Effect of NO Synthesis Blocker on Electrical Activity of Rat Stomach and Small Intestine in the Early Postoperation Period

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The effect of NO on electrical activity of the stomach and small intestine was studied in chronic experiments on rats during the early postoperation period. Generation of migrating myoelectric complex in the stomach and small intestine was impaired after abdominal surgery. Administration of NO synthesis blocker suppressed the inhibitory influences, which potentiated generation of the myoelectric complex in the small intestine. Our results suggest that NO is involved in the regulation of the migrating myoelectric complex in the small intestine during postoperation motor disturbances in the gastrointestinal tract.

Key Words: *NO; migrating myoelectric complex; stomach; small intestine*

The simplest chemical compound NO is continuously produced by the enzymatic pathway and plays a role of a general metabolic regulator in animals and humans [1]. In humans NO radical is formed from arginine in the reaction catalyzed by enzyme NO synthase found in neurons of the myoenteral plexus. NO causes rapid hyperpolarization and relaxation of smooth muscle cells in the gastrointestinal tract (GIT) [11]. NO acts as an inhibitory neurotransmitter of nonadrenergic noncholinergic pathways in the intestinal wall.

Abdominal surgery is usually associated with inhibition of propulsive motor activity of the intestine [6].

Adrenergic and cholinergic nerve influences have an antagonistic function and play a role in the development of postoperation motor disturbances. The general mechanism of suppression of intestinal contractions is transmission of inhibitory impulses through sympathetic nerves to smooth muscles of the intestinal wall and smooth muscle cells in blood vessels [2]. The study of the pathogenetic mechanism of motor disturbances in GIT during functional intestinal obstruction (FIO) showed that adrenoblockers and sympatholytic compounds can block the inhibitory influences. These agents decrease excessive activity of the sympathetic nervous system [4]. However, sympathetic blockade does not necessarily recover motor function. Administration of adrenoceptor antagonist reserpine in a dose of 5 mg/kg only partially restored intestinal transit in experimental rats with postoperation intestinal obstruction [5]. The decrease in motor activity can result from activation of the inhibitory influences on the intestine. Previous studies showed that abdominal surgery activated the inhibitory nonadrenergic noncholinergic pathways in experimental animals. It was hypothesized that activation of NO synthesis plays a role in the pathogenesis of postoperation FIO [5].

The influence of NO on motor activity was estimated by studying evacuation function of the intestine after abdominal surgery [5]. Here we studied the effect of NO on electrical activity of the stomach and small intestine in the early postoperation period. We evaluated the influence of NO on migrating myoelectric complex (MMC), which serves as a major criterion of propulsive activity of GIT.

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MATERIALS AND METHODS

Experiments were performed on adult male Wistar rats (n=10) weighing 400 g. Before the experiment the animals fed a complete diet with natural products. Postoperation FIO can be simulated by laparotomy and intestinal manipulations [5].

A probe was implanted into the initial portion of the jejunum after medial laparotomy. Needle electrodes were fixed in the wall of the antrum in the stomach and initial portions of the duodenum and jejunum [3]. The probes and electrodes passed subcutaneously through soft tissues of the abdominal wall and pelvic region emerge 5-6 cm from the end of the tail [3].

The experiments were performed in the early postoperation period (1-5 days after surgery). The animals were divided into control and experimental groups (5 rats per group).

Physiological saline was administered to the jejunum in control animals over 3 days after surgery. Experimental rats received NO synthase inhibitor N-nitro-L-arginine methyl ester hydrochloride (L-NAME, Sigma) in a dose of 100 μg/kg. The control and experimental rats received an equivalent volume of physiological saline and inhibitor (0.2 ml), respectively, to provide similar conditions of treatment.

Baseline electrical activity was recorded in fasting rats of both groups over 1 h. The test preparation was administered intraintestinally through a probe. Electrical activity was recorded for 2-3 h after treatment. The rats intraintestinally received glucose saline in a dose of 8 ml per 400 g body weight after recording of electrical activity (days 1 and 2). The animals fed a standard diet 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 air embolism.

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

RESULTS

Single action potentials and individual trains of weak action potentials were detected on electromyograms of control rats on day 1 after surgery. In the duodenum and jejunum alternating rhythms with rest periods (25±5 sec) and activity phases (50±10 sec) were recorded; MMC was absent (Fig. 1).

Administration of physiological saline into the jejunum produced no significant changes in electromyograms of the stomach, duodenum, and jejunum (Fig. 2, *a*).

Recording of baseline activity in the stomach on day 3 after surgery revealed groups of trains of weak action potentials. Spike activity was most significant on electromyograms of the duodenum and jejunum. The type of electrical activity corresponded to phase II of MMC. We also observed short-lasting and chaotic phases III of different length.

Phases III of abnormal length appeared on day 5 after surgery. Electromyograms of the jejunum included 3 normal-length phases of MMC. However, generation of these phases was irregular.

