Correction of Duodenal Smooth Muscle Contractility with Methacin and Proserin in Ulcer

S. V. Kuznetsov and N. N. Kuznetsova

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The aftereffects of experimental damage to the duodenal wall on the contractility are studied in isolated rat duodenum. Development of ulcer was associated with replacement of rhythmic contractions by slow-wave tonic activity. Methacin and proserin accelerate the repair processes and potentiate the compensatory reactions, promoting the shift of spontaneous activity of smooth muscles toward the slow part of the spectrum.

Key Words: *isolated intestine activity; ulcer; methacin; proserin*

Impairment of the mechanisms of nervous regulation of gastroduodenal activity underlies the development of gastroduodenal pathology. Disorders in the sympathic nervous function lead to predominance of the parasympathetic effects, which are paralleled by an increase in motor and secretory activities [3]. Stable pathological states can be corrected by a combination of the peripheral M-cholinolytic methacin and the acetylcholinesterase inhibitor proserin [5]. Experimental and clinical studies demonstrated a high efficacy of this therapy that normalizes the function and activates reparative processes in mediogastral and pyloroduodenal ulcers [1,6,7]. On the other hand, physiological mechanisms underlying the therapeutic effect are virtually unknown.

We studied spontaneous motor activity of duodenal smooth muscles during ulcer and therapy with cholinergic drugs.

MATERIALS AND METHODS

Experiments were carried out on isolated portions of the duodenum of male Wistar rats weighing 200-220 g. The duodenum from the pylorus to the U-loop was resected after ether anesthesia, laparotomy, and dissection of the common bile duct and pancreatic duct. In order to remove the intestinal contents, the preparation was washed with Krebs' solution of the following composition (mM/liter): 118 NaCl, 4.7 KCl, 2.52 $CaCl_2$, 1.64 $MgSO_4$, 24.88 $NaHCO_3$, 1.18 KH_2PO_4, and 5.55 $C_6H_{12}O_6$. Isolated duodenum was placed in a 25-ml incubation chamber (37.7°C) with Krebs' solution aerated with 4% CO_2/96% O_2 to attain pH of 7.4. The preparation was stretched with a micromanipulator to attain a half of the initial length and preincubated to stabilize motor activity. Contractions were recorded in isometric mode using a 6MKh1S mechanotrone with an N-339 autorecorder and output through a S9-8 oscillograph into a computer for spectral analysis. Digital information input was performed at 10 Hz frequency, the length of the processed site was 2048 digits, relevant realization time 204 sec. Power spectra were estimated using original software with the algorithm of Fourier's fast transforms in the 0-1 Hz band.

Three series of experiments were performed: with intact rat duodenum (n=11); with damaged duodenal wall (cryogenic exposure [2] 14 days before the examination, n=10); and rat duodenum after cryogenic exposure followed by drug correction of pathological changes (n=8). In the latter group, methacin was injected starting from day 4 after the operation twice daily intraperitoneally in a dose of 1 mg/kg and proserin subcutaneously in a dose of 0.1 mg/kg. The baseline activity of the duodenum and its changes after the addition of 0.25 ml methacin and proserin

I. M. Sechenov Institute of Evolutional Physiology and Biochemistry, Russian Academy of Sciences; Institute of Experimental Medicine, Russian Academy of Medical Sciences, St. Petersburg

