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

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The mechanisms of antinociception during the action of opiate analgesics, stress, electroacupuncture, and so on, have been shown to be catecholamine-mediated. The important role of these mechanisms has been established in experiments on animals subjected to systemic blocking of monoamine synthesis by intraperitoneal injection of reserpine, α-methylparatyrosine, and 6-hydroxydopamine [1-5, 9]. The role of descending monoamine mechanisms of the spinal cord in regulation of sensitivity to pain has been studied in the greatest detail in experiments on animals, in which damage to certain monoamine systems was induced 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 forebrain in the mechanisms of suppression of sensitivity to pain during various kinds of procedures One of the main pathways of monoamine innervation of these brain structures is the medial forebrain bundle (MFB), which arises from the locus coeruleus, substantia nigra, reticular nuclei, and ventral tegementum, and innvervates structures of the hypothalamus, corpus striatum, septum, and cerebral cortex.

The aim of this investigation was to study the efect of bilateral destruction of MFB in rats at different levels of the brain on antinociceptive activity before and after various procedures.

EXPERIMENTAL METHODS

Experiments were carried out on 82 albino rats weighing 200-250 g. MFB was blocked in rats anesthetized with chloral hydrate (8% solution, intraperitoneally, 8 ml/kg). A bipolar platinum electrode was inserted into the animals of group 1 (21 rats) at coordinates AP +5.4, VD −2.8, L ±1.4 [8] at the level of the anterior hypothalamus (rostral MFB − RMFB). In the 20 rats of group 2 the electrode was inserted into MFB at the level of the mammillary bodies (caudal MFB − CMFB) at coordinates AP +3.4, VD −2.8 mm, L ±1.1. MFB was destroyed by passing a current of 2.5 mA through it for 25 sec. A mock operation was performed on the control rats (group 1 − n = 21; group 2 − n = 20), in which an electrode was inserted at the corresponding coordinates but no current was passed through it. Sensitivity to pain was evaluated by measuring latent periods (LP) of the paw licking reflex (PLR) in response to placing the rats on a hot plate at T = 55°C, and the tail withdrawal response (TWR) to focusing a beam of radiant heat from a 150-W lamp on it. LP was measured before and after exposure at definite time intervals. Sensitivity to pain was inhibited by unavoidable painful electrodermal stimulation (PEDS) with a direct current of 2.5 mA for 5 min, 8 shocks per minute, by making the rats swim in water at T = 4°C for 2 min, and by injection of morphine chloride (5 mg/kg, intraperitoneally). After the experiments the rats' brains were fixed in 10% neutral formalin solution, sections were cut to a thickness of 60 μ, and damage to LFB was verified morphologically. All the results were subjected to statistical analysis.

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Table 1. Effect of Blocking Rostral Part of MFB on LP of PLR and TWR after PEDS, CS, and Action of Morphine

Exptl. conditions	Initial LP, %	Time after procedure, min						
		0	5	10	20	30	40	60
PEDS								
PLR								
control	10,4±1,9	22,3±1,7*	17,8±3,8*	14,2±3,2*	6,3±0,8*	5,8±3,8	8,5±5,5	—
expt.	9,0±1,6	14,0±5,8*	3,3±1,6**	4,8±3,6**	0,2±2,2**	1,9±1,9	7,0±7,7	—
CS								
PLR								
control	16,0±2,1	22,6±1,8*	22,5±2,2*	22,7±2,0*	22,0±2,6*	19,7±2,8*	14,7±4,4*	—
expt.	16,1±1,7	23,9±1,7*	23,9±1,7*	23,9±1,7*	23,9±1,7*	17,6±3,9*	11,7±3,9*	—
TWR								
control	2,9±0,2	2,9±0,6*	2,8±0,5*	2,2±0,4*	2,1±0,6*	1,4±0,3*	1,4±0,5*	—
expt.	2,9±0,3	3,2±0,7*	3,4±0,4*	1,7±0,4*	2,1±0,5*	1,5±0,5*	1,0±0,4	—
Morphine								
PLR								
control	12,1±1,6	—	—	10,0±3,6*	14,4±3,1*	11,8±3,3*	6,3±1,9*	7,6±1,8
expt.	12,6±0,8	—	—	1,8±2,5	2,0±2,2**	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*	1,1±0,2*	0,9±0,5	0,7±0,6
expt.	3,6±0,2	—	—	0,4±0,3	0,1±0,2**	0,1±0,2**	0,6±0,6	0,5±0,3

Legend. Here and in Table 2: *p < 0.05 compared with initial, **p < 0.05 compared with control.

