6. F. Hoffmeister and G. Kroneberg, Methods in Drug Evaluation, Amsterdam (1966), pp. 270-277.
7. R. H. W. M. Hoogen and F. C. Colpaert, Pharmacol. Biochem. Behav., 15, 515 (1981).
8. W. R. Martin, Pharmacol. Rev., 35, 283 (1983).
9. G. W. Pasternak, A. R. Gintzler, R. A. Houghten, et al., Life Sci., 33, 167 (1983).
10. N. Pfeiffer and P. Illes, Trends Pharmacol. Sci., 5, 419 (1984).
11. B. J. Pleuvry, Br. J. Anaesth., 55, 143 (1983).
12. F. Porreca, H. I. Mosberg, R. Hurst, et al., J. Pharmacol. Exp. Ther., 230, 341 (1984).
13. M. B. Tyers, Brit. J. Pharmacol., 69, 503 (1980).
14. B. L. Wolozin, S. Nishimura, and G. W. Pasternak, J. Neurosci., 2, 708 (1982).
15. T. L. Yaksh, Advances in Pain Research and Therapy, Vol. 6, New York (1984), pp. 197-215.

PLASMA β-ENDORPHIN AND STRESS HORMONE LEVELS DURING ADAPTATION AND STRESS

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It is stated in recent publications that activity of the system of opioid neuropeptides is increased during stress [8, 13], but the physiological significance of this phenomenon still remains unclear. The writers showed previously that exogenous administration of analogs of opioid peptides has a positive action on the course of stress [3, 4], so that their role in adaptation can be postulated.

This paper describes a comparative study of β-endorphin and stress hormone levels in the blood plasma of rats during stress and adaptation.

EXPERIMENTAL METHOD

Experiments were carried out on 80 male albino rats weighing 160-180 g. Stress was induced by the method in [9], the essence of which is the existence of a conflict between established conditioned avoidance reflex and unconditioned electrical stimulation at random time intervals.

Some animals were adapted to stress by means of several short sessions of immobilization [5] or by a course (8 days, sessional dose 1 ml/kg) of injections of the pharmacopoeial preparation *Rhodiola rosea* extract, which is a recognized adaptogen of plant origin [7].

The following groups of experimental animals were formed: control — intact rats, group 1) stress (4 h), 2) immobilization, 3) stress after a course of training in immobilization, 4) receiving a course of the adaptogen, 5) stress after a course of the adaptogen.

Immunoreactive β-endorphin in the blood plasma was assayed by means of a kit (Immunonuclear Corp., USA) after preliminary isolation of the β-endorphin fraction by affinity chromatography on sepharose; ACTH was assayed with a kit (CEA IRE Sorin, France), and cortisol, insulin, thyroxine (T_4), and tri-iodothyronine (T_3) by means of kits from "Izotop" (USSR).

The ratio, in percent, between the cortisol and insulin levels (C/I ratio) also was calculated, and its initial level was taken to be 100%.

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TABLE 1. β-Endorphin and Stress Hormone Levels in Blood Plasma in States of Stress (M ± m)

Parameter studied	Experimental group					
	control (n = 12)	1: stress (n = 12)	2: training in immobilization (n = 13)	3: stress after training (n = 11)	4: administration of adaptogen (n = 16)	5: stress after administration of adaptogen (n = 16)
β-endorphin, pmoles/liter	4,21±0,66	30,25±4,38*	7,31±1,25*	6,37±3,25	18,00±5,31*	16,14±3,27*
ACTH, pg/ml	164,08±10,09	151,05±9,65	179,84±14,27	201,76±36,85	160,96±33,68	119,33±34,28
Cortisol, nmoles/liter	12,98±2,88	40,55±5,80*	18,93±3,77	22,61±1,99*	13,10±0,96	16,1±1,66
Insulin, μU/ml	15,61±2,58	8,37±1,10*	13,34±1,75	13,00±1,68	12,40±1,36	12,13±1,58
C/I ratio	1	5,83	1,7	2,09	1,26	0,96
T_4, nmoles/liter	51,80±5,58	20,52±2,62*	24,41±3,16*	23,05±5,19*	42,8±5,7	35,97±4,32*
T_3, nmoles/liter	1,64±0,11	0,59±0,10*	1,19±0,17*	0,82±0,08*	1,95±0,38	2,07±0,19

Legend. *p < 0.05 compared with control; n) number of experiments.

EXPERIMENTAL RESULTS

It will be clear from Table 1 that exposure of the rats to stress for 4 h was accompanied by a more than sevenfold rise in the plasma β-endorphin level, in agreement with data in the literature on the stimulating effect of stress in the endogenous opioid system [8, 13]. Changes in the plasma hormone concentrations were characteristic of the "alarm phase of stress." For instance, the cortisol level in the rats of group 2 was three times higher than in the intact animals, whereas the insulin level was 46.4% lower. There was a marked increase in the C/I ratio under these circumstances, indicating a strain on the compensatory mechanisms [6]. The concentration of thyroid hormones also was reduced: T_4 by 60.4%, T_3 by 2.8 times.

The ACTH level in the group of stressed rats did not differ significantly from the control, which was evidently due to the more rapid changes in the corticotrophin response to stress. This was confirmed by the results of a separate series of experiments in which the ACTH level was significantly increased after 1 h of stress to 302.6 ± 42.9 pg/ml, and returned to the control level after 2 h of the experiment.

