NEUROIMMUNOREGULATORY PROPERTIES OF SHORT PROTEIN FRAGMENTS IN RATS SUBJECTED TO IMMOBILIZATION STRESS

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One of the newest and most rapidly developing fields in modern biology is psychoneuroimmunology, which has not only introduced new ideas on integration of processes regulated by the nervous, endocrine, and immune systems, but has also yielded evidence that peptide hormones and their receptors on nerve cells and immunocompetent cells (immunocytes) constitute the material basis for transmission of signals reciprocally between these systems [1, 4, 6]. A factor of particular importance in this intercommunication is the recently discovered ability of immunocytes to produce peptides, identical with pituitary hormones, formed during the biodegradation of protein (pro-opiomelanocortin — PMC), i.e., ACTH, opiate peptides, etc. [6], and also the discovery of thymus hormones in the brain [8]. Intensified degradation of protein, including precursors by a sharp rise in the blood levels of released stress hormones: ACTH, endorphins, substance P (SP), vasopressin, and so on [10].

It has been suggested [2, 3] that other protein molecules, which are sources of many of their metabolic products, may be no less important as protein precursors. From this aspect the striking similarity between the protein fragments involved in immune regulation, namely immunoglobulins, thymus hormones, and interferon [3], deserves particular attention.

The aim of this investigation was to study the ability of the IgG fragment tuftsin (Thr-Lys-Pro-Arg-OH), rigin (Gly-Gln-Pro-Arg-OH), and also structural analogs of IgG fragments, namely polarin SKD (Ser-Lys-Asp-OH) and thymopentin (Arg-Lys-Asp-Val-Tyr-OH), to regulate certain stress-induced neuroendocrine and immune changes in the body. Substance P (SP) (Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2), whose regulatory properties are already established [9], was used as the standard compound.

EXPERIMENTAL METHOD

The peptides were injected intraperitoneally into male rats weighing 180-220 g in doses of 100 and 500 μg/kg 30 min before subjection to immobilization stress [7]. Immobilization for 3 h was accompanied by immersion of the rats in water at 22°C. At the end of the experiment the rats were decapitated and the hypothalamus, corpus stratum, and adrenals were isolated for spectrofluorometric determination of noradrenalin and adrenalin [5, 11].

The serum corticosterone concentration was determined by radioimmunoassay, using a commercial kit (Radioassay Systems Laboratories, USA). Humoral immunity was estimated by the hemagglutination test, with titration of specific antibodies produced to sheep's red blood cells, which were injected in a dose of $5 \cdot 10^7$ cells in 1 ml of physiological saline, by the optimal scheme which we adopted for specific antibody production, 3 days after injection of the peptides. The antibody titer was determined at the peak of antibody formation, i.e., on the 7th day after immunization.

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EXPERIMENTAL RESULTS

SP, rigin, tuftsin, and thymopeptin could completely reverse (to the control level in unstressed animals) the stress-induced fall of the noradrenalin concentration in the hypothalamus. Polarin SKD did not change the response to stress. In the striatum, SP, thymopentin, rigin, and tuftsin were all particularly active correctors of the stress-induced lowering of the noradrenalin level. In the adrenals the adrenalin level was reversed by a greater degree by SP and thymopentin whereas SKD was inactive. The greatest reversal of the adrenalin level was produced by SP and rigin, and SKD caused only a tendency for the adrenalin level to rise. The stress-induced increase in the serum corticosterone concentration was restored completely to normal by SP and partly by rigin and thymopentin, whereas SKD had no significant effect on this parameter. The stress-induced increase in antibody production was regulated only by tuftsin and rigin.

The results show that short natural IgG fragments, namely tuftsin, rigin, and thymopeptin, can act as powerful correctors of changes induced by immobilization stress. Besides SP, the protein fragments rigin and thymopentin were found to be particularly active stress protectors, for they normalized considerable stress-induced changes in the catecholaminergic system of the brain and adrenals (evidently through their ability to release monoamines rapidly, as has been demonstrated for tuftsin and rigin [4]), and they also significantly reversed the corticosterone level. Unlike SP, which did not affect the stress-induced increase in antibody production, tuftsin and rigin completely restored the normal humoral immune response. Each peptide thus has its own special features in its action on the multifactorial manifestations of stress, which are evidently determined by the structurally dependent direction of the effect of the peptide on the individual stages of neuroimmunologic communication. This kind of combination of polar amino acids in peptide SKD is not optimal for stress protection. On the basis of the results described above we can postulate a functional role for similar endogeneously formed protein fragments, capable of acting as mutual regulators in order to preserve neuroendocrine and immune homeostasis in the living organism.

LITERATURE CITED

1. V. E. Kluša, N. A. Abissova, E. M. Kukain, et al., All-Union Symposium on the Goal-Directed Search for Physiologically Active Substances [in Russian], Riga (1981), p. 4.
2. V. E. Kluša, Peptides: Regulators of Brain Functions [in Russian], Riga (1984).
3. G. I. Cipens, Izv. Akad. Nauk Latv. SSR, No. 12, 93 (1984).
4. A. H. Anton and D. F. Sayre, J. Pharmacol. Exp. Ther., 138, No. 3, 375 (1962).
5. J. E. Blalock and E. M. Smith, Fed. Proc., 44, 108 (1985).
6. K. Kuriyama, K. Kanmori, and Y. Yoneda, Neuropharmacology, 23, 649 (1984).
7. K. K. Oates and A. L. Goldstein, TIPS, August (1984), pp. 347-353.
8. N. P. Plotnikoff and A. J. Murgo, Fed. Proc., 44, 92 (1985).
9. P. Oehme, M. Bienert, K. B. Hecht, et al., Ausgewählte Probleme der Chemie, Biochemie, Pharmakologie, Physiologie und Pathophysiologie, Berlin (1981), p. 185.
10. R. Ader (ed.), Psychoneuroimmunology, New York (1981).
11. M. C. Schellenberger and J. H. Gordon, Anal. Biochem., 39, 356 (1971).