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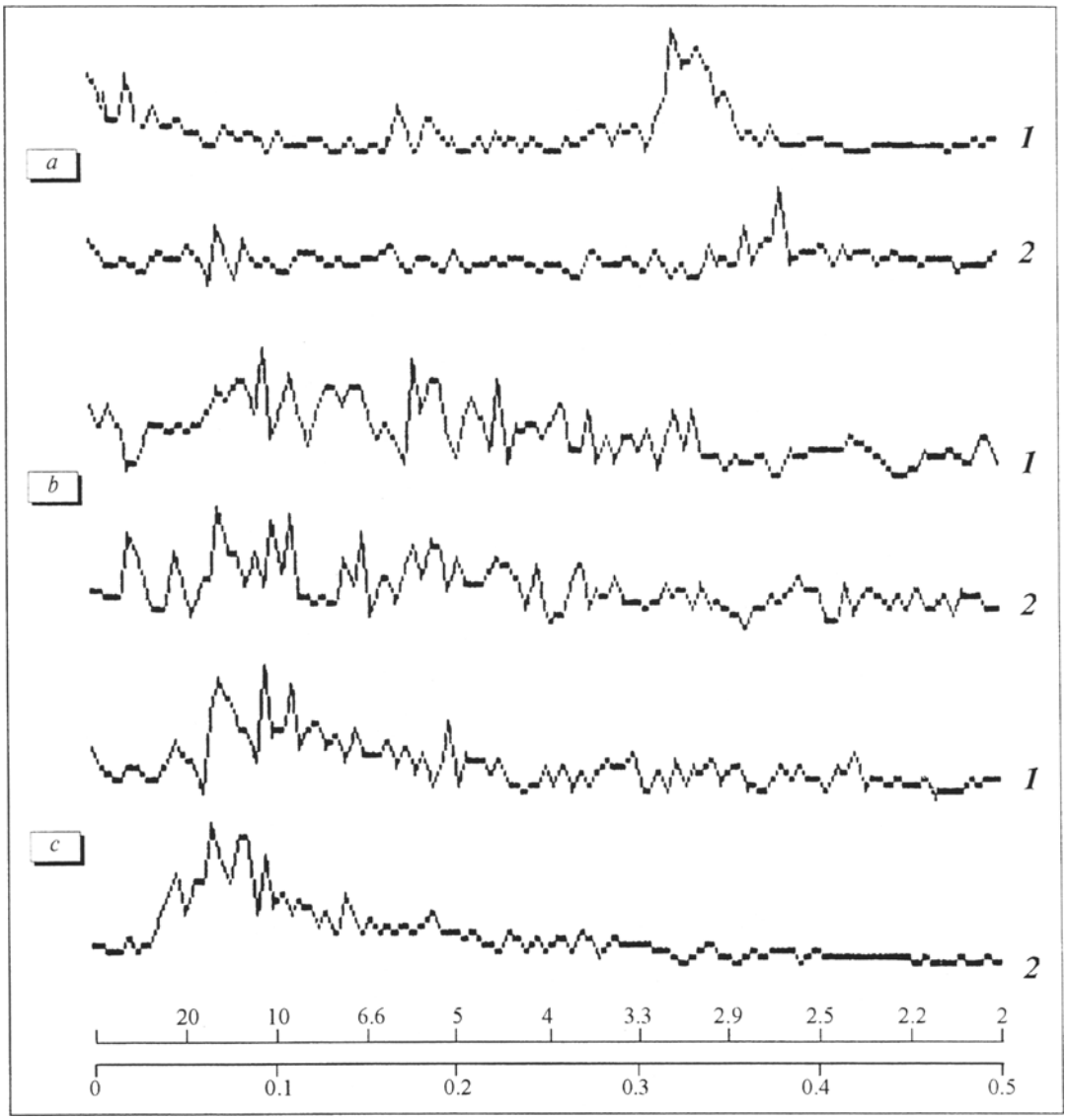

Fig. 1. Effect of the methacin—proserin combination on the spectrum of motor activity of isolated duodenum of intact rats (*a*) and of rats with cryogenic injury to the duodenal wall without (*b*) and with postoperative therapy (*c*). Mean values of 8-11 individual realizations are presented. Here and in Fig. 3: abscissa: upper scale — period of contractions, sec; lower scale — rhythm frequency, Hz. Ordinate: spectrum power, standard (maximum spectral component is taken for 1). Here and in Fig. 2: *1*) basal; *2*) after methacin and proserin (concentrations 10^{-8} and 10^{-9} M, respectively).

in concentrations of 10^{-8} and 10^{-9} M, respectively, were recorded in each series of experiments in order to assess muscle reactivity to this combination.

A series of experiments was carried out in 6 intact rat duodenum preparations with the addition of methacin and proserin in ascending concentrations (from 10^{-8} to 10^{-4} M and from 10^{-9} to 10^{-5} M, respectively). The preparations were washed after each solution.

