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EFFECT OF A TETRAPEPTIDAMIDE NITRO ANALOG AND OF MORPHINE ON THE CEREBRAL CIRCULATION

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Enkephalins perform the function of neurotransmitters or modulators in the CNS. Their interaction with mediator systems of the brain has been demonstrated. It has also been found that central adrenergic and GABA-ergic mechanisms participate both in regulation of the cerebral circulation [3, 5, 6] and in realization of the analgesic effect of morphine [10]. It is therefore important to study the effect of a synthetic analog of the enkephalins, namely a tetrapeptidamide nitro analog, which has an analgesic action on the cerebral circulation, and to compare its effects with those of morphine. No information on the effect of enkephalins and their analog on the cerebral circulation could be found in the literature. As regards morphine, according to observations made by most investigators, the drug increases the cerebral blood flow and lowers the tone of the cerebral vessels [2, 7-9].

The investigation described below was devoted to a study of the effect of the tetrapeptidamide nitro analog (TNA), compared with that of morphine, on the cerebral circulation and its nervous control. The cerebrovascular effects of these compounds were studied also after blockade of GABA-receptors by bicuculline.

EXPERIMENTAL METHOD

Experiments were carried out on 69 cats weighing 3-4 kg under general anesthesia (urethane, chloralose) with artificial ventillation of the lungs.

The flow of blood into the brain through the carotid artery was determined, after careful ligation of the extracranial branches by means of an electromagnetic flowmeter (Nihon Kohden). The EEG from the parietal region, the ECG in lead II, and the blood pressure in the femoral artery (BP) were recorded simultaneously. Tonic activity and reflex discharges were recorded in the sympathetic nerves of the renal plexus [1]. The vascular component of the action of the substances on the cerebral hemodynamics was differentiated by separate

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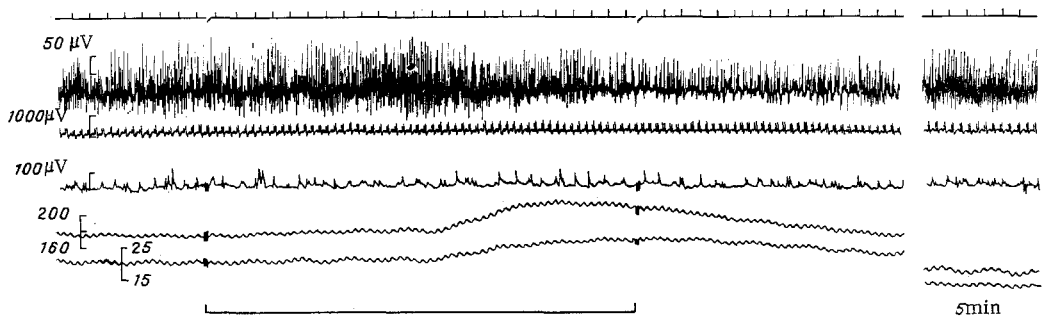

Fig. 1. Effect of TNA (1 mg/kg, intravenously) on cerebral blood flow in cat under general anesthesia. From top to bottom: time marker 1 sec, tonic activity in sympathetic nerve to kidney, ECG in lead II, EEG from parietal region, BP in femoral artery (in mm Hg), blood flow in carotid artery (in ml/min), marker of injection of preparation.

bilateral perfusion of the carotid and vertebral arteries [4]. The partial pressure of carbon dioxide (pCO_2) was determined in samples of arterial blood of the cats by the micro-Astrup method and maintained between limits of the control values (30-35 mm Hg).

The test substances were injected intravenously: TNA in a dose of 1 mg/kg, morphine in a dose of 1 mg/kg, and bicuculline in a dose of 0.15-0.2 mg/kg. The animals were killed with a mixture of urethane and chloralose.

EXPERIMENTAL RESULTS

The experiments showed that TNA (1 mg/kg) increased the cerebral blood flow on average by 25 ± 6% in the course of 2-5 min. The blood supply to the brain then fell below its initial level (Fig. 1). Under the influence of the drug, in most experiments a transient rise of BP was observed, followed by prolonged hypotension. TNA reduced vascular tone equally in the systems of the carotid and vertebrobasilar arteries by 16 ± 1 and 17 ± 2% respectively. BP fell under these circumstances by 48 ± 3%.

