Glyprolines and Semax Prevent Stress-Induced Microcirculatory Disturbances in the Mesentery

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One-hour immobilization stress considerably disturbed microcirculation in the mesentery: blood flow in small mesenteric vessels decreased or stopped and numerous hemorrhages appeared. Lymphatic vessels lost spontaneous activity and did not respond to norepinephrine. Administration of Semax and glyprolines 1 h before stress decreased the severity of stress-induced microcirculatory disturbances. PGP and GP were most effective in this respect.

Key Words: *stress; lymphatic vessels; glyprolines*

Stress induces various changes in the circulatory system. The adaptive phase of the stress reaction is characterized by selective redistribution of the blood into organs and tissues responsible for adaptation (*e.g.*, heart and skeletal muscles) at the expense of vasoconstriction in "inactive" organs, in particular, in the gastrointestinal tract. Long-term stress exposure can be followed by ischemic damage to these organs. The development of stress-induced ulcers in the stomach results from vasoconstriction, which is related to activation of adrenergic regulation, suppression of nitric oxide generation, and inhibition of the release of vasoactive compounds from mast cells [4,7].

Recent studies showed that glyprolines PGP, PG, and GP and $ACTH_{1-4}$ fragment Semax improved the resistance of the gastric mucosa to adverse factors [1,3,8]. This is probably associated with a role of peptides in the maintenance of adequate blood supply to tissues of the gastrointestinal tract [5,9].

PGP, GP, PG, and Semax in a wide range of concentrations (10^{-6}-10^{-20} M) increase contractility of lymphatic vessels in the mesentery [2].

Here we studied stress-induced changes in mesenteric microcirculation and evaluated the effect of glyprolines and Semax on the severity of injury.

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MATERIALS AND METHODS

Acute experiments were performed on male albino rats weighing 180-230 g and narcotized with urethane (2.4 g/kg). After laparotomy the animals were kept on a thermostatic table at 37°C. The intestinal loop and mesentery were isolated and placed on a light-carrying microscope table. The mesentery preparation was spayed with physiological saline. Microscopic images were transferred to a monitor of an industrial television device (Matritsa) for visual control. The state of microcirculation was determined by the time of irresponsiveness to norepinephrine (period when lymphatic vessels did not respond to application of 10^{-6} M norepinephrine), latency (period between application of norepinephrine and start of rhythmic contractions), number of contractions over the first minute of reaction, and the number of hemorrhages within one "window" (area of the mesentery between two large blood vessels). Special attention was given to mesentery appearance, lymph and blood flow rates in small vessels, and count of lymphocytes in vessels.

The microcirculatory bed was examined under normal conditions and after 1-h immobilization stress (fixation on the back to a table). One hour before stress the animals received intramuscular injections of Semax, PGP, PG, and GP in doses producing a protective antiulcer effect (0.05, 1, 0.6, and 0.6 mg/kg, respectively) [1,3,8,9]. Control rats received an equi-

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valent volume of physiological saline. Heart rate (HR) was recorded via an electrode implanted subcutaneously in the scapular area 12 h before the experiment.

RESULTS

In intact rats the mesentery was pink with intensive blood and lymph flow in vessels. Lymphatic vessels contained single lymphocytes. Lymphatic vessels responded to application of norepinephrine by a series of contractions. The latency and frequency of contractions were 23±5 sec and 10.8±1.5/min, respectively. Only individual small hemorrhages (less than 1 hemorrhage per "window" were seen, Fig. 1).

Immobilization stress was accompanied by a considerable increase in HR (by 25%) and changes in the microcirculatory bed of the mesentery: it looked pale, blood and lymph flow in microvessels was arrested. Lymphatic vessels attained a considerable number of lymphocytes. It should be emphasized that lymphatic vessels did not respond to application of norepinephrine for 74±21 min after stress. The latency of response increased to 52.0±9.7 sec. The number of hemorrhages considerably increased (4.2±0.5 per "window", Fig. 1). Therefore, 1-h immobilization stress caused pronounced microcirculatory disturbances in the mesentery.

Glyprolines and Semax administered 1 h before stress produced a protective effect and decreased the degree of poststress microcirculatory changes in the mesentery. PGP and GP were most effective: none of the poststress indexes differed from normal after treatment with these glyprolines. PG decreased the frequency of contractions and increased the number of hemorrhages after stress (statistically insignificant). Semax abolished stress-induced changes in lymphatic vessels, but had no effect on the number of hemorrhages (Fig. 1).

