Possible Mechanism Underlying the Effect of Semax on the Formation of Indomethacin-Induced Ulcers in Rats

S. E. Zhuikova, V. I. Sergeev, G. E. Samonina, and N. F. Myasoedov*

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Intraperitoneal injection of Semax (synthetic analogue of $ACTH_{4-7}$, MEHFPGP) in a dose of 50 mg/kg produced a protective effect on rats with experimental indomethacin-induced ulcers. Experiments on narcotized rats showed that Semax in the studied dose had no effect on basal blood flow in the stomach, but prevented reduction of blood flow induced by indomethacin. The antiulcer effect of Semax is probably related to improvement of blood flow in the gastric wall disturbed by indomethacin.

Key Words: *Semax; indomethacin; gastric ulcer; gastric blood flow*

Semax in a synthetic analogue of $ACTH_{4-7}$ (MEHFPGP) possessing no hormonal activity [2]. The compound exhibits antiamnesic [6] and antihypoxic properties [2], improves learning under various experimental conditions [2], increases blood supply to the brain in humans and animals [2], and possesses antithrombotic activity [1]. Previous experiments demonstrated pronounced antiulcer effects of Semax in animals exposed to water-immersion immobilization stress or receiving ethanol and acids [4].

It is currently accepted that nonsteroid antiinflammatory drugs (NSAID), including indomethacin, cause gastrointestinal disorders in humans. NSAID produce ulcers in the stomach and duodenum in 25% patients. In these patients the risk of various complications of ulcer disease (*e.g.*, bleeding and perforations) increases by 2-5 times [7,9,10].

The mechanism underlying ulcerogenic activity of NSAID remains unclear. The main factors facilitating ulcer formation after NSAID therapy are impaired prostaglandin synthesis, decreased production of mucus and bicarbonates, and enhanced generation of free radicals [7,15]. Ulceration can also result from circulatory disturbances in the stomach [11,12,14,15].

Here we studied the effect of Semax (synthesized at the Laboratory of Regulatory Peptides, Institute of Molecular Genetics) on indomethacin-induced ulceration in rats. For evaluation of the mechanism of antiulcer activity of Semax we determined its effects on basal blood flow in the stomach in normal and after treatment with indomethacin.

MATERIALS AND METHODS

Experiments were performed on male outbred albino rats weighing 200-250 g. Damages to the gastric mucosa (GM) were produced by intraperitoneal injection of 25 mg/kg indomethacin (Troya-Pharm) after 24-h starvation. The animals were killed 3 h after treatment. The area of damages was measured using a binocular lens equipped with an ocular micrometer. Semax in a dose of 50 mg/kg was injected intraperitoneally 10 min after administration of indomethacin. Control animals received an equivalent volume of 0.9% NaCl.

Gastric blood flow was determined in urethane-anesthetized rats (1 g/kg). Local circulation was estimated by the hydrogen clearance method after 24-h starvation. The curve of saturation and clearance of GM from inhaled hydrogen were recorded. Floating

Department of Human and Animal Physiology, Biological Faculty, M. V. Lomonosov Moscow State University; *Department of Chemistry of Physiologically Active Substances, Institute of Molecular Genetics, Russian Academy of Sciences, Moscow. ***Address for correspondence:*** Samonina@pisem.net. Samonina G. E.

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platinum microelectrodes (tip diameter 5-10 μ) were fixed in the wall of the gastric fundus [3,5]. The measurements were performed for 2.5 h with 10-min intervals. The stomach was protected from drying and light. Body temperature in animals was maintained at a constant level. Gastric circulation was reduced with 25 mg/kg indomethacin administered 30 min after recording of the basal blood flow.

Semax (50 mg/kg) was injected intraperitoneally 30 min after recording of the basal blood flow or 10 min after administration of indomethacin. Control animals received an equivalent volume of 0.9% NaCl. Changes in blood flow produced by preparations were expressed in percents of the baseline.

The results were analyzed by ANOVA.