RESULTS

Spontaneous contractility of isolated intact rat duodenum represents a complex periodical process characterized by the predominance of contractile rhythm with about 3-sec period, the contractions developing at the peak of 6-12-sec waves. The amplitude of contractions is modulated by the rhythm of slow waves with a period of about 50 sec (Fig. 1, *a*). The addition of methacin and proserin (MP) to incubation medium negligibly shifted the main rhythm and accelerated the rhythm with a period of about 14 sec, and the amplitude of contractions increased (Fig. 2, *a*). Subsequent (without washing the preparation) addition of the M-cholinolytic atropine in concentrations 10^{-9}-10^{-7} M virtually did not change the duodenal activity, whereas the N-cholinolytic ganglerone (1.5×10^{-4} M) markedly decreased the amplitude of

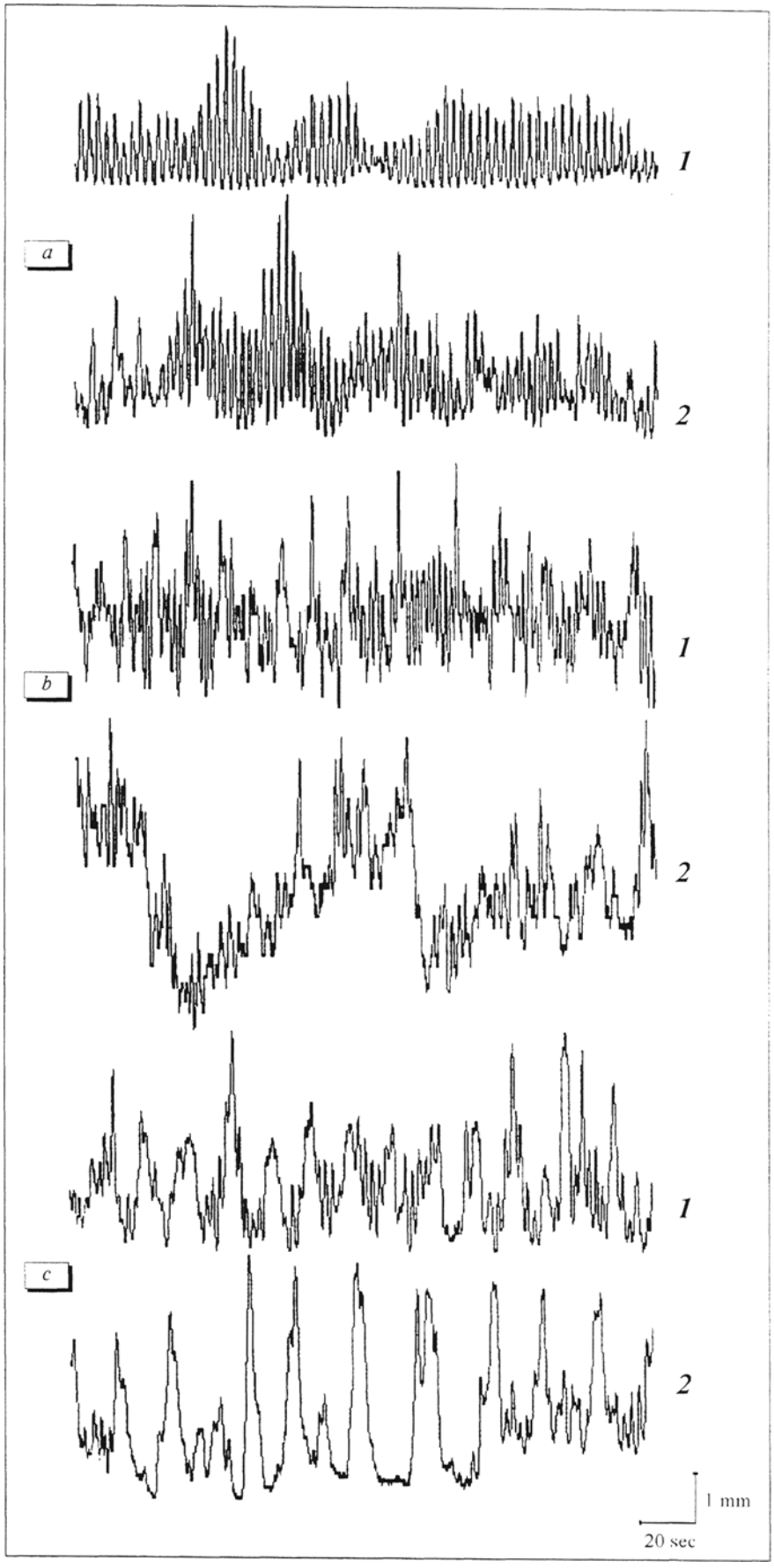

Fig. 2. Mechanograms of contractions of isolated duodenum of intact rats (*a*) and rats with cryogenic injury to the duodenal wall without (*b*) and with postoperative therapy (*c*) before (*1*) and after (*2*) addition of methacin and proserin in incubation medium.