The test peptides did not modulate the increase in HR during stress. The increase in HR during stress is related to activation of the sympathetic system and release of catecholamines from the adrenal glands. In our experiments peptides did not affect the degree of stress-induced tachycardia. This indirectly suggests that the release of catecholamines changes insignificantly after

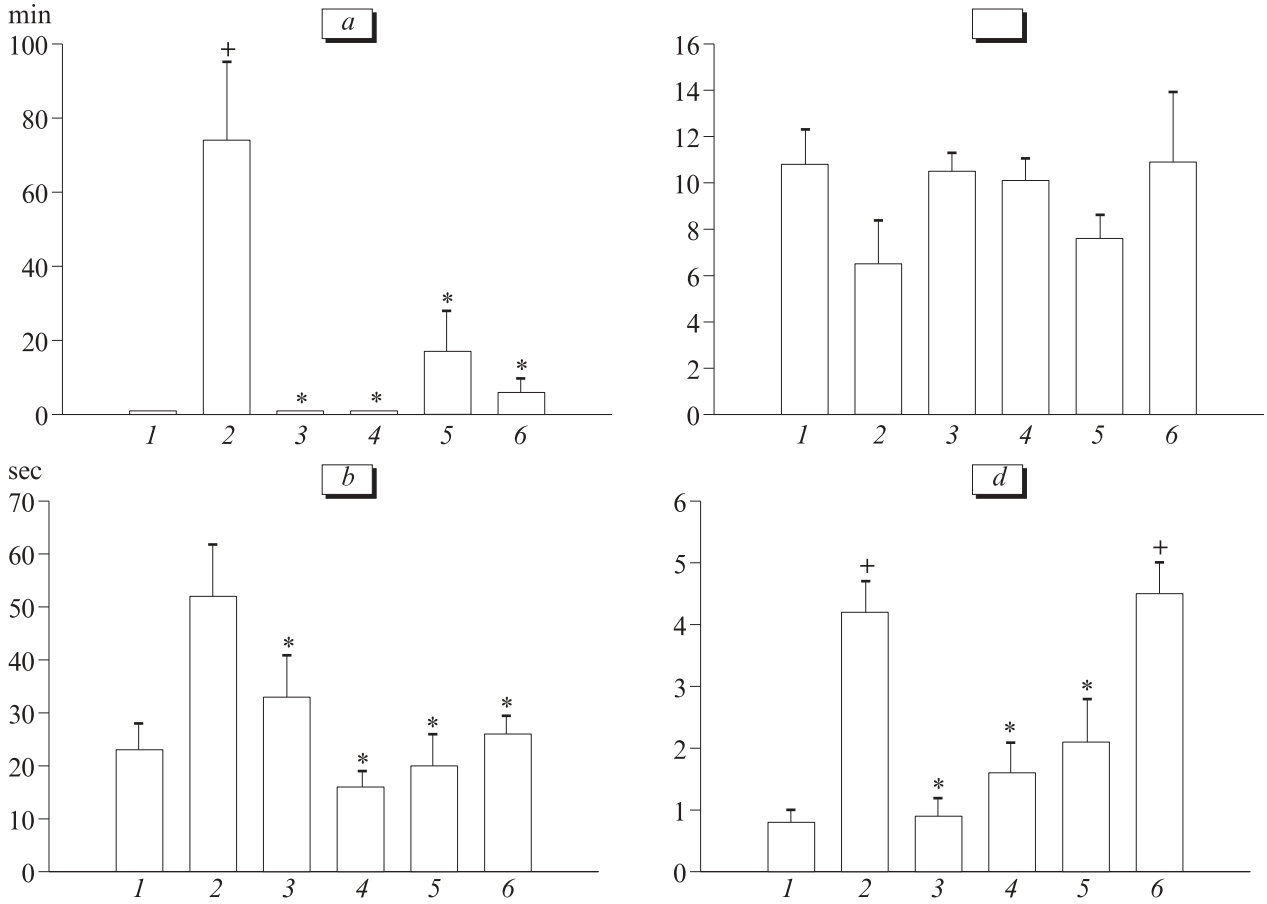

Fig. 1. Effect of peptides on stress-induced microcirculatory disturbances in the mesentery: irresponsiveness to norepinephrine (*a*), latency (*b*), frequency of contractions over the first minute of reaction to norepinephrine (*c*), and number of hemorrhages (*d*). Control animals (*1*) and stressed rats receiving physiological saline (*2*), PGP (*3*), GP (*4*), PG (*5*), and Semax (*6*). Each group consisted of 5 animals. $p<0.01$: +compared to group 1; *compared to group 2.

injection of peptides. Our previous studies showed that glyprolines and Semax decrease reactivity of mast cells and abolish the increase in their secretory activity after stress [6]. The protective effect of peptides on the microcirculatory bed during stress is probably related to stabilization of mast cells. It cannot be excluded that these peptides directly stimulate lymphatic vessels [2].

The maintenance of adequate blood supply to tissues of the gastrointestinal tract is a possible mechanisms underlying antiulcer activity of glyprolines and Semax.

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