INCREASED RESISTANCE TO EMOTIONAL STRESS PRODUCED BY THE ENDOGENEOUS PEPTIDE PROLACTIN

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The development of effective waves of increasing resistance to emotional stress still remains one of the most urgent social problems of modern physiology and medicine [3]. Experimental data and theoretical generalization based on them indicates the existence of natural endogenous peptidergic mechanisms of resistance to emotional stress [7], whose investigation can open up wide prospects for further research into effect peptide factors.

Prolactin (PRL) is an endogenous peptide hormone which performs several functions and, in particular, participates in the activation of lactation and the formation of maternal behavior [13]. PRL secretion is known to be under the control of dopaminergic, GABA-ergic, and serotoninergic mechanisms [10]. In turn, PRL has a central modulating influence on these neurochemical mechanisms. PRL is involved in the regulation of autonomic functions and, in particular, regulation of the blood pressure and cardiac reactivity in rats, it depresses the pressor response to angiotensin-2, and interacts with adrenal hormones [11]. In emotional stress, elevation of the serum PRL level is accompanied by activation of dopaminergic and GABA-ergic processes, determining adaptation and increased resistance to emotional stress [7]. It is quite evident that lactation and feeding offspring have a special biological significance for maintenance of the biological species. In this period survival of the progeny largely depends on the degree of stress to which the maternal organism is subjected, for we know that excessive stress may lead to termination of lactation and possible death of the offspring. In fact, psychological observations have shown that during the feeding period, the material organism becomes less reactive to stressors [13]. We have suggested that the emotional status in the period of feeding the yound is a natural physiological model of increased resistance to emotional stress, and that PRL, synthesized in the body, may be an effective factor of resistance to it.

This paper describes an experimental investigation of the possibility of increasing resistance to emotional stress by administration of PRL.

EXPERIMENTAL METHOD

As the experimental model for the formation of emotional stress we used a model of aggressive-conflicting behavior of our own design [8]. Rats were placed four to a cage with mild fixation of the tail with adhesive tape for 5 h on each of 5 successive days. On the days of the experiments the animals were kept in the same cages, with adequate quantities of water and food. During fixation the animals displayed aggressive-conflicting behavior, which led to the development of emotional stress with its characteristic manifestations. Experiments were carried out on 127 male August rats (weighing 220-250 g) and 67 noninbred male rats (weighing 250-300 g). The inbred August rats and the noninbred animals were specially chosen, for these animals are distinguished by an increased predisposition to emotional stress compared with other lines, such as Wistar and Wag rats [4, 5, 7]. All the experimental animals were divided into three groups: 1) intact animals, 2) animals exposed to stress after preliminary intraperitoneal injection of 1 ml of physiological saline, and 3) rats receiving PRL in 1 ml of solvent intraperitoneally before the formation of emotional stress. Bovine PRL, used in the experiments, was isolated at the Research Institute of Endocrinology and Hormone Chemistry, Academy of Medical Sciences of the USSR. Before injection the PRL

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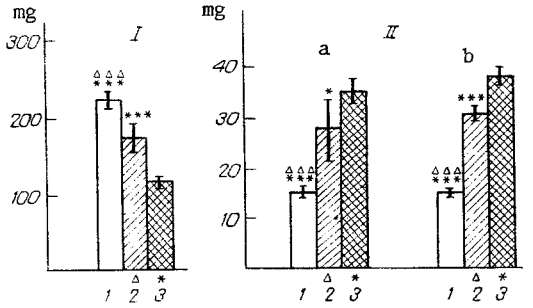

Fig. 1. Rate of thymus (I) and adrenals (II) in noninbred rats during emotional stress and injection of PRL. a) Right, b) left adrenals. 1) Intact rats (control), n = 11; 2) rats receiving PRL by intraperitoneal injection in a dose of 50 μg/kg followed by exposure to stress 1 h after injection (n = 12); 3) rats receiving intraperitoneal injection of 1 ml of physiological saline followed, 1 h after injection, by exposure to stress (n = 12).

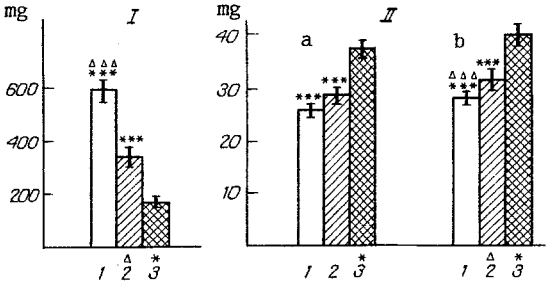

Fig. 2. Weight of thymus (I) and adrenals (II) in August rats during emotional stress and injection of PRL. 1) Intact groups of rats (control n = 12); 2) rats receiving PRL intraperitoneally in a dose of 250 μg/kg followed by exposure to stress after 15 days (n = 9); 3) rats receiving intraperitoneal injection of 1 ml of physiological saline followed 15 days layer by exposure to stress (n = 11). Remainder of legend as to Fig. 1.

was dissolved in 0.1 ml of 0.01 N HCl and then in 1 ml of physiological saline. In the experiments of series I and II, the August rats (63) of the experimental group received a single intraperitoneal injection of PRL in a dose of 50 μg/kg body weight, and 1 h after the injection, the development of emotional stress in these animals was induced. In the experiments of series III and IV, the 66 August rats of the experimental groups received a single intraperitoneal injection of PRL in a dose of 250 μg/kg and (unlike previous series), these animals were exposed to stress 15 days after the injection. In the experiments of series V and VI noninbred rats (67 animals) were used, and these also received a single intraperitoneal injection of PRL (in a dose of 50 μg/kg), and exposure of these animals to stress began 1 h after the injection. At the end of the experiments the animals of the experimental and control groups were decapitated. To determine resistance to emotional stress the intensity of the classical manifestations of emotional stress was investigated: involution of the thymus, hypertrophy of the adrenals, and the presence of ulcers in the stomach; the survival rate of the animals under conditions of 5-day aggressive-conflicting behavior also was taken into account. The data were subjected to statistical analysis by Student's test on the "Micron-2000" computer (West International, Norway).

