# PHARMACOLOGY AND TOXICOLOGY

# Selank and Its Metabolites Maintain Homeostasis in the Gastric Mucosa

**T. S. Pavlov, G. E. Samonina, Z. V. Bakaeva, Yu. A. Zolotarev, and A. A. Guseva**

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 143, No. 1, pp. 57-59, January, 2007
Original article submitted May 29, 2006

Antiulcer properties of a synthetic anxiolytic Selank and *in vivo* formed metabolites of this compound were studied on 3 experimental models of ulceration. The test peptides decreased the area of experimental gastric ulcers.

**Key Words:** *Selank; glyprolines; gastric ulcer*

Glyprolines belong to the family of regulatory peptides characterized by similar structure and biological activity (oligopeptides containing glycine and proline: GP, PG, and PGP). They enter the composition of some hybrid peptides, including synthetic heptapeptides MEHFPGP (Semax) and TKPRPGP (Selank, Thr-Lys-Pro-Arg-Pro-Gly-Pro) formed by $ACTH_{4-7}$ or tuftsin and tripeptide PGP, respectively. PGP was attached to stabilize tetrapeptides. However, hybrid molecules exhibit some properties typical of glyprolines [1].

Selank is a typical anxiolytic producing no side effects [6]. This preparation passed the third stage of clinical trials. Selank, some its derivatives obtained by consecutive detachment of amino acid residues from the N-terminal end (KPRPGP, PRPGP, and RPGP), and tuftsin had protective and therapeutic effects on the gastric mucosa in rats with experimental ulcers [5]. Further studies showed that these peptides are not immediate metabolites of Selank. Selank evenly labeled with tritium and retaining its physiological activity was obtained by high-temperature solid phase catalytic isotope exchange. Biodegradation of this peptide with the enzyme system of blood peptidases *in vivo* and *in vitro* leads to elimination of the C-terminal dipeptide Gly-Pro. The pentapeptide is then cleaved with the formation of TKP and RP [3]. This prompted us to study antiulcer activity of Selank and its immediate metabolites.

## MATERIALS AND METHODS

The protective antiulcer effect was studied on 2 experimental models of ulceration (ethanol-induced and stress ulcers). The effects of ethanol and stress are primarily mediated by peripheral and central mechanisms, respectively. The influence of peptides on ulcer healing was studied on the model of acetate-induced ulcers. The exposure to ulcerogenic factors leads to the formation of gastric ulcers. The effect of the test preparations can be estimated from changes in the area of ulceration. The experiments were performed on male outbred albino rats (ethanol- and acetate-induced ulceration) and male Wistar rats (stress-induced ulceration). Control animals (one group for each model) received physiological saline.

On the model of ethanol-induced ulceration in rats, ethanol (96%, 1 ml/200 g) was administered

Department of Human and Animal Physiology, Biological Faculty, M. V. Lomonosov Moscow State University. ***Address for correspondence:*** g_samonina@mail.ru. G. E. Samonina

intragastrically through a probe. The animals were killed with ether vapors 1 h after treatment [2]. Stress ulceration was induced by forced swimming in a reservoir with water (18°C) for 30 min. Gastric erosions induced by this procedure are considered as stress ulcers [7]. The test peptides and physiological saline were administered 1 h before exposure to the ulcerogenic factor.

Acetate-induced ulcers were assayed as described elsewhere [8]. The control and treatment groups consisted of male rats weighing 200-300 g. The abdominal cavity was opened under ether anesthesia. Glacial acetic acid was applied to the pyloric serosa with a cotton tampon (diameter 0.5 mm) for 15 sec. After application, the surface of the stomach was dried with filter paper, and the abdominal cavity was sutured. The test peptides and physiological saline were injected intraperitoneally one time a day for 4-6 days. Experimental ulcers were studied on day 7.

The test peptides were synthesized at the Institute of Molecular Genetics (Russian Academy of Sciences). Peptides were dissolved in physiological saline immediately before the experiment and injected intraperitoneally in doses of 3.7, 0.6, 0.37, and 0.037 μmol/kg (1 ml/200 g). Physiological saline was administered in an equivalent volume.

