ROLE OF PERIPHERAL CATECHOLAMINERGIC SYSTEMS IN THE ANTISTRESS ACTION OF NEUROPEPTIDES

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In the modern view the antistress action of many neuropeptides is due to their ability to modulate the intensity of mediator processes at the level of central and peripheral neurohormonal structures [1, 3, 4, 10]. In this connection the adrenergic innervation system and the adrenal medulla, i.e., components of the sympathicoadrenal system whose functional state largely determines the character of the stress response of the organism during development of the general adaptation syndrome, are ascribed an important role [2, 11, 12]. The authors previously showed that pharmacologic correction of the level of mediator activity of these peripheral catecholaminergic formations is possible in rats exposed to stress with the aid of various psychotropic substances [5, 6, 9].

The aim of the present investigation was to study the action of the opioid peptide dalargin (DAL) and a new heptapeptide analog of enkephalin (HAE), which was synthesized in the Institute of Molecular Genetics, Academy of Sciences of the USSR, by scientific assistants M. A. Ponomareva-Stepnaya and L. A. Andreeva (head of laboratory — Candidate of Chemical Sciences V. N. Nezavibat'ko).

EXPERIMENTAL METHOD

The investigation was conducted on a model of immobilization stress. Experiments were carried out on 62 male rats weighing 200 ± 20 g. The animals were fixed in special frames for 1, 4, 24, and 48 h. The duration of the experiments was chosen in accordance with the time course of somatic and hormonal manifestations of the stress response with this particular model of immobilization [6]. Adrenergic nerves of the dura mater and the adrenal medulla were used as the test material. Adrenergic nerves were identified by the histochemical fluorescence-microscopic method of Falck and Hillarp. The intensity of noradrenalin-induced luminescence (in conventional units) was estimated quantitatively by means of the FÉU-19 photosensitive attachment to the ML-2 microscope by the method described previously [8]. Concentrations of adrenalin and noradrenalin (NA) in the adrenals were determined spectrofluorometrically by the method of Von Euler and Lishajko. In all series of experiments somatic parameters of the stress response were studied: the weight of the lymphoid organs (thymus and spleen) and of the adrenals, the frequency of ulcer formation and the number of erosions in the gastric mucosa. DAL and HAE, in a dose of 150 μg/kg, were injected intraperitoneally 30 min before fixation of the rats. In the case of long-term immobilization, injection of the preparations was repeated twice a day.

EXPERIMENTAL RESULTS

Comparative analysis of the somatic parameters of the stress response in the immobilized rats showed that in the alarm stage (1 h) the effect of the preparations consisted mainly of prevention of involution of the thymic-lymphatic apparatus (the reduction in weight of the thymus and spleen did not exceed 25%). During subsequent periods of immobilization (4-24 h), corresponding to the period of adaptation, a decrease was observed in the number of erosions and punctate hemorrhages in the gastric mucosa, and the degree of hypertrophy of the adrenals was reduced. At the exhaustion stage (48 h) the combination of immobilization with administration of HAE had no significant effect on the

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TABLE 1. Effect of DAL and HAE on Catecholamine Concentrations in Adrenals and on Luminescence of Adrenergic Nerves of Rat Dura Mater during Immobilization Stress

Test object	Duration of immobilization stress, h			
	1	4	24	48
	Control			
A	687±85	342±31	186±31	94±12
B	661±93	601±66	213±23	120±24
C	12,0±1,4	15,1±2,6	16,9±1,8	11,2±1,5
	Stress + administration of DAL (150 μg/kg)			
A	693±133	333±58	251±33	167±19*
B	594±118	706±95	315±29*	216±28*
C	17,5±1,4*	18,2±3,1	19,1±2,9	16,6±1,2*
	Stress + administration of HAE (150 μg/kg)			
A	736±103	318±60	224±57	76±19
B	650±116	411±86	208±39	96±17
C	16,8±1,1*	17,1±3,4	18,4±4,2	14,8±3,4

Legend. A) Adrenal, adrenalin concentration (in μg/g); B) adrenal, NA concentration (in μg/g); C) dura mater, intensity of luminescence (in conventional units). Parameters measured under normal conditions have the following values: A) 640 ± 69 μg/g; B) 874 ± 75 μg/g; C) 20.2 ± 2.9 conventional units. Asterisk indicates significant difference from control at the $p \leq 0.05$ level.

somatic manifestations of the stress response: a decrease in weight of the lymphoid organs characteristic of this stage (the thymus to 51 ± 5.2%, the spleen to 48.7 ± 7.5%) was observed, hypertrophy of the adrenals increased (up to 231 ± 20.9%), and the number of ulcers and hemorrhages in the gastric mucosa increased again. Meanwhile in the experiments with injection of DAL, relative "normalization" of the somatic parameters was observed: ulceration of the mucosa virtually disappeared, hypertrophy of the adrenals was less marked 158.3 ± 18.2%), and the weight of the thymus and spleen was almost unchanged (79.2 ± 10.4% and 73.1 ± 9.4%, respectively).

