

Elevation of Gastric Blood Flow as the Mechanism of Antiulcer Effects of Pro-Gly-Pro

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Subcutaneous injection of indomethacin to pentobarbital-anesthetized rats markedly reduced gastric blood flow measured by hydrogen clearance method in the antrum and fundus of the stomach. Intraperitoneal injection of Pro-Gly-Pro 10 min after the administration of indomethacin normalized gastric blood flow. These data indicate that the elevation of reduced regional blood flow in the stomach is one of possible mechanisms of antiulcer effects of Pro-Gly-Pro.

Key Words: gastric blood flow; indomethacin; proline-containing oligopeptides

Recent data indicate that oligopeptides containing proline and glycine possess various biological activities [3]. Protective effects of proline-containing peptides, in particular of Pro-Gly-Pro (PGP), on the gastric mucosa (GM) were demonstrated on various experimental models of ulcer formation mediated by central and peripheral mechanisms [1]. For example, PGP attenuates GM injuries induced by indomethacin (IM) [1], which are primarily related to the peripheral factors impairing protective mechanisms. For instance, inhibition of prostaglandin synthesis suppresses mucus secretion and cell regeneration and reduces blood flow [6].

However, the mechanisms of antiulcer effects of PGP are poorly understood. Previous experiments showed that PGP attenuates the effect of aggressive factors, in particular, it inhibits secretion of hydrochloric acid [2]. It was proposed that PGP stimulates protective mechanisms. Studies of vascular resistance under conditions of perfusion of the posterior part of rat body revealed vasodilating properties of this peptide. It is well known that changes in gastric blood flow do not necessarily correspond to systemic blood pressure fluctuations. Blood flow in GM remains unchanged during considerable fluctuations of systemic blood pressure, and vice versa [7,8].

Here we evaluated the effects of PGP on IM-induced reduction of GM blood flow in narcotized rats.

MATERIALS AND METHODS

Experiments were performed on male outbred albino rats narcotized with 40 mg/kg pentobarbital and deprived of food for 24 h. Regional blood flow was estimated polarographically by the clearance of inhaled hydrogen gas [4]. Blood flow was recorded in the gastric fundus and antrum using a floating platinum electrode fixed on the gastric surface [5]. To avoid wide dispersion of the experimental data, we elaborated special approaches protecting the stomach from drying and light and maintaining constant rectal temperature and gastric temperature (37-38°C). In series I, gastric blood flow was recorded for 3.5 h (control). In series II, after 45-min recording of initial parameters, IM (25 mg/kg, Pharmachim) was injected subcutaneously and blood flow in the stomach was recorded for 3 h. In series III, PGP in doses of 0.5 and 2 mg/kg (Laboratory of Regulatory Peptides, Institute of Molecular Genetics) was injected intraperitoneally 10 min after administration of IM, and gastric blood flow was recorded for 3 h. The results were analyzed by Student's *t* and Wilcoxon—Mann—Whitney tests.

RESULTS

In control rats deprived of food for 24 h, blood flow rate varied from 50 to 160 ml/100 g/min depending on the region of recording, which was consistent with our previous data [5]. The variations in blood flow rate did

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not exceed 15% within the first 3 h (Fig. 1, 1). The rate of gastric blood flow considerably decreased 30 min after injection of IM, reached a minimum after 60-90 min, and remained at this level for 1.5 h (Fig. 1, 2). PGP attenuated the reduction of gastric blood flow observed 30 min after the injection of IM. PGP in a dose of 0.5 mg/kg slightly increased blood flow rate in the stomach (Fig. 1, 3). Under the effect of 2 mg/kg PGP, gastric blood flow rate returned to the initial level (Fig. 1, 4) or even surpassed it (in some observations).

Thus, PGP attenuated IM-induced reduction of gastric blood flow. These data suggest that the elevation of regional blood flow in the stomach is one of the mechanisms of antiulcer effects of proline-containing oligopeptides, in particular of PGP, under conditions of IM-induced ulcer formation. It cannot be excluded that protective effects of this peptide on GM observed under other experimental conditions are also related to the maintenance of blood flow in the stomach.

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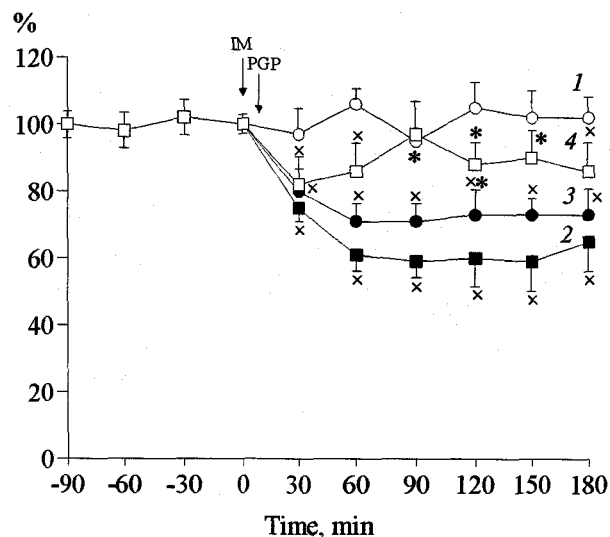


Fig. 1. Effect of PGP on gastric blood flow in narcotized rats treated with indomethacin (IM). Ordinate: changes in blood flow rate (% of the mean initial blood flow calculated from 3 observations). 1) control, 2) 25 mg/kg IM, 3) 0.5 mg/kg PGP, 4) 2 mg/kg PGP. $p < 0.05$: *compared with IM and *compared with the control.