COMPARATIVE ANALYSIS OF THE ROLE OF THE MEDIAL FOREBRAIN BUNDLE IN VARIOUS TYPES OF ANALGESIA

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Mechanisms of antinociception concerned in the action of opiate analgesis, stress, and electroacupuncture are mediated by catecholamine mechanisms. An important role of these mechanisms has been established in experiments on animals subjected to systemic blocking of monoamine synthesis as a result of intraperitoneal injection of reserpine, α-methylparatyrosine, and 6-hydroxydopamine [1-5, 9]. The role of descending monoamine spinal cord mechanisms in the regulation of nociceptive sensitivity has been studied in the greatest detail in experiments on animals, in which damage to particular monoamine systems was produced by injection of selective neurotoxins or electrolytically [2, 9]. Much less attention has been paid to the study of the role of ascending monoamine systems, innervating the anterior parts of the brain, in the mechanisms of inhibition of nociceptive sensitivity associated with exposure to factors of different kinds. One of the chief pathways of monoamine innervation of these brain structures is the medial forebrain bundle (MFB), which derives its origin from the locus coeruleus, substantia nigra, reticular nuclei, and ventral tegmentum, and innervates structures of the hypothalamus, corpus striatum, septum, and cerebral cortex.

Accordingly, in the present investigation the effect of bilateral destruction of MFB at different levels of the brain was studied on antinociceptive activity in rats before and after exposure to various influences.

EXPERIMENTAL METHOD

Experiments were carried out on 82 albino rats weighing 200-250 g. MFB was blocked in animals anesthetized with chloral hydrate (8% solution, 8 ml/kg, intraperitoneally). A bipolar platinum electrode was inserted into the rats of group 1 (n = 2) at coordinates of AP +5.4, VD −2.8, and L +1.4 [8] at the level of the anterior hypothalamus (rostral MFB—RMFB). An electrode was inserted into the rats of group 2 (n = 20) at the level of the mammillary bodies (caudal MFB — CMFB), at coordinates of AP +3.4, VD −2.8, and L +1.1. Destruction of MFB was carried out by passing a current of 2.5 mA for 25 sec. A mock operation was performed on animals of the control group, in which the electrode was inserted at the corresponding coordinates, but no current was passed through it. Nociceptive sensitivity was estimated by measuring latent periods (LP) of the paw licking response (PLR) to placing the rats on a hot plate at 55°C, and the tail withdrawal response (TWR) to application of a focused thermal beam from a 150-W lamp to it. LP was measured before and after exposure at definite time intervals.

Inhibition of nociceptive sensitivity was produced by unavoidable painful electrodermal stimulation (UPES) with a steady current (2.5 mA, 5 min, 8 pulses/min), by making the rats swim in water at 4°C for 2 min, and also by injection of morphine chloride (5 mg/kg, intraperitoneally). After the experiments the rats' brains were fixed in 10% neutral formalin, sections were cut to a thickness of 60 μ, and the site of injury to MFB was verified morphologically.

All the results were subjected to statistical analysis.

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TABLE 1. Effect of Blocking of the Rostral Part of MFB on LP (in sec) of PLR and TWR after UPES, Cold stress (CS), and the Action of Morphine (M ± m)

Experimental conditions	Initial LP	Time after procedure, min						
		0	5	10	20	30	40	60
UPES								
PLR								
Control	10,4±1,9	22,3±1,7[a]	17,8±3,8[a]	14,2±3,2[a]	6,3±0,8[a]	5,8±3,8	8,5±5,3	—
Experiment	9,0±1,6	14,0±5,8[a]	3,3±1,6[b]	4,8±3,6[b]	0,2±2,2[b]	1,9±1,9	7,0±7,0	—
CS								
PLR								
Control	16,0±2,1	22,6±1,8[a]	22,5±2,2[a]	22,7±2,0[a]	22,0±2,6[a]	19,7±2,8[a]	14,7±4,4[a]	—
Experiment	16,1±1,7	23,9±1,7[a]	23,9±1,7[a]	23,9±1,7[a]	23,9±1,7[a]	17,6±3,9[a]	11,7±3,9[a]	—
TWR								
Control	2,9±0,2	2,9±0,6[a]	2,8±0,5[a]	2,2±0,4[a]	2,1±0,6[a]	1,4±0,3[a]	1,4±0,5[a]	—
Experiment	2,9±0,3	3,2±0,7[a]	3,4±0,4[a]	1,7±0,4[a]	2,1±0,5[a]	1,5±0,5[a]	1,0±0,4	—
Morphine								
PLR								
Control	12,1±1,6	—	—	10,0±3,6[a]	14,4±3,1[a]	11,8±3,3[a]	6,3±1,9[a]	7,6±1,8
Experiment	12,6±0,8	—	—	1,8±2,5	2,0±2,2[b]	4,3±3,4	5,5±3,3	2,8±4,1
TWR								
Control	3,4±0,2	—	—	1,2±0,6	1,4±0,4[a]	1,1±0,2[a]	0,9±0,5	0,7±0,6
Experiment	3,6±0,2	—	—	0,4±0,3	0,1±0,2[b]	0,1±0,2[b]	0,6±0,6	0,5±0,3

Legend. Here and in Table 2: a) $p < 0.05$ compared with initial value, b) $p < 0.05$ compared with control.

