Effect of Drugs with Various Mechanisms of Action on Propulsive Activity of the Small Intestine

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We studied the effect of drugs with various mechanisms of action on propulsive activity of the small intestine in healthy rats. Blockade of the major inhibitory influences realized via nonadrenergic noncholinergic inhibitory effector neurons was not followed by stimulation of intestinal transit. Propulsive activity of the small intestine increased upon treatment with drugs, whose effects are realized via acetylcholine or acetylcholine and serotonin.

Key Words: *small intestine; propulsive activity; prokinetic agents*

The peristaltic reflex is realized via the enteric nervous system (ENS). Cell bodies of most ENS neurons are localized in the submuscular and submucosal plexuses [5]. The neuronal circuit regulating propulsive peristaltic activity probably consists of inhibitory and excitatory arches located in the intestinal wall (oroanal direction). The signal is transduced from afferent neurons to cholinergic or serotoninergic excitatory interneurons. Depending on the final result, this signal is transmitted to cholinergic excitatory or nonadrenergic noncholinergic inhibitory effector neurons [5].

There are several classes of drugs that interact with major receptors in ENS and modulate propulsive activity of the small intestine. The effects of these drugs were estimated by various methods for recording of propulsive activity under different treatment routes.

Here we studied the influence of peroral treatment with various drugs on propulsive activity of the small intestine in healthy rats.

MATERIALS AND METHODS

Experiments were performed on 50 adult male Wistar rats weighing 300 g. Before the experiment the animals fed a complete diet (natural products).

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The animals were deprived of food for 24 h. Control rats (n=5) perorally received 0.2 ml physiological saline. Prokinetic drugs proserine, Ubretid, calcium pantothenate, propranolol, Cerucal, Motilium, Coordinax, serotonin, and L-NAME were dissolved in physiological saline and given to experimental animals (5 rats per group).

Evans blue (0.1 ml, 50 mg in 1 ml 0.9% NaCl) was used as a marker and administered perorally after 40 min. The rats were euthanized 20 min after treatment. The small intestine was prepared after median laparotomy. We measured the length of the small intestine (from the pylorus to cecum) and distance passed by the marker over 20 min. The index of transit (%) was calculated as the ratio between the distance passed by the marker and total length of the intestine multiplied by 100%.

The results were analyzed by nonparametric Mann—Whitney T test. This test is used to estimate whether 2 independent samples come from the same population. We compared the results for experimental and control groups.

The differences were considered to be statistically significant (α=0.05) when we rejected the null hypothesis (no effect of preparation on the index of transit). The index of transit was expressed as the mean and standard deviation. The variation coefficient was calculated as follows:

$$V=(SD/M)\times 100\%.$$

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RESULTS

The marker was regularly distributed in control animals. The index of transit was 35.8±11.1%. This marker filled one-third of the small intestine. In animals receiving pharmacological drugs the marker moved in a shoot-like manner (considerable distance over a short time). The distribution of the marker in the intestine was characterized by the presence of filled and empty areas. Empty areas contributed to rapid passage of this marker in the intestine. The length of "shoots" was 1-20 cm, theit number was 1-2.

The variation coefficient was highest in control animals, which reflects a wide range of modulation of propulsive activity. The variation coefficient decreased after administration of the test drugs, which illustrates a narrowing of the range for regulation. It can be hypothesized that under control conditions the regulation involves all receptors. Exposure to certain agents results in activation of receptors whose function is modulated by these agents. These changes illustrate the decrease in informational saturation of the receptors.

Under normal conditions administration of the test preparations (except L-NAME) was accompanied by stimulation of intestinal transit (Table 1). Published data show that nitric oxide (NO) becomes involved during strong nociceptive stimulation of the intestine [9]. Our previous studies revealed a stimulatory effect of NO synthesis blocker under conditions of functional intestinal obstruction [4]. These findings suggest that 8 of 9 drugs stimulate transit of the marker.

The data were analyzed by means of Kruskal—Wallis test to compare the effectiveness of the test drugs. This test confirmed the null hypothesis. The test drugs did not differ in the ability to increase propulsive activity of the small intestine under normal conditions. Therefore, the influence on various receptor components produced similar changes. Structural "excessiveness" in healthy animals probably serves as a protective mechanism and reflects high reliability of the regulatory system.

The drugs increasing propulsive activity can be conventionally divided into 2 groups. Group 1 includes preparations stimulating acetylcholine secretion (proserine, Ubretid, calcium pantothenate, and Motilium). Proserine and Ubretid are synthetic anticholinesterase drugs. Cholinomimetic activity of these drugs is associated with reversible inhibition of cholinesterase and potentiation of the effect produced by endogenous acetylcholine: in the absence of anticholinesterase drugs, one nerve impulse induces one contraction, while after inhibition of cholinesterase one nerve impulse provokes several contractions. These changes are accompanied by an increase in the strength and duration of contractions [3]. Calcium pantothenate is involved in the synthesis of acetylcholine. Supply of additional pantothenic acid stimulates secretion of endogenous acetylcholine. Motilium increases the release of acetylcholine due to blockade of peripheral DA2 dopamine receptors in neurons of ENS [6].

Group 2 comprises drugs stimulating secretion of acetylcholine and serotonin (propranolol, Cerucal, Coordinax, and serotonin). The action of propranolol is related to blockade of β-adrenoceptors on smooth muscle cells, which contributes to an increase in the stimulatory effect of acetylcholine on smooth muscles of the small intestine. Blockade of β-adrenoceptors modulates the influence of serotonin, which activates mechanoreceptors [2]. Cerucal blocks DA2 dopamine receptors and promotes acetylcholine secretion [7,10]. Moreover, Cerucal serves as a 5-HT_4 serotonin receptor agonist and 5-HT_3 serotonin receptor antagonist.

TABLE 1. Effect of Pharmacological Drugs on Transit of a Marker in the Small Intestine

Drug	Dose, mg/kg	Index of transit, *M*±*SD*	Variation coefficient, %
Control (physiological saline)	0.2 (ml)	35.8±11.1	31.1
Proserine (neostigmine)	0.2	57.9±17.7*	30.6
Ubretid	0.07	57.6±16.8*	29.2
Calcium pantothenate	0.75	59.5±13.8*	23.2
Propranolol	0.15	52.2±10.2*	19.6
Cerucal (metoclopramide)	0.5	60.0±12.2*	20.4
Motilium (domperidone)	0.5	51.5±13.6*	26.3
Coordinax (cisapride)	0.2	51.4±10.3*	20.1
Serotonin	4	54.3±12.9*	23.9
L-NAME	0.05	40.7±12.2	29.9

Note. *α=0.05 compared to the control.

Cisapride acts as a 5-HT_4 receptor agonist and 5-HT_3 receptor antagonist [8]. This drug stimulates the release of acetylcholine by activating 5-HT_4 receptors that are mainly localized on cholinergic neurons of the myenteric plexus. Serotonin produces direct and indirect effects on smooth muscles. This compound affects 5-HT_4 receptors and modulates acetylcholine secretion from enteric cholinergic neurons [2].

Our results show that the test preparations (except L-NAME) increase propulsive activity of the small intestine under normal conditions. Blockade of the major inhibitory influences realized via nonadrenergic noncholinergic inhibitory effector neurons is not followed by stimulation of intestinal transit. It can be hypothesized that under normal conditions propulsive activity depends on excitatory influences realized via acetylcholine. Moreover, propulsive activity is determined by a direct stimulatory effect of serotonin on smooth muscles of the small intestine.

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