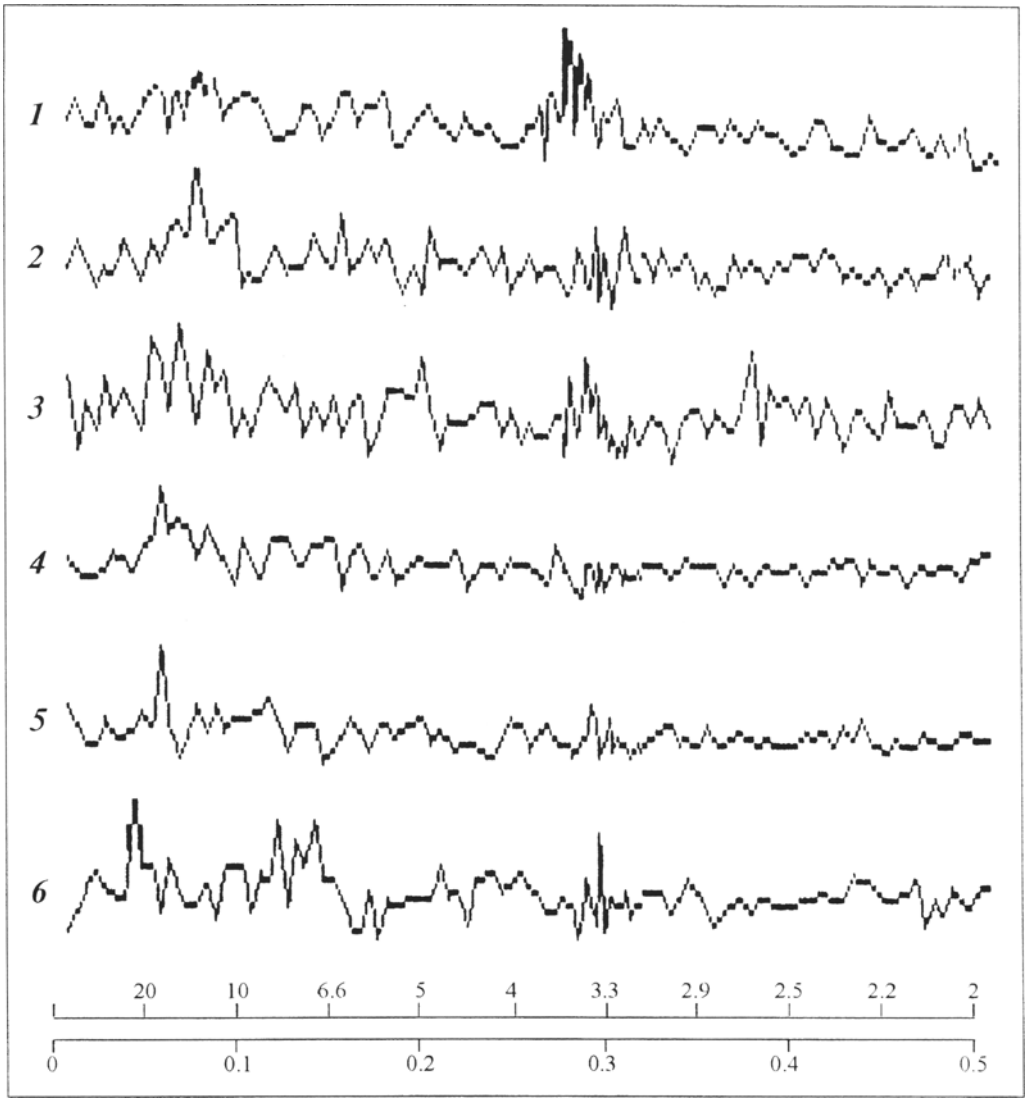

Fig. 3. Modified mean spectrum of the power of isolated duodenum of intact rats after addition of methacin and proserin in ascending concentrations. Basic activity (*1*); after methacin and proserin in concentrations 10^{-8} and 10^{-9} M (*2*), 10^{-7} and 10^{-8} M (*3*), 10^{-6} and 10^{-7} M (*4*), 10^{-5} and 10^{-6} M (*5*), and 10^{-4} and 10^{-5} M (*6*), respectively.

rhythmic (3-sec) contractions, although did not completely stop them. Analysis of basal rhythm showed a wide spectrum of contractions, including both the rhythmic (in our experiment mainly the penduliform) and fast and slow tonic contractions, in the duodenum isolated from the extramural nervous effects. The pronounced rapid tonic (propulsive) contractions correlate with inhibition of M-cholinoreceptors by methacin, while the amplitude increase may be due to activation of N-cholinoreceptors with proserin. Increased tonic contractions at various concentrations of MP in the incubation medium are shown in Fig. 3. The maximum power of the spectrum is shifted to the left with the dose increase, and the rhythm of about 30-sec period becomes predominant.