Preliminary training of the rats with short sessions of immobilization caused an increase in the basal immunoreactive β-endorphin concentration in the plasma by 73.6%, but abolished the rise of its level in response to subsequent stress in group 3 virtually completely. In the course of training no significant changes were found in the cortisol and insulin levels compared with the control, but the character of the response to the action of the stressor in the rats of group 3, adapted in this manner, was different: no decrease in the insulin concentration was observed, the increase in the cortisol concentration was significantly smaller than in the unadapted rats, and the C/I ratio was 2.8 times lower.

Meanwhile in the course of adaptation the hormone-producing activity of the thyroid gland was diminished: the T_4 level was 2.5 times and the T_3 level 2.8 times lower. All these observations indicate the development of changes in thyroid functions characteristic of stress [2]. However, in the course of these changes, a new level of resistance was evidently formed, as shown, not only by the changes in cortisol and insulin levels described above, but also by the hormonal responses of the thyroid gland of the "trained" rats of group 3 in response to stress. The T_4 level in these animals, while remaining low relative to the intact control, did not undergo any further fall compared with that observed in the rats of group 2. The T_3 level under these circumstances actually rose ($p < 0.01$).

A course of injections of *Rhodiola rosea* extract raised the basal β-endorphin level of the rats but had virtually no effect on concentrations of the other hormones studied. The reproduction of stress in rats receiving this adaptogen, however, was not accompanied by characteristic changes in the β-endorphin level of the hormonal spectrum, with the exception of a small decrease in the T_4 concentration.

The results thus indicate that stress induces a sharp rise of the β-endorphin level and characteristic changes in the plasma concentrations of hormones. Different types of adaptation (training by short exposures to stress or administration of an adaptogen of plant origin) may lead to a moderate increase in the blood level of immunoreactive β-endorphin and may prevent its subsequent rise during stress. At the same time, in the course of adaptation weakening or complete prevention of the hormonal changes characteristic of stress may be observed in the course of adaptation.

It can be postulated on the basis of the facts described above and data in the literature indicating a rise in the endorphin level in the body in response to such procedures as physical training [11], acupuncture [1, 12], hypnosis [10], and so on, that the system of endogenous opioid neuropeptides is a universal mechanism involved in the action of antistressor factors of varied nature, and which may increase the resistance of the body to stress.

Determination of plasma levels of β-endorphin and other opioids could evidently be an important method of assessing the state of resistance of the organism to stress.

LITERATURE CITED

1. E. O. Bragin, R. Dionne, L. Ng, et al., Vopr. Med. Khim., No. 4, 102 (1982).
2. A. A. Viru, Hormonal Mechanisms of Adaptation and Training [in Russian], Leningrad (1981).
3. Yu. B. Lishmanov and T. I. Lisina, Patol. Fiziol., No. 5, 14 (1985).
4. Yu. B. Lishmanov, V. D. Slepushkin, V. N. El'skii, et al., Abstract lodged in the All-Union Institute of Scientific and Technical Information on 22 May 1985, No. 3472-85.
5. F. Z. Meerson, L. M. Belkina, S. S. Dyusenov, et al., Kardiologiya, No. 10, 29 (1985).
6. L. E. Panin, Energy Aspects of Adaptation [in Russian], Leningrad (1978).
7. A. S. Saratikov, *Rhodiola rosea* [in Russian], Tomsk (1974).
8. S. Amir, L. Brown, and L. Amit, Neurosci. Biobehav. Rev., 4, 77 (1980).
9. O. Desiderato, J. R. MacKinnon, and H. Hisson, J Comp. Physiol., 87, 208 (1974).
10. A. Goldstein and E. R. Hilgard, Proc. Natl. Acad. Sci., USA, 72, 2041 (1975).
11. A. Grossman, Clin. Cardiol., 7, 255 (1984).
12. E. Malizia, G. Andreucci, D. Paolucci, et al., Lancet, 2, 535 (1979).
13. M. J. Millan and H. M. Emrich, Psychother. Psychosom., 36, 43 (1981).
14. A. H. Coons and M. H. Kaplan, J. Exp. Med., 91 1 (1950).
15. P. Powerlowicz and W. Dorsh, J. Allergy, 73, 129 (1984).

EFFECT OF LIGANDS OF OPIATE RECEPTORS ON EMOTIOGENIC CARDIOVASCULAR RESPONSES IN LOWER PRIMATES

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Numerous investigations have shown that the endogenous opioid system (EOS) participates directly in the regulation of many physiological processes taking place in the body, including regulation of activity of the cardiovascular system (CVS) [1, 2]. However, the facts confirm that the EOS has only a weak tonic effect directly on the blood pressure (BP) level and cardiac activity. The question accordingly arises of its role in the phasic regulation of responses of the CVS, including those to emotionally meaningful stimuli.

The aim of this investigation was to analyze the role of the EOS in the course of such responses in lower primates.

EXPERIMENTAL METHOD

Experiments were carried out on nine male baboons (*Papio hamadryas*) weighing 8-10 kg. Conditioned-reflex fear [5] was chosen as the model of the emotionally meaningful situation: for 1 min a conditioned acoustic stimulus (CS; 1000 Hz, 60 dB) was presented to the animal and was followed by an unconditioned stimulus (US), namely electrodermal stimulation of the anterior abdominal wall, with a burst of pulses, each with a duration of 1 msec, frequency 50 Hz, 5 mA, total duration 1 sec). After preliminary adaptation of the animals for 2 weeks

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