PHYSIOLOGY

Therapeutic Effects of Glyprolines (PGP, GP, and PG) in Rats with Stress-Induced Behavioral Disorders

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Experiments on male outbred albino rats showed that stress (10-min swimming) increased anxiety and inhibited orientation and exploratory activities. Poststress (15 min after the end of swimming) intranasal administration of peptides Pro-Gly-Pro and Gly-Pro in a dose of 3.7 μmol/kg prevented stress-induced behavioral disorders. This effect persisted for 3 h.

Key Words: *glyprolines; stress; behavioral disorders*

Short peptides containing glycine and proline (glyprolines) can cross the blood-brain barrier [3,4] and prevent stress-induced behavioral disorders in rats [1,2,6]. Peptides Pro-Gly-Pro (PGP) and Gly-Pro (GP) produce the most pronounced protective effects. The severity of poststress behavioral disorders was much lower in rats receiving these peptides (3.7 and 37.0 μmol/kg intraperitoneally or intranasally) 15 min and 3 h before stress. The stress-induced increase in anxiety and decrease in orientation and exploratory activity were less pronounced after pretreatment with the peptides. At the same time, these peptides had no effect on behavioral activity of nonstressed animals [5,7]. *In vitro* experiments showed that PGP and GP produce a neuroprotective effect, protect rat pheochromocytoma PC12 cells from oxidative stress, and increase their survival [8].

Our results and published data suggest that peptides PGP and GP affect structures of the central nervous system (CNS) involved in organism's reaction to stress factors and decrease the intensity of the stress response.

Here we studied the therapeutic effect of glyprolines and their ability to prevent stress-induced behavioral disorders.

MATERIALS AND METHODS

Experiments were performed on male outbred albino rats weighing 200-270 g. The animals were maintained in a vivarium under standard conditions and had free access to food and water.

Forced swimming in water (23°C, 10 min) served as the model of stress.

The animals were divided into groups: intact (unstressed), control (administration of physiological saline 15 min after stress), and treated animals (administration of the test peptide 15 min after stress). The tests were performed 30 min after stress (*i.e.*, 15 min after administration of physiological saline or peptide).

PGP, PG, and GP were synthesized at the Institute of Molecular Genetics (Russian Academy of Sciences) and administered intranasally (3.7 μmol/kg, 50 μl/200 g body weight). All preparations were

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dissolved in physiological saline immediately before administration.

Behavioral activity was studied in the hole-board and elevated plus maze tests in the absence of stress factors (silence, 15-W red light lamp). Testing was performed 15 min and 3 h after administration of the peptide (*i.e.*, 30 min or 3 h and 15 min after the end of stress).

The duration of each test was 3 min.

The results were analyzed by LSD test.

