ROLE OF THE LOCUS COERULEUS IN MECHANISMS OF VARIOUS TYPES OF ANALGESIA

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An important role in the mechanisms of the antinociceptive action of various drugs and reflex procedures has been shown to be played by monoamine systems descending into the spinal cord [1-3, 10]. Meanwhile, ascending noradrenergic systems, innervating the anterior portions of the brain through the dorsal noradrenergic bundle (DNB), the ventral noradrenergic bundle (VNB), and the serotonin ascending pathways, in the composition of the anterior midbrain bundle (AMB), are also involved in antinociception. It has been shown experimentally that blocking DNB, VNB, and AMB causes a change in activity of the antinociceptive mechanisms during various pain-relieving procedures [4, 9]. Since an important contribution to the formation of VNB and AMB, innervating the anterior zones of the brain, like the descending pathways into the spinal cord also, is made by axons of the locus coeruleus (LC) [5], it was decided to study the role of that structure in the development of antinociceptive affects arising under the influence of painful electrodermal stimulation (PEDS), cold-swim stress (CSS), and morphine-induced analgesia.

EXPERIMENTAL METHOD

Experiments were carried out on 52 albino rats weighing 200-250 g. LC was blocked in rats anesthetized with chloral hydrate (8 ml/kg, 8% solution, intraperitoneally). For this purpose, a bipolar platinum electrode was inserted into 28 rats at coordinates AP −1.4, VD −2.4, L ± 0.8 [11]. LS was destroyed by passage of a current of 2.5 mA for 25 sec. A mock operation was performed on the control rats (n = 23), in which the electrode was inserted at the same coordinates, but no current was passed through it. Sensitivity to pain was estimated from the value of the latent periods (LP) of the paw licking response (PLR) to placing the rats on a hot plate at 55°C and the tail flick response (TFR) to application of the focused beam from a 150 W lamp to it. LP was measured before and after the procedure at definite time intervals.

Sensitivity to pain was depressed by inescapable foot shock (IFS) with a direct 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 (10 mg/kg, intraperitoneally). After the end of the experiments the rats' brains were fixed in a 10% solution of neutral formalin, sections were cut to a thickness of 60 μ, and damage to LC was verified morphologically.

All the results were subjected to statistical analysis.

EXPERIMENTAL RESULTS

The lesion was located in the region of LC and extended 1.0-1.3 mm in the rostrocaudal direction. This lesion caused a sharp decrease in the number of noradrenergic terminals in the paraventricular nuclei of the hypothalamus, the preoptic region, the ventral part of the striae terminales, cortex, and hippocampus [5].

Measurement of LP or PLR in rats of the experimental and control groups after the operation showed no differences. For instance, in the experimental group LP of PLR was 13.7 ± 0.8 sec compared with 13.4 ± 0.9 sec in the control. A similar result also was obtained when LP

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TABLE 1. Changes in Duration of LP of PLR and TFR in Rats after Removal of LC (experiment) and in Animals Undergoing Mock Operation (control) after CSS and PEDS (M ± m)

Procedure	Parameter of sensitivity to pain	Group of animals	Initial value of LP	Time after procedure, min		
				1	5	20
CSS	PLR	Control (n = 9)	16,4±1,6	27,1±2,5[a]	23,6±2,8	—
		Experimental (n = 8)	16,0±1,5	13,7±2,0[a,b]	12,6±4,9[a,c]	—
	TFR	Control (n = 9)	3,4±0,3	3,3±0,3[a]	2,7±0,2[a]	—
		Experimental (n = 8)	4,3±0,4	1,6±0,6[a,b]	0,9±0,7[b]	—
PEDS	PLR	Control (n = 8)	11,4±1,1	22,0±4,1[a]	9,3±4,0[a]	3,6±1.4[a]
		Experimental (n = 10)	12,4±1,3	15±2,7[a]	0,7±2,0	0,9±1.0
	TFR	Control (n = 8)	2,7±0,2	1,1±0,3[a]	0,6±0,2[a]	—
		Experimental (n = 10)	2,9±0,2	0,6±0,2[a]	0,1±0,3	—

