EFFECT OF ENKEPHALINS ON ENERGY POTENTIAL OF THE LIVER AND CEREBRAL CORTEX OF RATS IN THE EARLY PERIOD OF TRAUMATIC SHOCK

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Different forms of shock are characterized by profound metabolic disturbances, the most important of which are disturbances of energy metabolism [9, 11, 13]. The latter play a decisive role in the development of irreversible shock [6, 9]. Accordingly, factors influencing bioenergetic processes have an important place in the treatment of shock [4, 6]. According to Laborit [6], therapeutic measures reducing energy expenditure of the cell, lowering the tissue oxygen demand, and also restricting the intensity of the postaggressive reaction of the body, are the most promising.

Investigation of endogenous opioid peptides has demonstrated their ability to exert an antishock, anti-ischemic, and antistressor action [2, 7, 8]. These facts provided a basis for the present invesitgation, the aim of which was to study the effect of a synthetic analog of Leu-enkephalin on the energy potential of the brain and liver in the early period of traumatic shock.

METHODS

Experiments were carried out on 86 male albino rats weighing 180-220 g. A model of traumatic shock was created by applying forceps to both hind limbs of the rats [5] for 3 h. The synthetic Leu-enkephalin analog D-Ala^2-Leu^5-Arg^6-enkephalin (synthesized in the Laboratory of Peptide Synthesis, All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR, Director Dr. Chem. Sci. M. I. Titov) was injected intraperitoneally in a single dose of 500 µg/kg body weight 10 min after the beginning of crushing. Intact rats served as the control. The animals were decapitated 1 h after removal of the forceps. All experiments were performed under superficial ether anesthesia. Weighed samples of liver and cerebral cortex were quickly transfered into liquid nitrogen. Concentrations of adenine nucleotides in the tissues were determined by enzymic methods: ATP with the aid of phosphoglycerate kinase, ADP and AMP in the course of successive reactions involving pyruvate kinase, lactate dehydrogenase, and myokinase [1]. The reagents were obtained from Boehringer (West Germany). Optical density was measured on a Specord M-40 spectrophotometer (East Germany). The energy charge (EC) of the adenine-nucleotide system was calculated by Atkinson's formula [10].

RESULTS

The experiments showed that crushing the rats' hind limbs for 3 h led to a fall of 33.6% in the ATP concentration in the cerebral cortex (Table 1). The ADP level in the brain tissues increased by 21.3%, and the AMP level by 4.1% compared with the control. The value of EC in the group of rats with traumatic shock, but untreated, was lower than in intact animals. Shock trauma caused a reduction of the ATP concentration in the animals' liver by half. The ADP concentration in these animals increased by 39.4% and the AMP by 20.5% compared with the control. The value of EC also was lower than in the control.

An important role in the pathogenesis of disturbances of energy metabolism in shock is played by peripheral circulatory disturbances, tissue hypoxia, and toxemia, which develop as

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TABLE 1. Concentrations of Adenine Nucleotides (in μmoles/g tissue) in Cerebral Cortex and Liver of Intact Rats and Rats with Shock, Receiving and Not Receiving Enkephalin (M ± m)

Tissue	Experimental conditions	ATP	ADP	AMP	EC
Brain	Control	1,96±0,18	0,312±0,016	0,348±0,014	0,81±0,015
	Shock	1,3±0,14*	0,396±0,021*	0,362±0,018	0,73±0,018*
	Shock + enkephalin	1,75±0,15	0,366±0,19	0,343±0,018	0,79±0,017
Liver	Control	2,42±0,08	0,790±0,061	0,161±0,01	0,84±0,018
	Shock	1,11±0,10**	1,101±0,082*	0,194±0,011*	0,69±0,016**
	Shock + enkephalin	1,72±0,22*	1,029±0,079*	0,174±0,01	0,76±0,016**

Legend. *P < 0.05; **P < 0.01 compared with corresponding control.

a result of the strong postaggressive response of the animal to trauma [6, 9]. As the experimental results showed, changes in the energy potential in the liver of rats with traumatic shock were more marked than those in the cerebral cortex, in agreement with data in the literature [9]. These differences are evidently associated with worsening of the blood supply and ischemia of the liver in the early period of shock [3, 6]. Conversely, peripheral vasoconstriction and centralization of the circulation help to maintain an adequate blood supply and adequate oxygenation of the brain [5, 6].

In animals with taumatic shock treated with enkephalin, the ATP concentration in the level was higher than in the group of untreated rats (P < 0.05), although it remained lower than the corresponding value (Table 1). The ADP level also remained raised by 30.3%, but the AMP concentration showed no significant change compared with the control. The value of EC was higher (P < 0.05) than in animals with trauma not treated with enkephalin.

The concentrations of the adenine nucleotides in the cerebral cortex of the rats did not differ from the control.

These results show that administration of the Leu-enkephalin analogs to animals with traumatic shock prevented changes in the energy potential in the liver and cerebral cortex. This result is evidence of a positive trend of bioenergetics under the influence of the synthetic analog.