On day 7 we recorded normal MMC propagating from the stomach to jejunum (Fig. 1). The duration of MMC and phase III was 650±50 and 210±60 sec, respectively. Generation of regular MMC on day 7 after surgery and recovery of total spike activity in various regions of GIT attest to normalization of coordinated

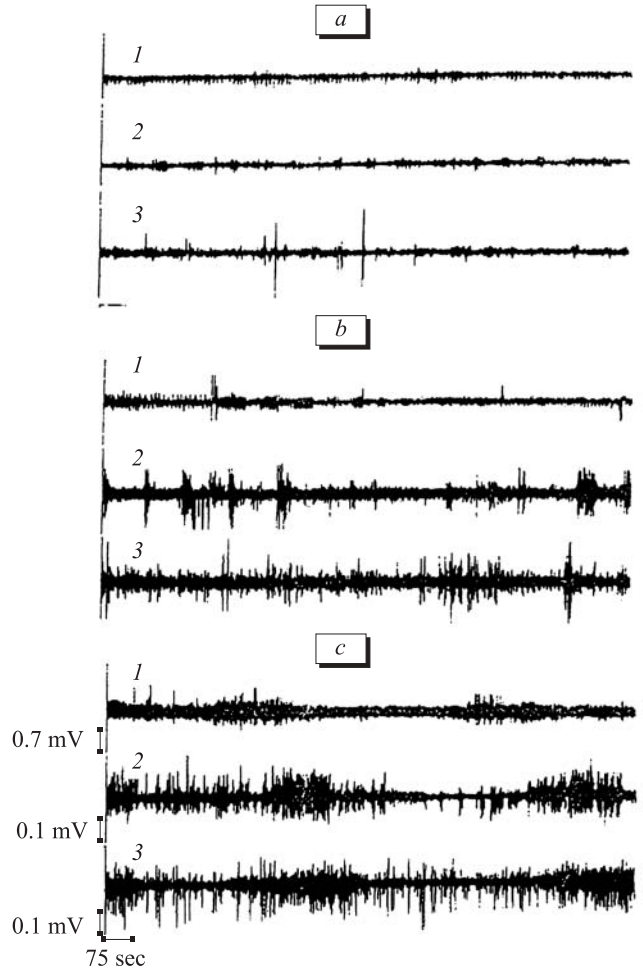

Fig. 1. Electrical activity of the stomach (*1*), duodenum (*2*), and jejunum (*3*) in control rats on days 1 (*a*), 3 (*b*), and 7 after surgery (*c*).

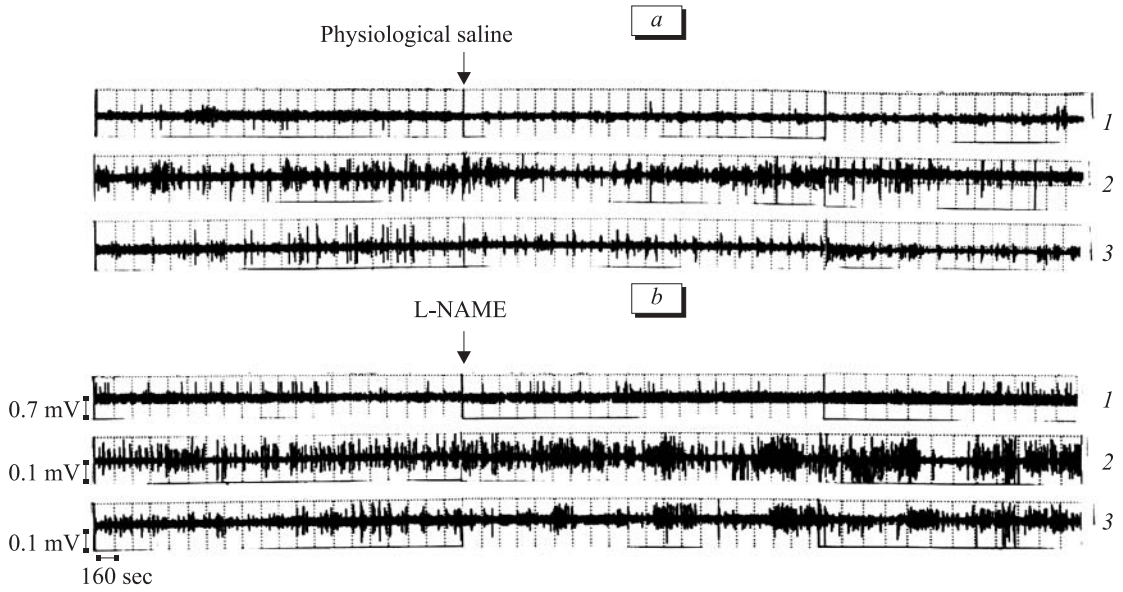

Fig. 2. Electrical activity of the stomach (*1*), duodenum (*2*), and jejunum (*3*) after administration of physiological saline into the jejunum of control (*a*) and L-NAME-receiving rats (*b*) on day 1 after surgery.