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

TABLE 2. Changes in Duration of LP in Rats after Removal of LC and in Animals Undergoing Mock Operation after Intraperitoneal Injection of Morphine (M ± m)

Parameter of sensitivity to pain	Group of animals	Initial value of LP	Time after injection, min		
			15	30	45
PLR	Control (n = 7)	12,8±1,4	4,0±2,3	23,8±6,7[a]	24,4±6,5[a]
	Experimental (n = 9)	12,2±1,1	5,9±2,5[a]	5,9±2,4[a,b]	8,9±2,6[a,b]
TFR	Control (n = 7)	2,9±0,2	2,4±0,4[a]	3,7±0,2[a]	2,4±0,7[a]
	Experimental (n = 9)	2,7±0,1	2,3±0,5[a]	2,1±0,5[a,b]	2,1±0,7[a]

of TFR was measured: 3.2 ± 0.2 sec in the experimental group and 3.0 ± 0.2 sec in the control. These results indicate that removal of LC does not affect the duration of nociceptive responses at rest, and they agree with data in the literature [6, 10]. However, there is evidence that injury to LC causes elevation of the threshold of nociceptive responses [12]. This effect is linked with a 31-39% fall in the brain noradrenalin level [12]. Meanwhile, other experiments have shown that a systemic and more marked inhibition of synthesis of monoamines, and also their exhaustion in the spinal cord, were not accompanied by any change in nociceptive responses at rest [1, 3, 10]. It can be postulated that in this case nociceptive responses were effected by monoamine systems which had been preserved from injury or by other mechanisms.

The experiments of series I showed that CSS caused an increase in LP of PLR in the control and in the experiment (Table 1). Comparison of LP of PLR showed that this parameter was significantly shorter after 1 min in the experimental group than in the control. On measurement of TFR, qualitatively similar results were obtained, but throughout the experiment in both groups of rats (Table 1). Hence it follows that blocking LC leads to partial inhibition of antinociceptive mechanisms activated by CSS.

In the experiments of series II the effect of PEDS was studied. The experiments showed that PEDS leads to lengthening of LP in the control and experimental groups of rats (Table 1). LP of PLR also was increased compared with the initial value in both groups of rats. No differences were found in the values of LP of PLR and TFR between the control and experimental groups after both types of operation. Consequently, destruction of LC and blocking of the ascending monoamine systems innervating the anterior regions of the brain, and also the descending systems of the spinal cord, had no effect on activity of antinociceptive mechanisms under the influence of PEDS.

In the experiments of series III the effect of morphine was studied on the duration of LP of PLR and TFR in rats after destruction of LC. These experiments showed that morphine in a dose of 10 mg/kg causes lengthening of LP of PLR compared with the initial value in the control group after the 30th minute, and in the experimental group after the 15th minute (Table 2).

Comparison of the groups revealed shorter LP of PLR in the experimental rats than in the control at the 30th and 45th minutes (Table 2). LP of TFR rose above its initial values at

all stages of the experiment, but the difference between the experimental and control was significant only after 30 min.

It can accordingly be concluded that bilateral destruction of LC leads to a partial diminution of analgesia induced by systemic administration of morphine.

In some investigations on rats with destruction of LC, analgesia in response to systemic administration of morphine was almost completely inhibited [7, 8, 12]. Other workers, however, showed that bilateral blocking of LC in rats does not reduce the antinociceptive effect of systemic administration of morphine [6, 10] or of its injection into the periaqueductal gray matter [10].

The results of the experiments described above thus indicate that LC performs a limited role in the regulation of sensitivity to pain under the influence of morphine and CSS.

It can thus be concluded that destruction of LC is not sufficient to reduce activation of ascending supraspinal inhibitory mechanisms of pain suppression and of those descending into the spinal cord, during various antinociceptive procedures. The functional role of LC and of the ascending and descending noradrenergic systems arising from it differs in the mechanisms of realization of antinociceptive effects arising through different procedures.

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