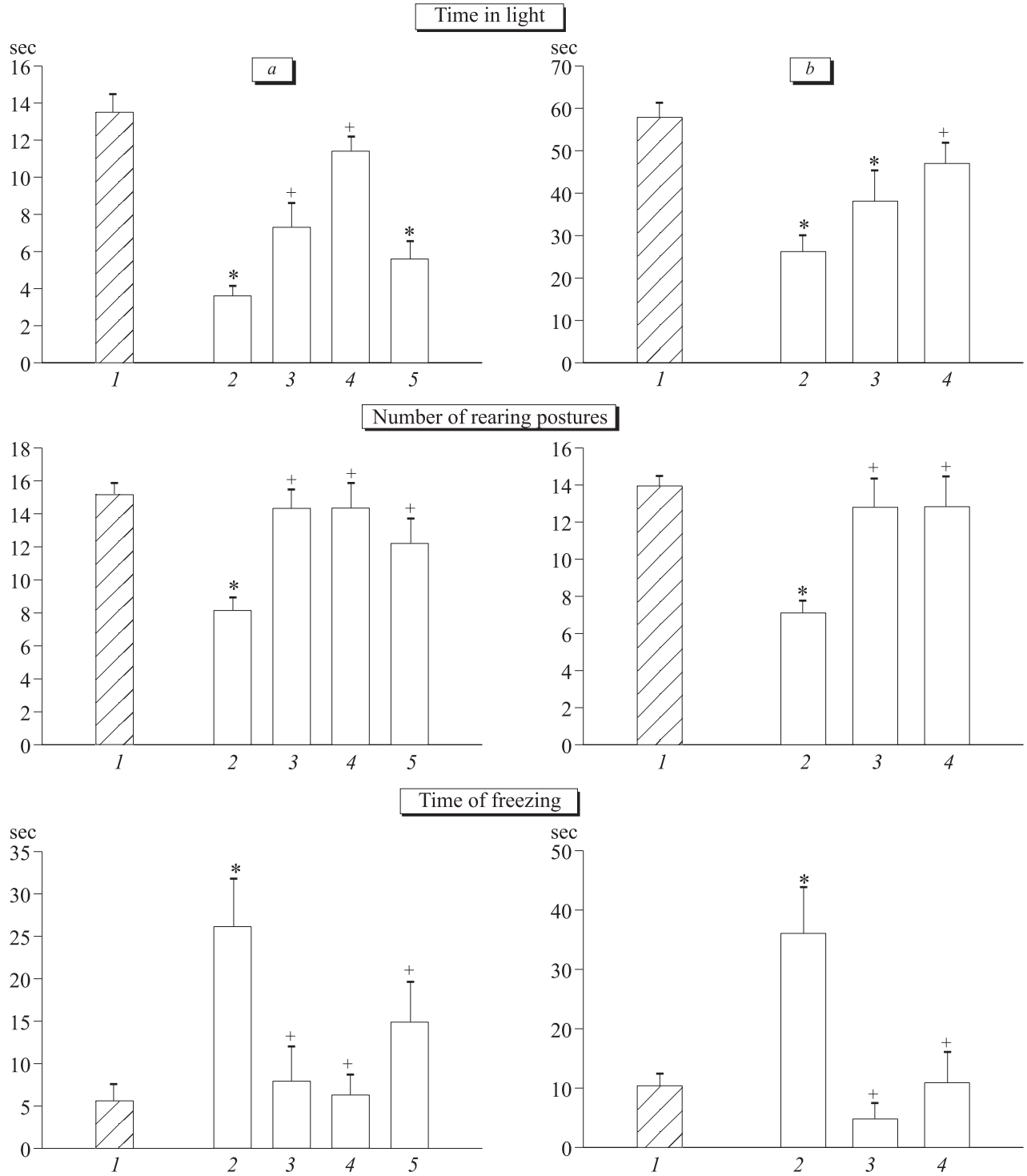

Fig. 1. Behavioral activity of stressed rats in the elevated plus maze 15 min (*a*) and 3 h (*b*) after administration of glyprolines. Here and in Fig. 2: intact animals (*1*); stressed rats receiving physiological saline (control, *2*), PGP (*3*), GP (*4*), and PG (*5*). *2-5*: stress exposure 15 min before administration of the peptide or physiological saline. $p<0.05$: *compared to intact rats; +compared to the control.

RESULTS

The time spent in the light compartment and number of explored holes and rearing postures in animals of the control group decreased 30 min after stress; the time of freezing significantly increased during this period (Figs. 1, *a*; 2, *a*). These changes reflect increased anxiety and decreased orientation and exploratory activity and are consistent with published data [9,10]. The stress-induced behavioral disorders in animals were much less significant or disappeared 15 min after administration of PGP or GP. The test parameters in these rats returned to normal. The effect of PG in an equimolar dose was

