BLOOD SUPPLY TO THE BRAIN AND β-ENDORPHIN AND ACTH LEVELS UNDER THE INFLUENCE OF THYROTROPHIN RELEASING HORMONE

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The writers showed previously that thyrotrophin releasing hormone (TRH) significantly increases the cerebral circulation in intact animals and in hemorrhagic shock [3]. Analysis of the mechanism of action of TRH on the blood supply to the brain and on arterial pressure (BP) has revealed the importance of adrenergic structures of blood vessels in the realization of its cerebrovascular and hypertensive effects.

For the reasons given above, and on the basis of data in the literature on the role of TRH in the transmission of nervous impulses or their modulation in the CNS, there is an urgent need to investigate its effects on nervous regulation of the cerebral circulation. The cerebrovascular effects of TRH have been studied by comparison with blood and CSF levels of β-endorphin, and of ACTH, which is linked with it structurally and functionally [5, 6]. Our attention was drawn to β-endorphin because of its possible mediator role, and also because of data in the literature on antagonistic relations between TRH and the endogenous opioid system of the brain [7].

EXPERIMENTAL METHOD

Experiments were carried out on 44 cats weighing 3-4 kg under general anesthesia (urethane with chloralose, pentobarbital) and with artificial ventilation of the lungs. The inflow of blood (in ml/min) into the brain through the carotid artery after careful ligation of its extracranial branches was determined by an electromagnetic flowmeter (Nihon Kohden, Japan). The ECG in lead II and BP (in mm Hg) in the femoral artery were recorded at the same time. Tonic activity and reflex discharges were recorded in the sympathetic nerves of the renal plexus [1]. The vascular component of the action of the hormone on the cerebral hemodynamics was differentiated by the method of separate bilateral perfusion of the carotid and vertebral arteries [4]. The recording was carried out on a Mingograf-81 apparatus. The partial pressure of carbon dioxide (pCO_2) in samples of the cats' arterial blood was determined by the micro-Astrup method and maintained within limits of control values (30-35 mm Hg). Reflex responses of the cerebral vessels were evoked by electrical stimulation of the central end of the divided tibial nerve (20-40 V, 20-40 stimuli/sec, 2 msec, for 15 sec).

Blood for determination of peptides was obtained from the innominate vein, and CSF from the cisterna magna before and 3 and 20 min after injection of TRH. β-Endorphin was determined by radioimmunoassay using kits from INC (USA), and ACTH was determined by using kits from CEA Sorin (France). The β-endorphin level was determined after its separation from the β-lipotrophin fraction.

TRH was injected intravenously in a dose of 1 mg/kg. The animals were killed with a mixture of urethane and chloralose.

EXPERIMENTAL RESULTS

In the experiments with recording of the cerebral blood flow, TRH significantly increased the blood supply to the brain during the period of formation of the vasomotor reflex

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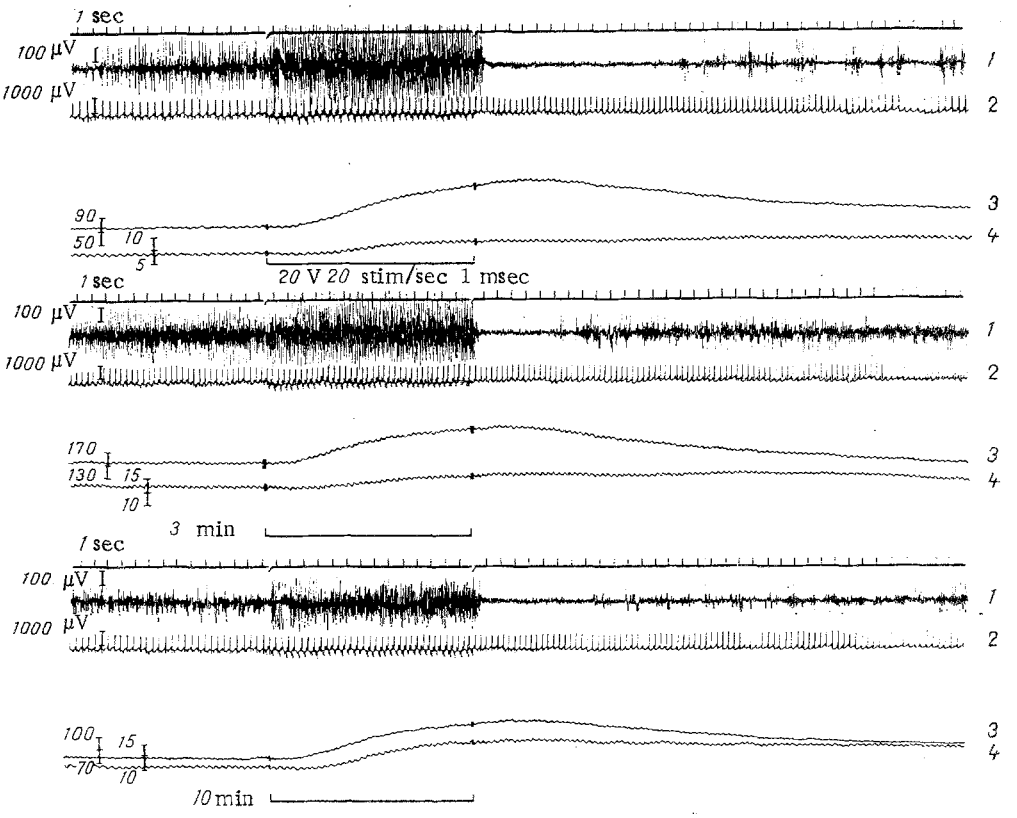