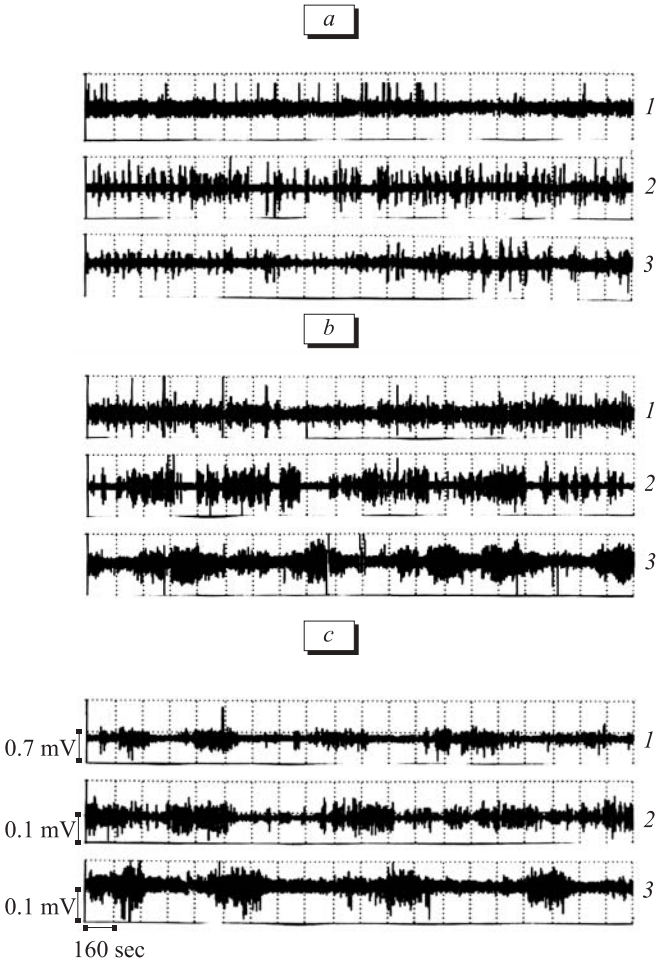

Fig. 3. Electrical activity of the stomach (*1*), duodenum (*2*), and jejunum (*3*) in experimental rats on days 1 (*a*), 3 (*b*), and 7 after surgery (*c*).

propagation of contractions along GIT and contractile activity of smooth muscles in the stomach, duodenum, and jejunum.

Experimental animals exhibited weak irregular spike activity of the stomach on day 1 after surgery. Single trains of weak action potentials were seen on electromyograms of the duodenum and jejunum. Periods of rest (25±5 sec) alternated with phases of activity (25±5 sec). MMC was absent (Fig. 3).

L-NAME produced no significant changes in spike activity of the stomach (Fig. 2, *b*). The study of electromyograms from the duodenum and jejunum revealed aboral propagation of MMC 13-15 min after L-NAME administration. The length of MMC phase III was 325±75 sec, which did not differ from normal. The duration of MMC significantly surpassed the normal (1200±100 sec).

On day 3 after surgery, irregular spike activity of the stomach manifested in trains of medium-amplitude action potentials. MMC propagating from the duodenum to jejunum was recorded (Fig. 3). The duration of phase III and MMC was 300±60 and 700±80 sec, respectively, which did not differ from normal.

Normal MMC propagating from the stomach to jejunum was recorded on day 5 after surgery (Fig. 3). The duration of MMC and phase III was 680±30 and 280±40 sec, respectively.

Electrical activity of GIT was markedly impaired in the early postoperation period. There is no general agreement about the time period for postoperation recovery of MMC. MMC phases in various portions of GIT are normalized over different periods. Normalization of MMC in one portion does not necessarily

reflect the recovery of coordinated motor activity in all portions of GIT. In our experiments motor activity of the stomach and jejunum retuned to normal on day 7 after surgery. L-NAME shortened the time of motor activity recovery (5 days).

Administration of L-NAME into the jejunum was followed by the appearance of MMC propagating from the duodenum to jejunum. Irregular spike activity was detected in the stomach. Our results are consistent with published data that NO is involved in the regulation of motor activity in the small intestine [10]. Examination of healthy volunteers showed that nonadrenergic noncholinergic inhibitory pathways have no effect on the time period of MMC in the antrum of the stomach, but modulate the duration of intestinal MMC. Infusion of L-arginine, which serves as a substrate of NO synthesis, lengthens the duration of MMC and inhibits spike activity of the small intestine. A phase I-similar pattern can be recorded under these conditions [9]. It was hypothesized that inhibitory impulses of NO suppress contractions of the small intestine and initiates MMC phase I [12].

In vitro experiments showed that nonadrenergic noncholinergic inhibitory impulses are conveyed to smooth muscles of the stomach. NO can play a role in the generation and modulation of inhibitory transmission [8]. These data suggest that NO is involved in the regulation of gastric MMC under normal conditions, but has little role in the postoperation inhibition of motor activity.

Our results suggest that generation of MMC in the stomach and small intestine is impaired during the early postoperation period. Suppression of inhibitory influences with NO synthesis inhibitor (nonadrenergic noncholinergic neurotransmitter) is followed by the appearance of MMC in the small intestine. It can be hypothesized that NO is involved in the regulation of small intestinal MMC during the early postoperation period.

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