Shift of the spectrum of contractions towards slow-wave activity is characteristic of rats with ulcerative involvement of the duodenal wall. The maximum of spectrum power is not clearly expressed (Fig. 1, *b*), and the decasecond rhythm predominates, on which 3- and 5-sec rhythms are superimposed (Fig. 2, *b*). Addition of MP prolonged the period and, to a lesser extent, the amplitude of the basal rhythm of contractions. The 3-sec rhythm is reduced. The smooth-muscle preparation relaxes and the period of the rhythm of tonic contractions expands to about a minute (Fig. 2, *b*). Inhibition of rhythmic contractions in our experiments agrees with the results of experiments on vagotomized animals. The hungry motor activity of the duodenum is characterized by almost twofold decreased frequency of rhythmic segmentation [4]. On the other hand, the presence of both 3- and 5-6-sec rhythms in the intact rat duodenum and their different expression in ulcer

and drug treatment permits us to hypothesize that the rhythm of 12 contractions per minute is tonic.

The rhythm of spontaneous contractions of the duodenum is decelerated in rats subjected to operation and therapy. The 11-14-sec rhythm predominates in the polymorphous activity including 5- and 20-25-sec waves (Fig. 1, *c*). Oscillations of 3-sec rhythm developing at the height of slow waves are weak. Addition of MP induced reactions similar to those observed in previous group, but without pronounced changes in tonic activity of smooth muscles (Fig. 2, *c*). Addition of atropine and ganglerone did not change the amplitude or period of the basic (decasecond) rhythm of contractions, suggesting the presence of myogenic mechanisms of slow contractility. Cooling of duodenal preparation at 2°C for several hours, which causes selective death of myoenteral cholinergic nervous structures containing α-adrenoreceptors [11] and inhibition of the peristaltic reflex [12], virtually did not change the reaction of smooth muscles to MP.

Morphological control on day 15 after operation showed a smaller damage to the duodenum of rats treated with cholinergic drugs than in untreated animals (ulcer area 2.0±0.5 and 5.5±0.7 mm^2, respectively).

These results demonstrate similar activities of isolated rat duodenum with ulcer and of duodenum in patients with duodenal ulcer. Gastric secretion with low pH in such patients flows into the duodenum during the entire second phase (solitary nonpropulsive waves) of the digestive cycle [4]. Acceleration of the second phase and intensification of the third phase (more frequent generation of the migrating myoelectric complex) are believed to be a peculiar defense and compensatory reaction of the antral portion of the intestine to functional disorders caused by increased gastric acid secretion [4,10]. It is noteworthy that a tendency towards generation of tonic (peristaltic) contractions, which developed during 14 days after cryogenic injury, was fixed at the level of smooth muscles. The probability of autoregulation of enzymatic and transport processes at the level of individual systems or even an individual cell has been discussed [9]. The development of tonic contractions is inversely related to the activity of M-cholinoreactive structures, but their origin is, if not myogenic, at least noncholinergic. The mechanisms leading to disappearance of rhythmic contractions in duodenal ulcer are unknown. An increase in the frequency and amplitude of 3-sec rhythm of intact rat smooth muscle contractions after the addition of MP and suppression of the amplitude with ganglerone imply an N-cholinergic regulation of this type of activity. The absence of potentiating effect of the studied combination of drugs in ulcer can be explained by impaired contractility of the circulatory muscles participating, along with the longitudinal muscles, in the penduliform contractions of the duodenum.

Thus, our results indicate that the coordination of duodenal smooth muscle contractility in ulcer is impaired. Mechanisms leading to replacement of rhythmic activity by tonic (peristaltic) activity are localized at the level of the intestinal wall and can function during complete external denervation. The therapeutic effect of the methacin—proserin combination accelerating the reparative processes is not due to normalization of the functional shifts in the intestinal motor activity, but to potentiation of the compensatory defense mechanisms aimed at intense release of the duodenum from gastric acid.

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