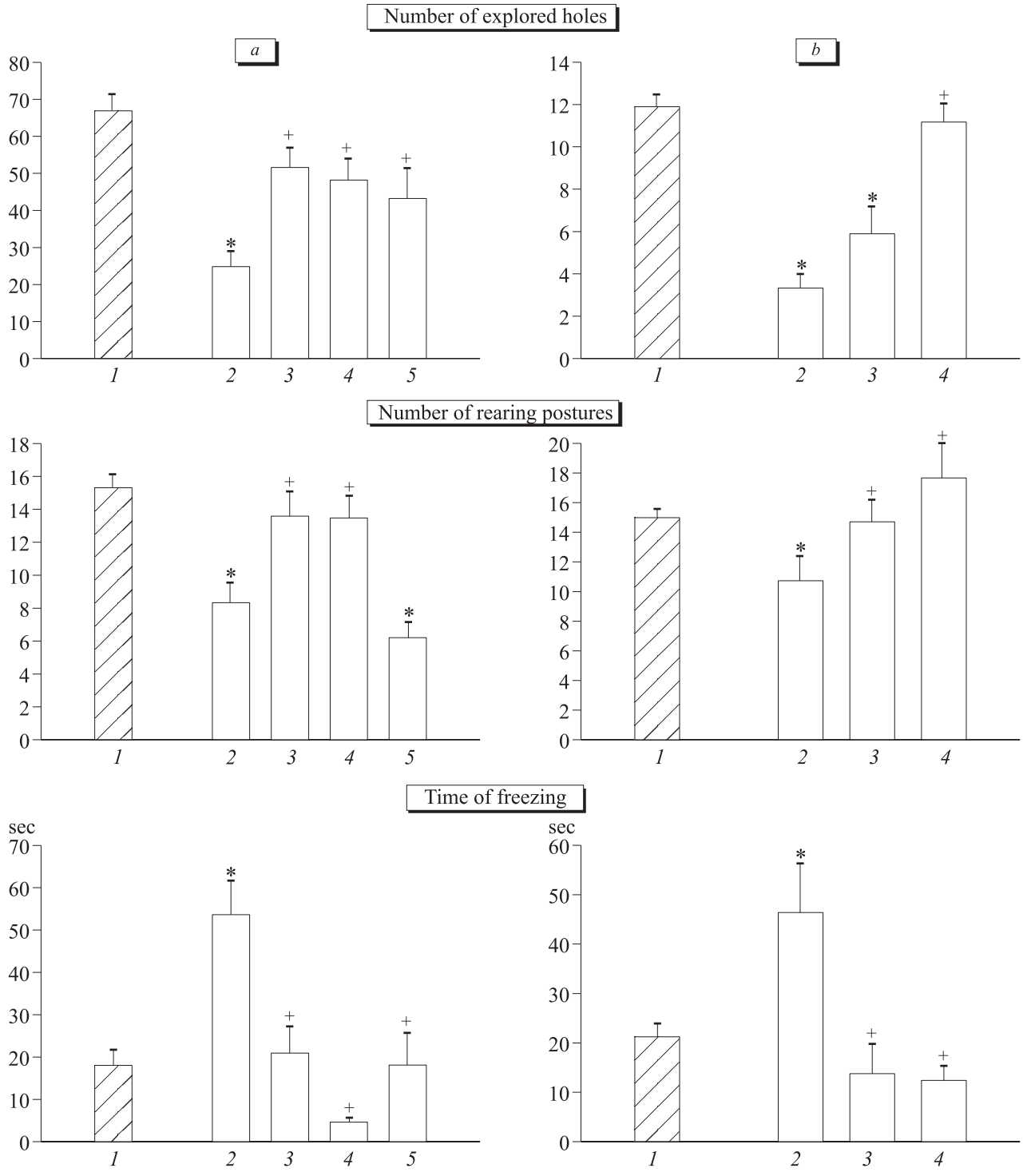

Fig. 2. Behavioral activity of stressed rats in the hole-board test 15 min (*a*) and 3 h (*b*) after administration of glyprolines.

less pronounced: most parameters of behavioral activity changed after PG administration, but still differed from the basal values. Previous studies also showed that the protective effect of PG is less significant compared to that of PGP and GP [2]. Hence, PG was not used in further experiments.

Our results indicate that peptides PGP and GP produce a therapeutic anxiolytic effect and normalize behavioral activity of animals impaired after stress exposure.

The stress-induced behavioral disorders in control animals persisted 3 h after treatment. However, in this period stress-induced behavioral disorders were not revealed in rats receiving PGP or GP (Fig. 2). Therefore, the anxiolytic effect of these peptides persists for at least 3 h.

We conclude that peptides PGP and GP produce a strong therapeutic neuroprotective effect, normalize function of CNS, and decrease the severity of stress-induced behavioral disorders in rats.

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