EFFECT OF LEU- AND MET-ENKEPHALINS ON BRAIN REINFORCING SYSTEMS

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The reinforcing systems of the brain are known to play an important role in the formation of predilection for and dependence on drugs [3]. It has been suggested that the activity of these systems may be modulated by endogenous morphine-like peptides — enkephalins and endorphins [4]. However, information on the direct effect of enkephalins on the reinforcing system is limited and contradictory [10, 12]. Moreover, there have been virtually no studies of the effect of Leu- and Met-enkephalins (LE and ME respectively) on the "punishment" system.

The object of this investigation was to compare the effects of ME and LE on activity of the positive and negative reinforcement systems.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 250-300 g, which were anesthetized with pentobarbital (50 mg/kg body weight, intraperitoneally) and monopolar electrodes were inserted into their central gray matter (CGM) and cannulas introduced into the right lateral cerebral ventricle. The effects of central aversive stimulation were assessed by the active avoidance (AA) method in a shuttle box, when the animal switched on stimulation of its brain (300-500 μA, 1 msec, 100 Hz) when it ran into the opposite compartment. The effect of the preparations on positive reinforcing mechanisms of the brain was studied by a technique of self-stimulation (SS) (250 μA, 1 msec, 100 Hz) of fixed duration of 250 msec, by pressing a pedal. The preparations were injected into the lateral ventricle in a volume of 10 μl in doses of 50-200 μg/kg body weight. The effect of the preparations on the latency of AA was determined 5, 20, and 35 min after injection. The original latency of blocking of central aversive stimulation did not exceed 2.5-6 sec in all groups. The effect of LE and ME on the SS reaction was assessed over a period of 30 min starting 5 min after injection. The number of times the animal pressed on the pedal during each 10 min of the experiment was counted. In control experiments sterile water was injected.

EXPERIMENTAL RESULTS

ME and LE had opposite actions on the SS response. ME inhibited brain SS responses. A decrease in the intensity of SS was observed after injection of the preparation in the lowest dose of 50 μg/kg (—19.9 ± 4.8%). With an increase in the dose of the peptide to 100 and 200 μg/kg the intensity of SS fell by 26.4 ± 7.7 and 26.0 ± 5.6% respectively. Injection of naloxone in a dose of 0.25 mg/kg 15 min before microinjection of ME weakened the inhibitory action of the preparation on the SS response (Fig. 1A).

LE had the opposite action on the SS response (Fig. 1B). After injection of LE in doses of 50 and 100 μg/kg SS was facilitated by 37.7 ± 11.1 and 69.7 ± 10.7%. After injection of LE in a dose of 200 μg/kg the increase in SS was not significant, probably on account of the development of catatonia. Naloxone (0.25 mg/kg intraperitoneally) reduced the facilitatory action of 100 μg/kg LE on the SS response (Fig. 1B).

LE and ME inhibited the AA response (Fig. 2). ME lengthened the latency of AA in doses of 50, 100, and 200 μg/kg. The latency of blocking of central aversive stimulation was in-

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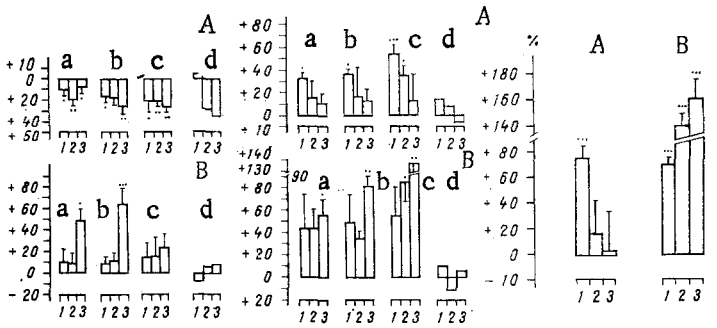

Fig. 1 Fig. 2 Fig. 3

Fig. 1. Effect of ME (A) and LE (B) on brain SS response. Ordinate, change in number of presses on pedal during each 10 min of experiment (in %). 1, 2, and 3) 5, 15, and 25 min respectively after injection of preparation. a-c) Doses of 50, 100, and 200 μg/kg, d) peptide in dose of 200 μg/kg + naloxone 0.25 mg/kg. ·P < 0.05, ··P < 0.01, ···P < 0.001 (Student's t-test); circle — P < 0.05 (Wilcoxon's nonparametric two-sample test).