Similar changes in the cerebral hemodynamics were observed under the influence of morphine, which increased the cerebral blood flow by 17 ± 3%. Morphine caused a long decrease of BP. In some experiments, however, this was preceded by a brief hypertensive reaction. Under the influence of morphine cerebral vascular tone was reduced in both the carotid (by 17 ± 2%) and the vertebrobasilar (by 13 ± 1%) arterial systems of the brain. Under these conditions morphine depressed BY by 31 ± 4%. These results are in agreement with data in the literature [2, 7-9] on the ability of morphine to increase the blood flow into the brain as a result of a decrease in resistance of the cerebral vessels to the blood flow.

The effect of TNA and morphine on nervous regulation of the cerebral circulation was next studied. The experiment showed that under the influence of TNA cerebrovascular reflexes in the carotid and vertebrobasilar systems were inhibited by 90 ± 6 and 89 ± 9% respectively. At the same time the pressor reaction of BP was reduced on average by 75 ± 6%. In most experiments the preparation weakened tonic and reflex activity in the sympathetic nerves. Morphine weakened reflex constrictor reactions of the vessels in the carotid system by 74 ± 7% and in the vertebrobasilar system by 72 ± 11%. The pressor reaction of BP was inhibited under these circumstances by 66 ± 8%.

To analyze the mechanism of the cerebrovascular effect of TNA and morphine a series of experiments was undertaken in which these compounds were tested after blockade of GABA-receptors by bicuculline. Against the background of the action of bicuculline TNA was found to lower vascular tone of the carotid and vertebrobasilar systems by 18 ± 2 and 20 ± 5% respectively. BP was lowered under these circumstances by 44 ± 6%. Under analogous conditions morphine reduced the resistance to the blood flow in the carotid system by 12 ± 2% and in the vertebrobasilar system by 17 ± 4%. Against the background of the action of bicuculline, morphine reduced BP by 37 ± 4%.

TNA administered after bicuculline had a depressant effect on reflex constrictor responses of vessels of the carotid (by 72 ± 9%) and vertebrobasilar (by 81 ± 11%) systems. The pressor response of BP under these conditions was inhibited by TNA by 76 ± 8%.

The cerebrovascular reflexes in the carotid and vertebrobasilar systems were inhibited by morphine during blockade of GABA-receptors by 74 ± 7 and 57 ± 11% respectively. Aginst the background of the action of bicuculline, morphine inhibited reflex responses of BP by 5 ± 8% (Fig. 2).

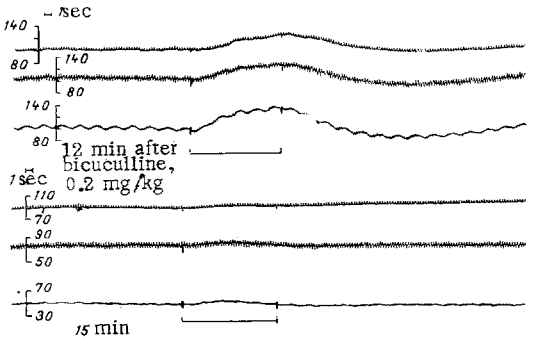

Fig. 2. Effect of morphine (1 mg/kg, intravenously) on constrictor responses of cerebral vessels after preliminary injection of bicuculline (0.2 mg/kg, intravenously). Control reactions shown in top part of figure. Below – 15 min after morphine. From top to bottom: perfusion pressure in carotid system, in vertebrobasilar system, BP (in mm Hg), marker of stimulation (20 V, 40 stimuli/sec, 2 msec, 15 sec).

The results are thus evidence of the ability of TNA and morphine to induce a small and transient increase in the cerebral blood flow, by lowering vascular tone in both arterial systems of the brain. It was found that TNA and morphine have a marked depressant effect on nervous regulation of the cerebral circulation, inhibiting reflex constrictor reactions of the cerebral vessels. The effects of these preparations revealed in these experiments are manifested also after blockdage of GABA-receptors, evidence that these properties of TNA and morphine are independent of bicuculline-sensitive GABA-ergic processes.

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