Experimental Gastric Ulcer: Gastro- and Duodenoprotective Effects of Sibusol

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We studied the influence of pretreatment with chemical mildronate analogue sibusol on the course of experimental gastric ulcer in rats. Sibusol produced a protective effects on the stomach and duodenum.

Key Words: *stomach; duodenum; sibusol; experimental ulcer*

Aggressive factors of the gastric juice [1], changes in motor and evacuation functions of the stomach and duodenum [3], and variations in regional circulation [2] modulate the resistance of the gastroduodenal mucosa to exogenous and endogenous ulcerogenic agents. Rheogastrography revealed impaired arterial blood supply and venostasis in patients with peptic ulcer disease. These changes lead to the development of hypoxia in the gastric and duodenal mucosa [6].

Changes in the intensity of lipid peroxidation and dysfunction of the antioxidant system in the gastroduodenal mucosa are aggressive factors that promote ulceration [5]. Oxygen partly bypasses the major enzymatic reduction pathway and is involved in free radical processes of lipid peroxidation, which results in generation of reactive oxygen species and lipid peroxides. These abnormalities of lipid peroxidation in the gastroduodenal mucosa play an important role in local mechanisms of ulcerogenesis.

Mildronate normalizes vascular tone, inhibits platelet aggregation and fatty acid oxidation, and optimizes oxygen consumption during myocardial ischemia [4]. Here we evaluated whether the mildronate analogue sibusol can be used for prevention of ulceration.

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MATERIALS AND METHODS

Gastric ulcer was produced by application of 100% acetoacetic acid to the serosa of the greater curvature at the boundary between antral and fundal portions of the stomach. Electromotor activity (EMA) of the stomach and duodenum was recorded before and during application of chemical irritant. Experiments were performed on male and female Wistar rats under Narcoren anesthesia (35 mg/kg intramuscularly). EMA of the stomach and duodenum was recorded using bipolar extracellular silver electrodes (contact surface area 1.5-2.0 mm^2, interelectrode distance 1.5-2.0 mm). We recorded the amplitude and frequency of slow and rapid waves in EMA of the stomach and duodenum. Sibusol was administered in a dose of 100 mg/kg.

RESULTS

The baseline frequency and amplitude of slow waves in EMA of the gastric fundus in intact rats were 4.0±0.3 oscillations per minute (opm) and 0.13±0.04 mV, respectively. The baseline frequency and amplitude of slow waves in EMA of the gastric antrum were 4.5±0.5 opm and 0.27±0.30 mV, respectively. The baseline frequency of slow waves in EMA of the duodenum was 29.6±1.4 opm. It should be noted that slow waves were arranged in bursts of 8.1±0.7 slow waves (3.7±0.6 bursts per minute). The amplitude of slow waves in bursts increased from 0.16±0.04 (initial point) to 0.4±0.1 mV (mid-maximum point, Fig. 1, *a*).

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Sibusol changed EMA of the gastric fundus. The frequency and amplitude of slow waves in EMA increased to 6.0±1.3 opm (50%, $p<0.05$) and 0.26±0.02 mV (by 2 times, $p<0.05$), respectively. Spike activity was revealed in 20% records. Administration of sibusol was accompanied by changes in EMA of the gastric antrum. The frequency of slow waves in EMA increased to 6.0±0.8 opm (33%, $p<0.05$). However, the

