Role of Serotonin in the Recovery of Electrical Activity in the Stomach and Small Intestine of Rats during the Early Postsurgery Period

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The effects of serotonin and 5-HT_4 receptor agonist cisapride on electrical activity of the stomach and small intestine were studied in rats with postoperative ileus. Postoperative ileus was accompanied by the absence of the migrating myoelectric complex in the stomach and small intestine. All phases of the migrating myoelectric complex were successively recovered in the jejunum, duodenum, and stomach. Administration of serotonin and 5-HT_4 receptor agonist cisapride into the jejunum was followed by the appearance of spike activity, which spread from the stomach to the jejunum. Intraintestinal treatment with cisapride and serotonin shortened the period to recovery of the migrating myoelectric complex to 3 and 4 days, respectively. Our results suggest that serotonin plays a role in the regulation of the migrating myoelectric complex at the early postoperation period.

Key Words: *serotonin; cisapride; migrating myoelectric complex; stomach; small intestine*

Migrating myoelectric complex (MMC) serves as a major criterion of electrical activity of the gastrointestinal tract (GIT) in healthy animals. Serotonin is involved in the regulation of MMC. Previous studies showed that administration of serotonin or its precursor 5-hydroxytryptophan increases the rate of MMC, while antagonists of neural serotonin receptors decelerate MMC [10]. Moreover, destruction of enteric serotoninergic neurons interrupts MMC [8].

High concentrations of serotonin were detected in enterochromaffin cells (EC) located in GIT mucosa. EC cells of the small intestine secrete serotonin into the vascular bed and intestinal lumen, which is mediated by independent mechanisms of regulation. Nervous regulation of serotonin release in the duodenum and jejunum involves cholinergic, β-adrenergic, and NANC pathways [13]. Serotonin secreted by EC cells serves as the source of endogenous serotonin for 5-HT_4 receptor. These receptors are found on sensitive nerve endings in the mucosa [9]. Moreover, 5-HT_4 receptors are present on cholinergic interneurons of the myenteric plexus [11]. Activation of 5-HT_4 receptors increased acetylcholine release from enteric cholinergic neurons and stimulates motor activity of the intestine [12].

Motor activity of GIT decreases after abdominal surgery, which is manifested in the impaired generation of MMC [6]. Nitric oxide (NO) is a major inhibitory neurotransmitter in the intestinal wall. The intensity of NO synthesis increases after laparotomy [7]. NO directly inhibits basal secretion of serotonin into the intestinal lumen [13]. It can be hypothesized that serotonin release into the intestinal lumen is associated with activation of NO synthesis in the early postsurgery period. If suppression of MMC in the postsurgery period is rela-

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ted to a decrease in serotonin concentration in the intestinal lumen, intraintestinal administration of serotonin or its agonist should recover MMC.

Here we studied whether serotonin plays a role in the recovery of MMC after abdominal operations.

MATERIALS AND METHODS

Experiments were performed on 15 adult Wistar rats weighing 400 g. Before the study the animals fed a diet with natural products.

The animals were deprived of food for 18 h. Medial laparotomy was performed under hexenal anesthesia. A probe was implanted into the initial portion of the jejunum. Needle electrodes were fixed in the wall of the antrum in the stomach and initial portions of the duodenum and jejunum [1]. The probes and electrodes passed through soft tissues of the abdominal wall and pelvic region. They ran subcutaneously to emerge at a distance of 5-6 cm from the end of the tail [1].

Experiments were performed in the early postsurgery period (1-7 days after surgery). The animals were divided into 3 groups (5 rats per group).

Physiological saline was administered into the jejunum of control animals over 3 days after surgery. Group 2 and 3 rats received 4 mg/kg serotonin adipinate and 0.2 mg/kg cisapride (Coordinax). To provide similar conditions of treatment the volume of physiological saline in control rats was brought to the volume of dissolved drugs in experimental animals (0.2 ml).

Baseline electrical activity was recorded in fasting rats over 1 h. Electrical activity was recorded for 2-3 h after intraintestinal administration of the test preparation through a probe. On days 1 and 2 the rats intraintestinally received 8 ml glucose-saline solution after recording of electrical activity. A standard diet was given starting from the 3rd day. After surgery the rats had free access to water (except for the period of electrical activity recording). The animals were killed by a lethal dose of narcotic.