Fig. 2. Effect of ME (A) and LE (B) on latency of AA response. Ordinate, change in latency of AA response (in %). 1, 2, and 3) 5, 20, and 35 min respectively after injection of preparation. Remainder of legend as to Fig. 1.

Fig. 3. Effect of enkephalins on latency of initiation of running away (time from beginning of brain stimulation to beginning of running) during AA response. Ordinate, change in latency of initiation of running away (in %). 1, 2, and 3) 5, 15, and 25 min respectively after injection of ME (A) and LE (B) in dose of 200 μg/kg. Remainder of legend as to Fig. 2.

creased by the above-mentioned doses on average by 31.8 ± 4.7, 33.4 ± 5.2, and 52.9 ± 7.6% respectively (Fig. 2A). The action of ME was virtually completely abolished by naloxone in a dose of 0.25 mg/kg. The effect of LE on AA was stronger than the action of ME (Fig. 2B). However, the maximal effect of LE did not develop until 35 min after injection. The latency of AA was increased on average by 53.7 ± 14.9, 80.4 ± 10.9, and 130.0 ± 24.4% respectively. The action of the preparation also was completely blocked by naloxone.

To rule out any effect of catatonia following injection of the enkephalins in a dose of 200 μg/kg, not only the total duration of blocking of central stimulation, but also the time from the start of brain stimulation until the beginning of running away was taken into account. It will be clear from Figs. 2 and 3 that the dynamics of significant inhibition of AA following injection of the enkephalins in the period from the start of brain stimulation until the beginning of running away was similar to the original pattern, from which it can be concluded that it was mainly the perceptual component of the negative reinforcement system that was inhibited.

These results confirm the hypothesis that enkephalins participate in the regulation of activity of the basal appraisal systems of the brain. The data on the inhibitory action of ME on SS described above are in agreement with those obtained by other workers [4]. The facilitatory action of LE and ME on the SS response was evidently not connected with any particular feature of the periaqueductal brain structures which were stimulated, for the experimental results were independent of the location of the electrodes in CGM.

The opposite direction of the effects of LE and ME is probably due to their different functional roles, which can be explained on the grounds of the different localization of the enkephalins in the CNS and their different affinity for particular types of opiate receptors [8, 9]. The existing data on the different analgesic and reinforcing properties of LE and ME [1, 4, 14] suggest that the opposite character of their effects may be due to the action of these neuropeptides on different types of opiate receptors, the possible existence of which has been postulated [5, 8, 11]. The results of the present experiments and data in the literature relating to the ability of LE to stimulate activity of the "reward" system may be evidence of the important role of the Leu-enkephalinergic component of endogenous brain systems in the development of demand for drugs and drug dependence. Meanwhile, an indirect role of endorphinergic systems and mechanisms in the activating effect of LE cannot

be ruled out. It can be tentatively suggested that during the action of LE, like that of morphine, their effects are brought about through the liberation of endorphins [13], which have a high euphorigenic potential [14].

Enkephalins inhibit activity of the negative reinforcement system by their action on its perceptual and emotional components [1]. The inhibiting effect of LE is stronger than that of ME, evidently due to its stimulating action on the "reward" system, which reciprocally depresses the activity of the negative reinforcement system [2]. Information in the literature on the modulating action of enkephalins on serotoninergic brain mechanisms [6], which play a direct part in the functioning of reinforcement system [2], suggest an important role for this substrate in the mechanism of the effect of these peptides on "reward" and "punishment" systems.

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INFLUENCE OF THE STATE OF BRAIN CATECHOLAMINERGIC SYSTEMS ON PSYCHOTROPIC EFFECTS ON EMOTIONAL REACTIVITY AND BEHAVIOR UNDER STRESS

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Variations in reactivity of certain animals to stress [10] and differences in the effects of psychotropic drugs depending on the type of emotional reaction of different individuals [3] are associated with individual variations in concentration and turnover of brain catecholamines (CA) [14].

In the investigation described below particular features of the action of some psychotropic drugs on behavioral manifestations in an acute stress situation were studied in animals after preliminary destruction of catecholaminergic terminals and also in intact animals, allowing for their original type of emotional-behavioral reactivity. The functional level of the catecholaminergic system of the brain was judged from activity of tyrosine hydroxylase (TH), the key enzyme of CA biosynthesis.

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