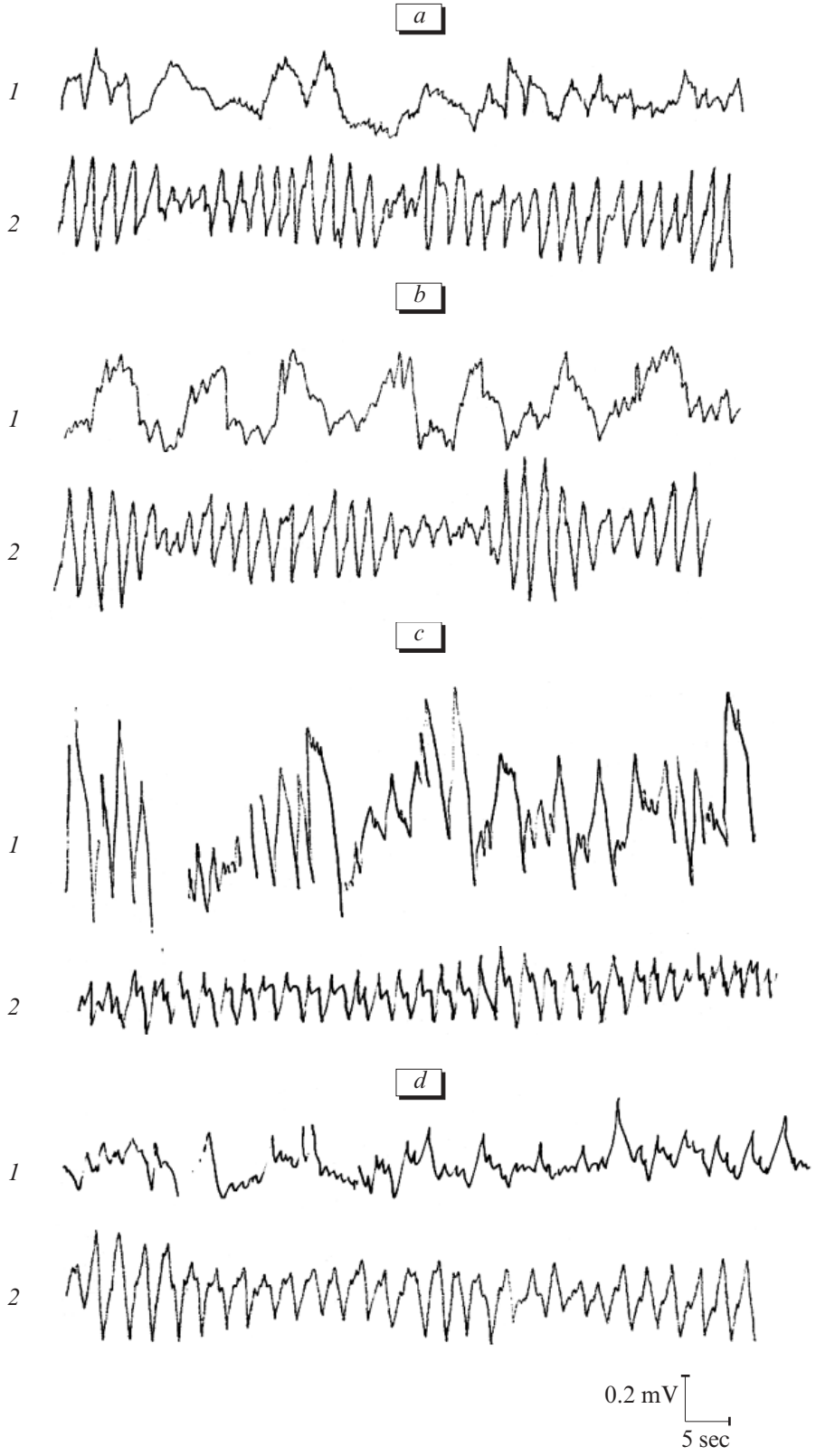

Fig. 1. Electromotor activity of the gastric antrum (*1*) and duodenum (*2*) before (*a*) and during administration of sibusol (*b*). Modeling of gastric ulcer (*c*) after pretreatment with sibusol (*d*).

amplitude of slow waves remained practically unchanged (0.32±0.05 mV, 18%, $p>0.05$). Sometimes we observed low-amplitude spike activity (0.22±0.07 mV) with a frequency of 0.33±0.07 spikes per 100 slow waves. These changes reflected the increase in contractile activity of smooth muscles in the stomach (Fig. 1, *b*).

Sibusol affected EMA of the duodenum. The frequency of slow waves in EMA was 28.9±3.3 opm (3%, $p>0.1$). Slow waves were arranged in bursts of 6.9±0.7 slow waves (lower by 18%, $p<0.05$). Their frequency remained practically unchanged (3.8±0.4 bursts per minute). The amplitude of slow waves in bursts increased from 0.22±0.07 (initial point, by 37.5%, $p>0.05$) to 0.6±0.1 mV (mid-maximum point, by 50%, $p<0.05$). These variations in EMA of the duodenum reflect an increase in the amplitude and decrease in the frequency of slow waves. Therefore, sibusol produced ionotropic and chronotropic metabolic changes.

Application of acetoacetic acid to the boundary between the antral and fundal portions of the stomach sharply increased EMA of the gastric antrum (Fig. 1, *c*). During application of this irritant the amplitude and frequency of slow waves in EMA sharply increased and reached 1.1±0.1 mV (210%, $p<0.05$) and 14.0±0.5 opm (350%, $p<0.05$), respectively. Application of the chemical irritant increased the frequency and amplitude of slow waves in EMA of the gastric fundus to 17.5±0.5 opm (272%, $p<0.05$) and 0.35±0.06 mV (191%, $p<0.05$), respectively. The frequency of spike activity was 0.76 spikes per 100 slow waves. Application of acetoacetic acid to the boundary between the fundal and antral portions of the stomach increased the amplitude of slow waves in EMA of the duodenum to 0.25±0.03 mV (13%, $p>0.05$). The frequency of spike activity was 0.72 spikes per 100 slow waves (Fig. 1, *c*).

Modeling of gastric ulcer 0.5 h after sibusol administration only slightly changed EMA in the fundal and antral portions of the stomach. The frequency and amplitude of slow waves in EMA of the gastric antrum were 5.2±0.6 opm (13%, $p>0.05$) and 0.34±0.06 mV (6%). Low-amplitude spike activity with a frequency of 0.40±0.08 spikes per 100 slow waves was observed in 50% recordings (21%, $p>0.05$, Fig. 1, *d*).

Minor changes were revealed in EMA of the duodenum. The frequency of slow waves in EMA of the duodenum was 27.6±2.2 opm (4%). Slow waves were arranged in bursts of 6.9±0.7 slow waves. The amplitude of slow waves in bursts increased from 0.20±0.04 (initial point) to 0.52±0.18 mV (mid-maximum point, 13%).

Our results indicate that pretreatment with sibusol prevents the increase in motor activity of the stomach and duodenum during experimental gastric ulcer. Therefore, sibusol produces a protective effect on the stomach and duodenum.

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