There are data in the literature to show that endogenous opioid peptides, administered systematically, do not pass through the blood-brain barrier [12]. It can accordingly be postulated that normalization of energy metabolism in the cerebral cortex of rats with traumatic shock after treatment with enkephalin evidently took place as a secondary phenomenon connected with the antistressor action of opioid peptides [7, 8]. As regards the improvement of the energy potential of the liver in rats with shock under the influence of enkephalin, the direct anti-ischemic and antihypoxic action of endogenous opioids and their analogs [3, 8] probably plays a particularly important role in this case.

Administration of D-Ala^2-Leu^5-Arg^6-enkephalin thus leads to improvement of energy metabolism and normalization of the energy potential of the liver and cerebral cortex in the early period of traumatic shock.

LITERATURE CITED

1. V. S. Asatiani, Enzymic Models of Analysis [in Russian], Moscow (1969).
2. V. V. Zakusov, V. V. Yasnetsov, R. U. Ostrovskaya, et al., Byull. Éksp. Biol. Med., No. 12, 680 (1984).
3. I. V. Zarubina and B. I. Krivoruchko, Byull. Éksp. Biol. Med., No. 7, 22 (1984).
4. A. P. Zil'ber, Clinical Physiology in Anesthesiology and Resuscitation [in Russian], Moscow (1984).
5. V. K. Kulagin, The Pathological Physiology of Tauma and Shock [in Russian], Leningrad (1978).
6. H. Laborit, Regulation of Metabolic Processes [Russian translation], Moscow (1970).
7. Yu. B. Lishmanov, E. N. Amosova, V. D. Slepushkin, and K. V. Yaremenko, Byull. Éksp. Biol. Med., No. 8, 199 (1984).
8. F. Z. Meerson, Pathogenesis and Prevention of Stressor and Ischemic Lesions of the Heart [in Russian], Moscow (1984).

9. V. I. Nigulyanu, V. N. El'skii, B. I. Krivoruchko, and A. A. Zor'kin, The Long-Term Crush Syndrome [in Russian], Kishinev (1984).
10. E. Newsholme and C. Start, Regulation in Metabolism, London and New York (1973).
11. V. Rudovskii, V. Nazilovskii, V. Zitkevich, and K. Zinkevich, Theory and Practice of Treatment of Burns [in Russian], Moscow (1980).
12. E. I. Chazov, M. I. Titov, V. A. Vinogradov, et al., Vopr. Med. Khimii, No. 3, 47 (1984).
13. D. P. Cuthbertson, J. Roy. Coll. Surg. Edin., 15, 239 (1970).

REACTIVITY OF THE HYPOTHALAMO-HYPOPHYSEO-ADRENOCORTICAL SYSTEM IN RATS WITH INHERITED ARTERIAL HYPERTENSION

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In the study of the causes and pathogenesis of arterial hypertension, great attention has been paid in the literature to analysis of stressor reactivity [2, 10, 11]. In many publications a setate of stress is regarded as an important factor leading to the development of arterial hypertension [2-4, 8, 12]. This is connected with the fact that stress hormones such as adrenalin and gluco- and mineralocorticoids play a direct part in the regulation of blood pressure (BP). Increased stressor reactivity may therefore by one of the most important causes of development of essential hypertension. It has been shown [5] that the level of stressor reactivity in populations of experimental animals (rats or mice) is highly variable, largely due to genetic factors. Consequently, selection for raised BP under conditions of stressor stimulation has been possible [7]. As a result a population of rats with inherited stress-induced arterial hypertension (ISIAH) has been obtained, in which the systolic BP in the 15th generation of selection was 183 ± 2.9 mm Hg. With the appearance of this model of essential hypertension, the way was open for experimental research in several directions [6, 7].

The aim of this investigation was to study reactivity of the hypothalamo-hypophyseo-adrenocortical system (HHAS) to stress and to stimulation of the neurochemical mechanisms of the brain in rats with ISIAH.

METHODS

Experiments were carried out on male rats aged 5-6 months of two genetic groups: with ISIAH (15th generation of selection) and Wistar rats, from which rats with ISIAH were obtained by selection.

One week before the experiment the animals were put into single cages. Emotional stress was induced by placing the animal for 1 h in a cylindrical wire cage, which restricted the movements of the rat drastically (restriction). Combined stress was induced as follows: for 2 min the rat was exposed to ether vapor and 1 ml blood was quickly taken from the tip of the tail, after which the rat was placed in an unfamiliar situation for 1 h. In both the 1st and the 2nd cases, 1 h after the beginning of exposure to stress blood samples were taken from the tip of the tail to measure the concentration of 11-hydroxycorticosteroids (11-HCS). After a recovery period of 5 days, steel guiding microcannulas were inserted into the lateral ventricle of the brain, and 4 days later the response of the HHAS to intraven-

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