TABLE 2. Effect of Blocking the Caudal Part of MFB on LP (in sec) of PLR and TWR after UPES, CS, and the Action of Morphine (M ± m)

Experimental conditions	Initial LP	Time after procedure, min						
		0	5	10	20	30	40	50
UPES								
PLR								
Control	16,5±1,8	10,1±2,0[a]	12,7±2,4[a]	2,0±2,1	3,1±2,6	1,5±2,5	1,3±2,8	—
Experiment	14,5±1,2	9,7±3,0[a]	3,7±2,0b	0,4±1,7	0,7±1,7	3,3±3,4	3,8±4,3	—
CS								
PLR								
Control	14,6±2,1	25,4±2,1[a]	25,4±2,1[a]	25,4±2,1[a]	25,4±2,1[a]	7,3±5,9	2,7±3,1	—
Experiment	16,3±2,9	23,7±2,8[a]	23,7±2,8[a]	20,0±5,6	20,4±0,8[a]	23,7±2,8[a,b]	18,1±2,8[a,b]	—
TWR								
Control	3,8±0,4	2,6±0,8[a]	2,2±1,0[a]	2,7±0,8[a]	2,5±1,0[a]	1,9±0,9	1,6±1,1	—
Experiment	4,1±1,0	2,9±0,1[a]	2,9±0,1[a]	2,9±0,1[a]	2,9±0,1[a]	2,9±0,1[a]	2,0±0,5[a]	—
Morphine								
PLR								
Control	10,4±1,5	—	—	8,9±3,7[a]	8,0±3,4[a]	8,8±3,8[a]	8,4±2,2[a]	0,8±1,2
Experiment	13,5±1,9	—	—	15,8±3,5[a]	7,2±3,5[a]	8,4±4,1[a]	7,9±4,2	6,1±4,1
TWR								
Control	3,3±0,1	—	—	1,9±0,5[a]	1,5±0,5[a]	2,0±0,4[a]	1,8±0,5[a]	2,2±0,5[a]
Experiment	3,5±0,3	—	—	0,9±0,4	1,5±0,5[a]	1,8±0,6[a]	1,3±0,6	1,5±0,6[a]

EXPERIMENTAL RESULTS

The results of the morphological control showed that the damage was localized to the region of RMFB and CMFB at the level of the mammillary bodies of the rostral hypothalamus, and measured 1.2-1.7 mm in the rostrocaudal direction. Such a lesion leads to complete disappearance of the dopamine terminals in nucleus caudatus, the putamen, and nucleus accumbens and to a marked decrease in the number of noradrenergic terminals in the paraventricular nuclei of the hypothalamus, preoptic region, ventral part of the striae terminales, cortex, and hippocampus [10].

Changes in LP of PLR in rats of the experimental and control groups showed no difference. For instance, LP of PLR in the experimental group was 13.2 ± 0.97 sec compared with 13.4 ± 1.2 sec in the control. A similar result was obtained when LP of TWR was measured: 3.3 ± 0.21 sec in the experimental group and 3.2 ± 0.15 sec in the control. Qualitatively similar data were found in rats with destruction of CMFB. These results show that removal of MFB does not affect the duration of nociceptive responses (LP) at rest. However, there is evidence that damage of MFB at the level of the lateral hypothalamus lowers the threshold of jumping responses [6, 7]. The authors cited explain this effect by a fall of 38-40% in the serotonin and adrenalin concentrations in the brain. Meanwhile, other experiments have shown that a systemic and more marked inhibition of monoamine synthesis is not accompanied by any change in nociceptive responses at rest [2, 9].

It can be postulated that in this case nociceptive responses are realized by monoamine systems which have been preserved from injury.

The experiments of series I showed that UPES causes a significant increase in LP of PLR in the control until the 20th minute of the recovery period, whereas in the experiment it did so only until the 5th minute (Table 1). Comparison of LP of PLR showed that this parameter was significantly shorter after 5-20 min in the experimental group than in the control. Qualitatively similar results were obtained in rats after removal of CMFB (Table 2). Hence it follows that blocking of MFB leads to inhibition of antinociceptive mechanisms activated by UPES.

The effect of cold stress (CS), namely making the rats swim in water at 4°C, was studied in the experiments of series II. These experiments showed that CS leads to a significant and more than twofold increase in LP of PLR in the control and experimental groups in rats with destruction of RMFB and CMFB (Tables 1 and 2). LP of TWR also was significantly increased compared with the initial value in both groups. No differences could be found in LP of PLR and TWR between the control and experimental groups as a result of these two types of procedures. Consequently, destruction of MFB and blocking of ascending monoaminergic systems, innervating the anterior zones of the brain, do not affect activity of the antinociceptive mechanisms under the influence of CS.

In the experiments of series III the effect of morphine on the duration of LP of PLR and TWR was studied in rats after destruction of RMFB. It was found that morphine in a dose of 5 mg/kg causes significant lengthening of PLR in rats of the control group, starting from the 10th until the 40th minutes (Table 1). In the experimental group no significant increase in LP of PLR was observed throughout the course of the experiment. On comparison of LP, significantly shorter values of PLR were found in rats of the experimental group compared with the control only after 20 min (Table 1). Similar results were obtained by measurement of LP of TWR, and in this case significant differences between the experiment and control were observed at the 20th and 30th minutes.

In the case of destruction of CMFB, equal lengthening of LP of PLR and TWR was observed in the experimental and control groups, compared with the initial value, throughout the period of the experiment (Table 2).

It can accordingly be concluded that RMFB and the monoamine systems of the forebrain connected with it may play a more important role than CMFB in activation of the mechanisms of antinociception during the action of morphine.

It can thus be concluded from the results that blocking RMFB and CMFB does not affect pain sensitivity at rest. Destruction of RMFB and CMFB has no effect on activity of antinociceptive mechanisms during the action of CS. The rostral part of MFB plays a more important role than its caudal part in the activation of antinociceptive mechanisms during the action of morphine. Different types of analgesia are realized by neurochemical mechanisms which differ from one another.

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