During recording of electrical activity the electrodes were connected to an amplifier (sensitivity 0.1 mV). Recording was performed within a narrow range of frequency (1-100 Hz). The output signal was transmitted to a computer. Study of the electromyogram included measurement of the following temporal characteristics: duration of MMC and length of phase III. The results were analyzed by pairwise Student's t test. The differences were significant at $p<0.05$.

RESULTS

Chaotic single action potentials and trains of weak action potentials were detected in the stomach, duodenum, and jejunum of rats on day 1 after surgery. Administration of physiological saline, serotonin adipinate, or cisapride was accompanied by the appearance of short-term action potentials (20 sec) on electromyograms of the jejunum. This effect was probably associated with direct stimulation of the mucosa. Electrical activity of the stomach, duodenum, and jejunum in control rats remained practically unchanged after administration of physiological saline. In group 2 and 3 animals, spikes of actions potential spreading from the stomach to the jejunum were observed 30-40 min after administration of the test preparations (Fig. 1). After treatment with cisapride actions potentials more rapidly spread to the jejunum (compared to experiments with serotonin). The pattern of electrical activity was similar to phase II of MMC (irregular activity). However, we revealed alternating phases of action potentials spreading from the stomach to the jejunum (1-2 min) and rest periods (5 min). Synchronous and chaotic potentials were not detected.

Electrical activity was recorded 1-7 days after surgery. All phases of MMC were subsequently recovered in the jejunum, duodenum, and stomach of control rats. Normal MMC spreading from the stomach to the jejunum was detected only on day 7 (Fig. 2, *a*). The duration of MMC and phase III was 650±50 and 210±60 sec, respectively.

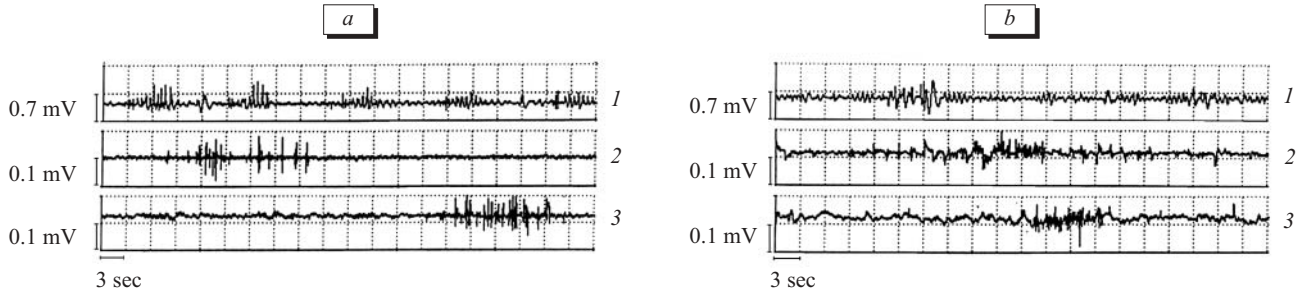

Fig. 1. Spread of action potentials from the stomach (*1*) to the duodenum (*2*) and jejunum (*3*) after intraintestinal administration of serotonin (*a*) and cisapride (*b*) on day 1 after surgery.