RESULTS

Indomethacin damaged GM and induced the formation of hemorrhages in the gastric body. Semax decreased the area of damages by 70% compared to the control (0.54±0.22 and 1.58±0.46 mm^2, respectively, $p<0.05$). Hence Semax possesses protective activity during ulceration produced not only by stress, ethanol, and acetic acid [4], but also by NSAID.

Ulceration is often accompanied by reduction of regional blood flow in the stomach. Substances that improve GM circulation produce an antiulcer effect [14]. The data on the effect on indomethacin on microcirculation in the stomach are contradictory. It was shown that indomethacin has no effect on the basal blood flow, but reduces circulation in animals with ulcers induced by acetic acid [8]. Other authors reported that indomethacin increases blood concentration of endothelin [12], increases the amplitude and rate of gastric contractions [15] and, therefore, reduces basal blood flow in the stomach.

In our experiments indomethacin in a dose of 25 mg/kg caused a significant and long-lasting reduction of blood flow in GM. In control animals gastric circulation remained unchanged for 2.5-3 h (85 ml/100 g tissue/min). The intensity of blood flow in the stomach 10-20 and 30-40 min after administration of indomethacin decreased by 20 and 40%, respectively, and remained low to the end of observations (Fig. 1).

Intraperitoneal injection of Semax in a single dose of 50 mg/kg had no effect on the basal blood flow in the stomach, but abolished indomethacin-induced reduction of gastric circulation in narcotized rats. Semax injected 10 min after indomethacin attenuated reduction of blood flow (by 2 times, Fig. 1). Our results show that Semax enhances gastric circulation in the stomach, which is probably associated with its ability to improve rheological properties of the blood. *In vivo* experiments demonstrated that Semax possesses anti-

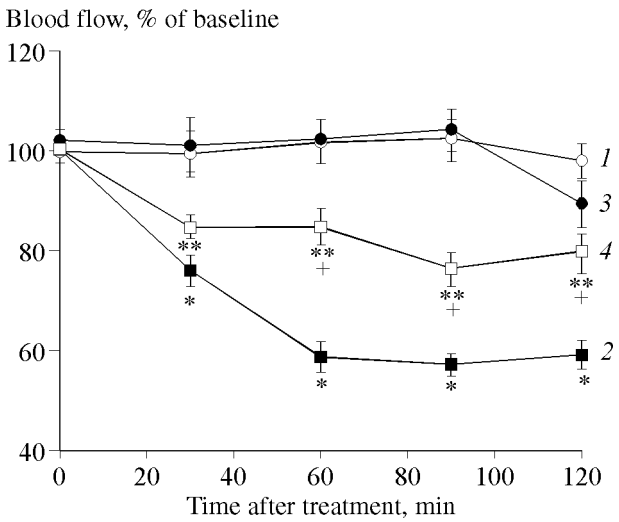

Fig. 1. Effects of Semax on basal blood flow and indomethacin-induced reduction of gastric ulceration: control (*1*), 25 mg/kg indomethacin (*2*), 50 mg/kg Semax (*3*), and Semax injected 10 min after indomethacin administration (*4*). *$p<0.001$ and **$p<0.01$ compared to the control; $^+p<0.01$ compared to indomethacin.

coagulant and fibrinolytic activities and prevents platelet aggregation [1].

The incidence of GM ulcers in patients receiving NSAID correlates with the extent of blood flow reduction produced by these drugs. The ability of drugs to restrict gastric circulation decreases in the following order: phenylacetic acid-oxycams-propionic acid. Therefore, the incidence of ulceration is higher in patients treated with phenylacetic acid [13]. Our results indicate that indomethacin reduces blood flow in the stomach, which probably underlies the formation of GM injuries produced by this NSAID.

Semax improves gastric circulation impaired by indomethacin, which contributes to the protective effect of this peptide during indomethacin-produced ulceration. It should be emphasized that Semax decreases the severity of GM damages induced by other ulcerogenic factors, which is probably related to the improvement of gastric circulation.

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