## RESULTS

Undegraded Selank decreased the area of ulcers on various models of ulceration, which is consistent with previous results [4]. This peptide significantly decreased the severity of gastric erosions in treated rats compared to the control and only in a minimum dose of 0.037 μmol/kg it had little effect in animals with stress ulcers (Table 1).

Tripeptide TKP produced a similar effect. Dipeptide RP in a dose of 0.37 μmol/kg was ineffective in animals with stress ulcers and acetate-induced ulcers. However, RP in low doses (0.37 and 0.037 μmol/kg) significantly decreased the severity of ethanol-induced ulcers (Table 1). Published data show that dipeptide GP exhibits high protective activity in stress ulcers, but increases the severity of ethanol-induced ulceration [2]. GP in a dose of 0.37 μmol/kg improved healing of acetate-induced ulcers. This dipeptide decreased ulcer area by 56% on day 7 after surgery.

Our results show that Selank and *in vivo* metabolites of this compound protect the gastric mucosa, which manifested in decreased area of lesions induced by central and peripheral ulcerogenic factors. Selank, TKP, and GP accelerate healing of acetate-induced ulcers. A possible mechanism for the protective effect of these compounds is the maintenance of adequate blood supply and lymph circulation in the gastric mucosa [5]. Selank and TKP produced similar effects on various models of ulceration (Table 1). RP tended to decrease the severity of ulceration (statistically insignificant). Antiulcer activity of Selank is probably associated with the influence of its molecule, as well as with individual and/or combined effect of biodegradation products.

This work was supported by the Russian Foundation for Basic Research (grant No. 06-04-48833A).

**TABLE 1.** Area of Ulcerative Lesions in the Gastric Mucosa on Various Models of Ulceration (% of Control)

| Dose of peptide, μmol/kg | | Model of ulceration | | |
|---|---|---|---|---|
| | | ethanol-induced | stress | acetate-induced |
| TKPRPGP | 3.7 | 45.5* | 17.3* | — |
| | 0.6 | 47.9* | 8.6* | — |
| | 0.37 | 32.7* | 6.5* | 39* |
| | 0.037 | 47* | 31.3 | — |
| TKP | 3.7 | 27.9* | 3.2* | — |
| | 0.6 | 22.2* | 38.22 | — |
| | 0.37 | 35.5* | 10.8* | 45.2* |
| | 0.037 | 53.1* | 38.9 | — |
| RP | 3.7 | 71.8 | 29.2 | — |
| | 0.6 | 103.1 | 59.9 | — |
| | 0.37 | 40.8* | 57.3 | 74.5 |
| | 0.037 | 22.2* | 75.6 | — |

**Note.** Control, 100%. *$p<0.05$ compared to the control.

## REFERENCES

1. I. P. Ashmarin, E. P. Karazeeva, L. A. Lyapina, and G. E. Samonina, *Biokhimiya*, **63**, No. 2, 149-155 (1998).
2. S. E. Zhuikova, K. E. Badmaeva, and Z. V. Bakaeva, *Izv. Ros. Akad. Nauk. Ser. Biol.*, No. 5, 585-588 (2004).
3. Yu. A. Zolotarev, A. K. Dadayan, O. V. Dolotov, *et al*., *Bioorgan. Khim*., **32**, No. 2, 80-88 (2006).
4. T. S. Pavlov and G. E. Samonina, *Dokl. Akad. Nauk*, **397**, No. 4, 1-3 (2004).
5. T. S. Pavlov, L. Ts. Sanzhieva, G. E. Samonina, *et al*., *Ros. Fiziol. Zh*., **91**, No. 2, 178-183 (2005).
6. S. B. Seredenin, M. M. Kozlovskaya, Yu. A. Blednov, *et al*., *Zh. Vyssh. Nervn. Deyat*., **48**, No. 1, 153-159 (1998).
7. L. P. Filaretova, A. A. Filaretov, and G. B. Makara, *Am. J. Physiol*., **274**, No. 6, Pt. 1, G1024-G1030 (1998).
8. S. Okabe, J. L. Roth, and C. J. Pfeiffer, *Am. J. Dig. Dis*., **16**, No. 3, 277-284 (1971).