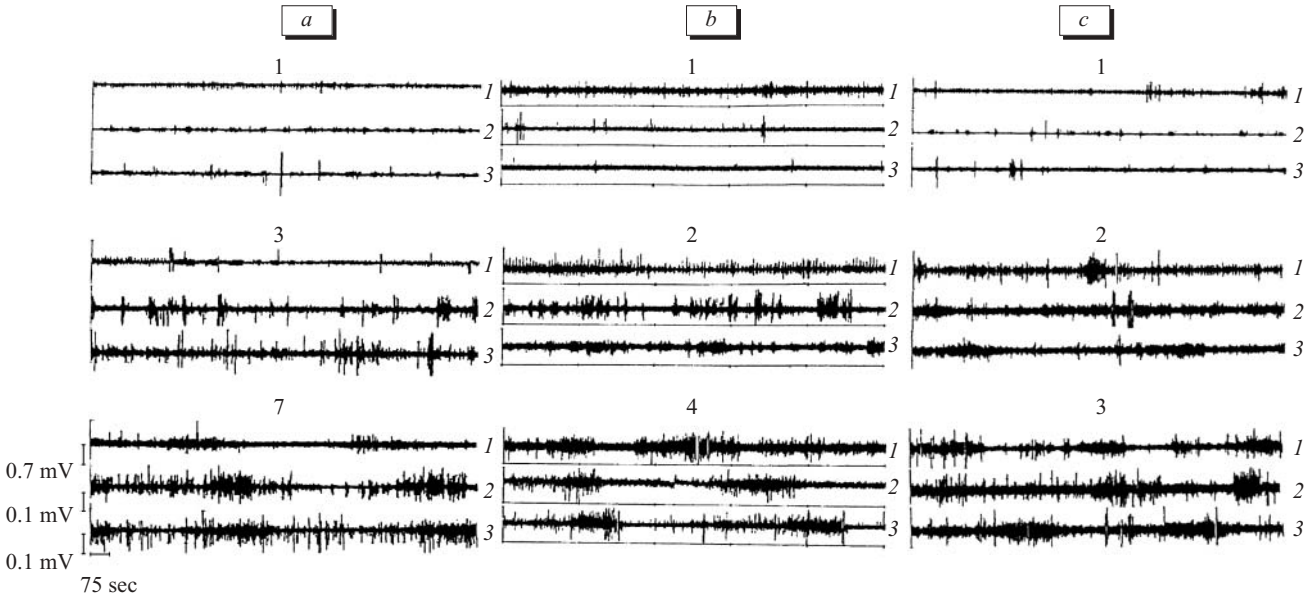

Fig. 2. Electrical activity of the stomach (*1*), duodenum (*2*), and jejunum (*3*) in rats of groups 1 (control, *a*), 2 (*b*), and 3 (*c*) at various periods after surgery.

Recording of baseline activity in group 2 rats on day 2 after surgery revealed MMC-like complexes that spread from the stomach to the jejunum (Fig. 2, *b*). The electromyogram included all phases of MMC. However, the length of phases II and III increased compared to normal. Baseline recording on day 4 after surgery revealed normal MMC spreading from the stomach to the jejunum. The duration of MMC and phase III was 660±35 and 260±45 sec, respectively.

Recording of baseline activity in group 3 rats on day 2 after surgery revealed MMC complexes of normal length, but reduced amplitude (Fig. 2, *c*). They spread from the stomach to the jejunum. The electromyogram included all phases. Baseline recording on day 3 after surgery found normal MMC, which began in the stomach and spread to the jejunum. The duration of MMC and phase III was 680±30 and 280±40 sec, respectively.

The test substances were administered intraintestinally, since serotonin produces a local effect and serves as a signal molecule in the mucosa to activate the peristaltic reflex [3,5]. Serotonin has an effect on 5-HT_4 receptors located on endings of afferent neurons [9]. Stimulation of these receptors causes peristaltic contraction, which is mediated by an excitatory neurotransmitter acetylcholine [2].

The prokinetic action of cisapride is associated with its antagonistic activity relative to 5-HT_4 receptors [2,4,5]. Previous studies showed that treatment of the mucosa with selective 5-HT_4 receptor agonists triggers the peristaltic reflex in the intestine of humans, rats, and guinea pigs [5]. The effect of exogenous cisapride on 5-HT_4 receptors on endings of afferent neurons in the mucosa is similar to that of serotonin (activation of the peristaltic reflex).

Our findings indicate that serotonin and 5-HT_4 receptor agonist cisapride are capable of triggering spike activity that spreads from the stomach to the jejunum. These results support the hypothesis that serotonin present in the intestinal lumen is involved in the regulation of peristalsis.

The impairment of electrical activity in GIT and disappearance of MMC were revealed in the early postsurgery period. The recovery of MMC spreading from the stomach to the jejunum occurred on day 7 after surgery. Intraintestinal administration of cisapride and serotonin shortened the period to recovery of MMC to 3 and 4 days, respectively. It can be hypothesized that serotonin plays a role of the excitatory neurotransmitter and regulates MMC at the early postsurgery period.

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