EXPERIMENTAL RESULTS

In all the series of experiments the antistressor action of a single injection of PRL was observed (Figs. 1 and 2). The ability of PRL to increase resistance to emotional stress

was manifested as significant abolition of changes in involution of the thymus and hypertrophy of the adrenals, induced by emotional stress in rats exposed to it, by a significant increase in the survival rate of August rats exposed to experimental emotional stress, and complete prevention of the development of gastric ulcers, which occurred in 22% of rats exposed to emotional stress and not receiving PRL.

The action of a single injection of PRL was long-lasting, as was shown in the series of experiments with the subsequent development of emotional stress, and also, particularly clearly, in the series of experiments in which exposure of the animals to stress was delayed by 2 weeks. This long-term effect, as has been shown, is characteristic of several peptides [1, 7, 15], and the results agree with the long-term antistressor action of substance P, which like PRL can increase resistance to emotional stress for a long time after a single injection for several weeks, demonstrated previously [2, 6, 12].

The investigations thus showed for the first time that the endogenous peptide PRL can increase the resistance of animals to emotional stress significantly and for a long time.

On the basis of the well known facts of interaction of PRL with dopaminergic and GABAergic processes, we can put forward certain suggestions concerning the mechanism of the antistressor action of PRL. It has been shown that the increase in resistance to emotional stress correlates with an increase in the noradrenalin and dopamine concentrations in the hypothalamus. Following single systemic administration of substance P the increase in resistance to emotional stress is accompanied by a long-term increase in concentrations of noradrenalin and dopamine in the hypothalamus and midbrain [7]. PRL also has a modulating effect on dopaminergic processses, causing elevation of the dopamine concentration in emotiogenic structures of the brain [14]. It can therefore be postulated that one possible mechanism of the antistressor action of PRL is its participation in central neurotransmitter integration of negative emotional excitation. Participation of PRL in the pituitary-adrenal mechanism of emotional stress likewise cannot be ruled out. The results described above open up wide prospects for the study of the role of PRL in peptidergic mechanisms of resistance to emotional stress, the discovery of its role in the genetic determination of resistance to emotional stress, and also the individual sensitivity of animals to emotional stress.

LITERATURE CITED

1. I. P. Ashmarin, Goal-Directed Search for New Neurotropic Drugs [in Russian], Riga (1983), p. 6.
2. K. V. Sudakov, E. A. Yumatov, K. Hecht, and Yu. G. Skotselyas, 8th All-Union Conference on Biochemistry of the Nervous System: Proceedings [in Russian], Minsk (1980), p. 196.
3. K. V. Sudakov, Systemic Mechanisms of Emotional Stress [in Russian], Moscow (1981).
4. K. V. Sudakov, E. A. Yumatov, and V. A. Dushkin, Vest. Akad. Med. Nauk SSSR, No. 12, 32 (1981).
5. E. A. Yumatov and Yu. G. Skotselyas, Zh. Vyssh. Nerv. Deyat., No. 2, 345 (1979).
6. E. A. Yumatov, K. Hecht, Yu. G. Skotselyas, and E. V. Bykova, Vasoactive Peptides [in Russian], Sofia, Bulgaria (1980), p. 44.
7. E. A. Yumatov, "Central neurochemical mechanisms of resistance to emotional stress," Author's abstract of dissertation for the degree of Doctor of Medical Sciences, Moscow (1986).
8. E. A. Yumatov, O. A. Meshcheryakova, and E. I. Pevtsova, "Resistance of rats of different lines to emotional stress in an experimental model of aggressive-conflicting behavior," Manuscript Lodged with the All-Union Institute of Scientific and Technical Information on October 10, 1987, No. 7697-V87.
9. H. Koji, T. Fujita, K. Chihara, et al., Neuroendocrinology, 4, 6 (1985).
10. I. Login, A. M. Judo, and R. M. Macleod, Am. J. Physiol., 250, No. 6, E731 (1986).
11. D. E. Mills and R. R. Ward, Proc. Soc. Exp. Biol. (New York), 181, No. 3, 3 (1986).
12. P. Oehme, K. Hecht, L. Piesche, et al., Acta Biol. Med. Germ., 39, 469 (1980).
13. F. Peters, F. Geisthovel, and M. Brechwoidt, Acta Endocrinol. (Copenhagen), 109, No. 4, 463 (1985).
14. M. J. Reymond and J. C. Porter, Hormone Res., 22, No. 3, 142 (1985).
15. T. Unger, W. Rasehes, C. Schuster, et al., Eur. J. Pharmacol., 71, 33 (1981).