Table 2. Effect of Blocking Caudal Part of MFB on LP of PLR and TWR after PEDS, CS, and Action of Morphine

Exptl. conditions	Initial LP, %	Time after procedure, min						
		0	5	10	20	30	40	50
PEDS								
PLR								
control	16,5±1,8	10,1±2,0*	12,7±2,4*	2,0±2,1	3,1±2,6	1,5±2,5	1,3±2,8	—
expt.	14,5±1,2	9,7±3,0*	3,7±2,0**	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*	25,4±2,1*	25,4±2,1*	25,4±2,1*	7,3±5,9	2,7±3,1	—
expt.	16,3±2,9	23,7±2,8*	23,7±2,8*	20,0±5,6	20,4±0,8*	23,7±2,8*, **	18,1±2,8*, **	—
TWR								
control	3,8±0,4	2,6±0,8*	2,2±1,0*	2,7±0,8*	2,5±1,0*	1,9±0,9	1,6±1,1	—
expt.	4,1±1,0	2,9±0,1*	2,9±0,1*	2,9±0,1*	2,9±0,1*	2,9±0,1*	2,0±0,5*	—
Morphine								
PLR								
control	10,4±1,5	—	—	8,9±3,7*	8,0±3,4*	8,8±3,8*	8,4±2,2*	0,8±1,2
expt.	13,5±1,9	—	—	15,8±3,5*	7,2±3,5*	8,4±4,1*	7,9±4,2	6,1±4,1
TWP								
control	3,3±0,1	—	—	1,9±0,5*	1,5±0,5*	2,0±0,4*	1,8±0,5*	2,2±0.5
	3,5±0,3	—	—	0,9±0,4	1,5±0,5*	1,8±0,6*	1,3±0,6	1,5±0,6

EXPERIMENTAL RESULTS

Data from the morphological control are given in Tables 1 and 2. Damage was localized to the region of RMFB and CMFB at the level of the mammillary bodies of the rostral hypothalamus, for a distance of 1.2-1.7 mm in the rostro-caudal direction. This damage caused complete disappearance of the dopamine terminals in the caudal nucleus of the putamen and nucleus accumbens and a distinct reduction of noradrenergic terminals in the paraventricular nuclei of the hypothalamus, the preoptic region, the ventral part of the striae terminales, cortex, and hippocampus [10].

Measurement of LP of PLR in rats of the experimental and control groups showed no difference. In the experimental group, for instance, LP of PLR was 13.2 ± 0.97 sec, compared with 13.4 ± 1.2 sec in the control. The same result was obtained on measuring LP or TWR: 3.3 ± 0.21 sec in the experimental group and 3.2 ± 0.15 sec in the control group. Qualitatively similar values were obtained in rats with destruction of CMFB. These results indicate that removal of MFB does not affect the duration of nociceptive response (LP) at rest. However, there is evidence that damage to MFB at the level of the lateral hypothalamus causes lowering of the threshold of jumping responses [6, 7]. The authors cited explain this effect by fall of 38-40% in the brain serotonin and adrenalin levels. Meanwhile other experiments have shown that a systemic and more marked inhibition of monoamine synthesis is not accom-

panied by changes in nociceptive responses at rest [2, 9]. It can be tentatively suggested that in this case the nociceptive responses are effected by monoamine systems protected against injury.

The experiments of series I showed that PEDS causes a significant increase in LP of PLR in the control until the 20th minute of the recovery period, but in the experiment, 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 than in the control group. Qualitatively similar results were obtained on rats after removal of CMFB (Table 2). Hence it follows that blocking MFB leads to inhibition of antinociceptive mechanisms actived by PEDS.

In the experiments of series II the effect of cold stress (CS), namely making the rats swim in water at T = 4°C, was studied. It was shown that CS leads to a significant and more than twofold increase in LP of PLR in rats of both control and experimental groups and with destruction of RMFB and CMFB (Tables 1 and 2). LP of TWR also was significantly increased compared with initial levels in rats of both groups. No differences were found in LP of PLR and TWR between the control and experimental groups after both types of operation. Consequently, destruction of MFB and blocking of ascending monoamine systems innervating the forebrain have no effect on activity of antinociceptive mechanisms under the influence of CS.

In the experiments of series III the effect of morphine was studied on the duration of LP of PLR and TWR in rats after destruction of RMFB. It was shown that morphine, in a dose of 5 mg/kg, causes a significant increase in the duration of PLR in rats of the control group from 10 to 40 min (Table 1). No significant increase in LP of PLR was found in the experimental group throughout the experiments. Comparison of LP revealed significantly shorter PLR in rats of the experimental group compared with the control only at the 20th minute (Table 1). Similar results were obtained on measuring LP of TWR, and differences between the experiment and control were significant at the 20th and 30th minutes.

In case of destruction of CMFB, equal lengthening, significant compared with initially, of LP of PLR and TWR was found in the experimental and control groups at all times during the experiments (Table 2).

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

Blocking of RMFB and CMFB thus does not affect sensitivity to pain at rest, and destruction of RMFB and CMFB has no effect on activity of the antinociceptive mechanisms under the influence of cold stress. During activation of nociceptive mechanisms associated with the action of morphine a more important role is played by the rostral part of MFB than the caudal part, and different types of analgesia are realized by different neurochemical mechanisms.

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