Fig. 1. Effect of TRH on tonic activity in sympathetic nerve (1), ECG (2), BP (3), and cerebral blood flow (4) in cats under general anesthesia. Time marker (1 sec) shown above. Horizontal line indicates injection of TRH.

on average by 122 ± 31% (Fig. 1). The ability of TRH to depress cerebrovascular reflexes was established in experiments in which vascular tone was recorded directly by the technique of separate bilateral perfusion of the cerebral arteries. In most experiments TRH inhibited vasoconstrictor reflexes in the carotid and vertebrobasilar regions by 62 ± 7.9 and 70 ± 10.8% respectively. The pressor response of BP under these circumstances was weakened by 65 ± 10.5%. Analysis of electrical activity in the sympathetic nerves showed that TRH causes initial enhancement of tonic activity, which falls below the initial level after 8-10 min. Reflex discharges in most experiments were inhibited immediately after injection of TRH (Fig. 1).

The results served as a basis for the suggestion that the cerebrovascular effects of TRH are mediated through the opioid system of the brain. It has been shown that enkephalins and β-endorphin depress central mechanisms controlling BP [7, 9, 11]. In a separate series of experiments the effect of TRH was therefore studied on the concentrations of immunoreactive β-endorphin and the functionally related ACTH in the CSF also. The concentrations of peptides were determined 3 and 20 min after injection of TRH, at a time when maximal changes in cerebrovascular tone and reflexes were exhibited. The experiments showed that the blood β-endorphin level 3 and 20 min after injection of TRH did not differ significantly from the original concentration of the peptide. The β-endorphin level in the CSF also was unchanged by the action of TRH.

A different picture was found on determination of ACTH. TRH caused a considerable rise in the blood ACTH level, on average by 75 ± 18%, 3 min after its injection. In most experiments the ACTH concentration remained high even 20 min after administration of TRH. A decrease in the ACTH concentration in the CSF was found, on the other hand, under the influence of TRH. The fall in the peptide concentration 3 min after injection of TRH amounted to 41 ± 13%. A further fall in the ACTH level was observed 20 min after injection of TRH, on average by 63 ± 9.1% of its initial level.

The investigation thus showed that TRH has a marked depressant effect on cerebrovascular vasoconstrictor reflexes. The absence of changes in the concentration of immunoreactive β-endorphin in the blood and CSF is evidence that the cerebrovascular effects of the prepara-

tion are evidently not mediated through the opioid system, but are caused by the direct effect of TRH on the central mechanisms of regulation of the cerebral circulation. Elevation of the blood ACTH level causes an increase in BP and in the tone of the cerebral vessels, which were observed in the present experiments. ACTH is known to cause a rise in BP and an increase in resistance of the cerebral vessels to the blood flow [2]. Our data showing absence of correlation between the β-endorphin and ACTH levels in the blood and CSF under the influence of TRH agree with results of investigations of several workers who found that changes in these peptides are not always identical in direction [8, 10]. Opposite changes in blood and CSF ACTH levels under the influence of TRH may be the results of the action of a negative feedback mechanism, whereby the high blood ACTH level has an inhibitory effect on ACTH synthesis in brain tissue.

LITERATURE CITED

1. É. A. Bendikov and V. G. Butuzov, in: Pharmacology of Monoaminergic Processes [in Russian], Moscow (1971). p. 24.
2. M. D. Gaevyi, Pharmacology of the Cerebral Circulation [in Russian], Moscow (1980), p. 121.
3. V. V. Zakusov, V. M. Bulaev, T. S. Gan'shina, et al., Byull. Éksp. Biol. Med., No. 9, 61 (1983).
4. R. S. Mirzoyan, Fiziol. Zh. SSSR, No. 6, 966 (1973).
5. R. Guillemin, T. Vargo, J. Rossier, et al., Science, 197, 1367 (1977).
6. E. Herbert, Trends Biol. Sci., 6, 184 (1981).
7. J. W. Holaday, Ann. Rev. Pharmacol. Toxicol., 23, 541 (1983).
8. J. M. Kuhn, J. P. Luton, and H. Bricaire, Ann. Med. Interne, 133, 148 (1982).
9. M. A. Petty, W. De Jong, and D. De Wied, Life Sci., 30, 1835 (1982).
10. R. Przewlocki, V. Hollt, and A. Herz, Europ. J. Pharmacol., 51, 179 (1978).
11. J. M. A. Sitsen, J. M. Van Ree, and W. De Jong, J. Cardiovasc. Pharmacol., 4, 883 (1982).