Effect of Semax on Homeostasis of Gastric Mucosa in Albino Rats

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The $ACTH_{4-7}$ analogue Semax administered intraperitoneally in a dose of 50 μg/kg 1 h before exposure to ulcerogenic factors (ethanol, water immersion immobilization stress) protected gastric mucosa from damage. Postoperative treatment with Semax for 5 days after application of glacial acetic acid on the mucosa prevented acetic acid-induced ulcers and promoted their healing. The antiulcer effects of Semax in the studied dose were comparable with those of tripeptide Pro-Gly-Pro in a dose of 1 mg/kg.

Key Words: *proline-containing oligopeptides; Semax; gastric ulcer*

We have previously shown that some short proline-containing peptides protect gastric mucosa (GM) from damage caused by ethanol, indomethacin, forced swimming, stress, glacial acetic acid, and pyloric ligation [1,4]. The most stable antiulcer effects were produced by tetrapeptide Gly-Pro-Gly-Gly [1] and tripeptide Pro-Gly-Pro (PGP) [1,4].

In the present study we tested Semax as a potential modulator of GM homeostasis. Semax is a synthetic analogue of $ACTH_{4-7}$ with C-terminal Pro-Gly-Pro sequence [3] possessing no hormonal activity. Semax stimulates learning in different behavioral tests under normal and pathological conditions [3,10], exerts antihypoxic [3,5,9] and antiamnestic [9] effects, and improves cerebral circulation [3,6,8] in humans and animals. Semax is used in clinical practice for the treatment of ischemic stroke [7].

Antiulcer activity of this peptide has not been studied yet, therefore, in this work we compared the effects of Semax and PGP on GM resistance to various ulcerogenic factors (ethanol, stress, and glacial acetic acid).

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MATERIALS AND METHODS

Three experimental models were used for evaluation of antiulcer potency of test oligopeptides: intragastric administration of ethanol, water-immersion immobilization stress, and application of glacial acetic acid of GM. Immobilization stress was modeled on male Wistar rats weighing 190-250 g. Other experiments were performed on male outbred rats of the same weight.

The animals were deprived of food, but were allowed free access to water for 24 h before the experiments. Ethanol (96%, 1 ml/200 g body weight) was introduced through a gastric tube and the animals were decapitated 1 h after administration. In the model of immobilization stress the animals fixed in the supine position were immersed into water (16°C) for 3 h. Acetic acid was applied as described earlier [15]. Glacial acetic acid was applied to the gastric serous membrane for 15 sec under ether anesthesia and the rats were sacrificed 5 days after surgery.

After decapitation, the stomach was isolated and cut along the lesser curvature. The severity of damage was measured as the total lesion area of GM using a binocular microscope with ocular micrometer.

Both Semax and PGP were synthesized at the Laboratory of Regulatory Peptides, Institute of Molecu-

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TABLE 1. Effects of Semax and PGP on Ulceration and Healing of Gastric Mucosa in Rats (*M*±*m*)

Index	Control (*n*)	Semax (*n*)	PGP (*n*)
Area of gastric lesions, mm²			
after ethanol	21.3±4.2 (19)	6.0±1.2* (18)	8.9±1.8* (17)
after immobilization stress	1.9±0.3 (26)	0.8±0.1** (10)	1.2±0.2*** (22)
The number of rats with cicatrized acetic acid-induced ulcers on day 5 after surgery, %	26.8±6.5 (24)	72.5±11.1*** (24)	54.4±3.6*** (11)

Note. *$p<0.001$, **$p<0.01$, ***$p<0.05$ in comparison with the control.

lar Genetics, Russian Academy of Sciences. In the ethanol and stress models, Semax (0.05 mg/kg) or PGP (1 mg/kg) were injected intraperitoneally in a volume of 0.5 ml/200 g body weight 1 h before the exposure. For evaluation of the effect of Semax and PGP on acetic acid-induced ulceration, the peptides were injected immediately after surgery and then daily for 4 days. The control group received the same volume of isotonic NaCl.

The data were analyzed statistically using Student's *t* test and Wilcoxon—Mann—Whitney nonparametric *U* test.

RESULTS

Intragastric administration of ethanol caused extensive hemorrhagic lesions located primarily on the surface of gastric folds (Table 1). Semax and PGP exhibited similar protective effect (Table 1) and reduced the severity of lesion by 72% and 59%, respectively (difference is insignificant).

Compared to ethanol, stress caused less pronounced damage to GM: these were small scattered ulcers, which are usually referred to as stress-induced ulcers [12]. Semax and PGP reduced the severity of GM lesions by 60 and 38%, respectively (Table 1). Similarly to the ethanol model, the difference in their efficiency was insignificant.

Topical applications of glacial acetic acid to the gastric serous membrane caused single ulcer with wall-encircled deep craters. Postoperative treatment with both Semax and PGP accelerated ulcer healing: on day 5 after surgery, the percentage of rats with cicatrized acetic acid-induced ulcers in both experimental groups was significantly higher than in the control (Table 1). In addition, PGP significantly decreased the mean area of acute ulcers (3.4±1.2 *vs.* 9.1±1.7 mm² in the control, $p<0.05$). In rats treated with Semax, this area did not significantly differ from the control (12.2±2.9 mm², $p>0.05$).

Thus, our data indicate that Semax protects GM from acute damage caused by ethanol and stress. It also prevents acetic acid-induced ulceration and promotes healing of these ulcers. Since Semax was effective in a considerably lower dose compared to PGP, its effect is most probably determined by the whole Semax molecule rather than PGP fragment formed after its proteolysis.

The protective effect of Semax can be explained by its ability to improve hemodynamics. It is known that ethanol [13] and water-immersion immobilization stress [11] considerably impair GM circulation. There are no data on the effects of Semax on gastric circulation, however it exhibits spasmolytic effect on brain vessels [6] and improves rheological properties of the blood due to anticoagulant and fibrinolytic activities and inhibition of platelet aggregation [2]. This probably explains accelerated healing of acetic acid-induced ulcers in Semax-treated animals, since drugs improving GM circulation also showed antiulcer activity in this model [14].

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