractions of the small intestine (in 31 of 128 tests, or 24%). In 7 experiments the same stimulation was applied against the background of propranolol (β-adrenoceptors blocker), then dihydroergotoxine (α-adrenoceptors blocker) was applied and the vagus nerve was stimulated against the background of both drugs. In other 7 experiments, dihydroergotoxine was administered before propranolol. It was found that vagal stimulation against the background of propranolol produced less pronounced inhibition of intestinal contractions, and the inhibitory reactions were observed less frequently than in control dogs (5 of 53 tests, 9.5%, Fig. 1, *b*). The same stimulation applied against the background of dihydroergotoxine evoked inhibitory response in 5 of 31 cases (16%). Vagal stimulation applied after combined administration of propranolol and dihydroergotoxine (blockade of α- and β-adrenoceptors) produced no inhibition (Fig. 1, *c*), whereas weak vagal stimulation prior to propranolol evoked the inhibitory response in the same dogs (Fig. 1, *c*).

Our data indicate that inhibition of intestinal contractions induced by weak vagal stimulation is mediated by catecholamines released from sympathetic terminals in response to excitation of their muscarinic acetylcholine receptors. In sympathetic terminals these receptors are activated by acetylcholine released from postganglionic cholinergic terminals of the parasympathetic nervous system (cholinergic neurons of intramural moiety are the effector neurons of the parasympathetic nervous system). These data also illustrate the mechanism of interaction between parasympathetic and sympathetic subdivisions of the autonomic nervous system. Vagus nerve can also regulate GIT via sympathetic (adrenergic) nerves, which produces an opposite effect. This inference contradicts current concept [3,5] that activation of muscarinic receptors on sympathetic postganglionic terminals does not enhance, but inhibits the release of catecholamines.

It should be noted that this concept resulted from experiments performed on the intestinal strips stimulated directly with various bioactive substances and mediators and also from the data on blockade of various effector and neural receptors with pharmacological preparations. The concentrations and target sites of drugs applied under these conditions are incomparable with those produced by vagal stimulation, as in our *in vivo* experiments when the mediator were released from both pre- and postganglionic nerve fibers in response to nervous pulses. Our data agree with some reports on this problem, which however contained no such conclusions. Specifically, it was found that stimulation of the vagus lobes in Neopterygii (osseous) fishes (pike, perch, and pike-perch) produce both the increase and (to a smaller degree) inhibition of stomach contractions. Both effects were abolished by atropine, a blocker of muscarinic receptors.

Our hypothesis does not contradict the current opinion about purinergic mechanism of inhibition of smooth muscle contraction in GIT. According to some authors, this mechanism of vagal regulation is characteristic only of the stomach [7,10].

Why in some cases the inhibitory effect of the vagus nerve surpasses its excitatory effect? We assume that weak stimulation predominantly excite sym-

pathetic terminals due to their higher excitability, while moderate and strong stimulation produces predominantly direct (i.e., cholinergic) vagal effects. Normally, the inhibitory and stimulatory vagal effects on intestinal motility are determined by the interaction between local and central regulatory mechanisms and meet the necessities of the organism.

Further studies are needed to reveal the mechanism of regulation of catecholamine release from sympathetic terminals mediated via presynaptic muscarinic receptors.

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