According to the results of the spectrofluorometric analysis, an increase in the duration of immobilization led to a decrease in concentration of catecholamines (adrenalin and NA) in the adrenal medulla. However, as Table 1 shows, the concentrations of these hormones remained at a higher level after 24 and 48 h of immobilization under the influence of DAL.

The authors showed previously [8] that at the alarm stage of immobilization stress the intensity of noradrenalin luminescence of the adrenergic innervation of the dura mater falls sharply (by 40-50% compared with intact animals). In experiments with DAL and HAE administration, no such decline in neurotransmitter activity took place. According to our observations (Fig. 1; Table 1), under the influence of these neuropeptides the adrenergic nerves exhibited near-normal intensity of luminescence. A sufficiently high level of luminescence also was preserved throughout the period of adaptation (4-24 h). Only with an increase in the duration of the experiments and the transition into the exhaustion stage did the intensity of luminescence of the adrenergic nerves fall, to reach 60-70% of the initial level after immobilization for 48 h. This is 20-25% higher than in the experiments with control immobilization. Comparative analysis of histochemical preparations of the dura mater showed that the adrenergic innervation as a whole was characterized by higher neurotransmitter activity against the background of the action of DAL at all stages of immobilization stress.

The observations described above indicate that effective correction of the neurotransmitter activity of peripheral catecholaminergic systems under conditions of stress can be undertaken with the aid of neuropeptides such as DAL and HAE. The more marked stress-protective properties of the first of these substances can be explained by the presence of a

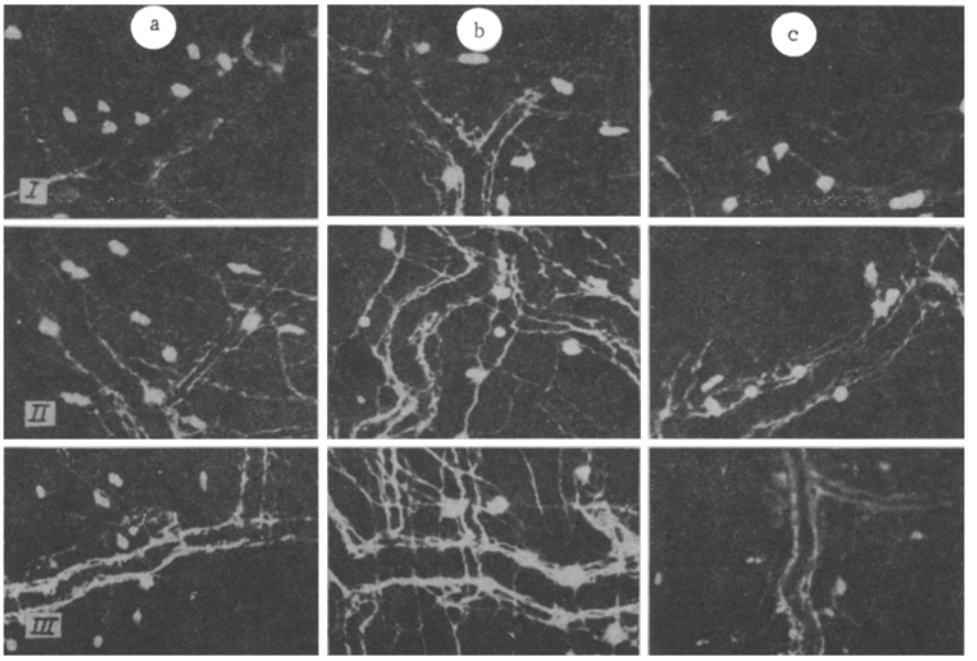

Fig. 1. Adrenergic innervation of rat dura mater. I) Control immobilization, II) under the influence of DAL, III) under the influence of HAE. a) 1 h, b) 24 h, c) 48 h. Method of Falck and Hillarp, 350 ×.

terminal arginine component in its molecule, endowing the neuropeptides with enhanced antistress action [4]. An important role in the mechanism of this action is played by the stimulating effect of neuropeptides on opiate receptors of the neuronal structures of the brain, and also on the inhibitory GABA-ergic system, so that the stressor response is limited at the alarm stage and resistance to the action to stress-inducing factors may be formed in the course of development of the general adaptation syndrome [1, 3, 10]. The possibility of direct interaction between the neuropeptides and α-adrenoreceptors of sympathetic ganglia and of the innervation system of the adrenal medulla must also be taken into account. This mechanism causes inhibition of pulsed monoamine release and leads to an increase in the monoamine concentration both in adrenergic neurons and in the cytoplasm of the chromaffin cells [4, 7, 13]. Neuropeptides can thus behave as modulators of functional activity of the sympathicoadrenal system and of the adaptive properties of the body as a whole at different stages of stress.

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