postulated that T can exhibit immunosuppressor activity, potentiating the response of suppressor macrophage formation.

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SELECTIVE ROLE OF THE NUCLEUS MAGNUS RAPHE IN MECHANISMS OF ANALGESIA DURING ELECTRODERMAL NOCICEPTIVE STIMULATION, COLD STRESS, AND ACTION OF MORPHINE

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Analgesia during the action of morphine and of electrical stimulation of various parts of the brain is mediated through the nucleus magnus raphe [5, 13], whose serotoninergic (5-HT) neurons are the source of descending 5-HT pathways which reach the posterior horns of the spinal cord in the funiculus posterolateralis [6]. Division of this funiculus suppresses analgesia following systemic intracerebral injection of morphine, electrical stimulation of the central periaqueductal gray matter, the nucleus magnus raphe, and locus coeruleus, as well as certain types of pain-induced stress [5, 15]. Meanwhile there is evidence that suppression of 5-HT synthesis in the nucleus magnus raphe [1-3, 8] has no significant effect on the formation of antinociceptive responses during auricular electroacupuncture, certain types of unavoidable painful electrical stimulation, electrical stimulation of the central gray matter, and injections of morphine (M) into it. These facts suggest that the role of the nucleus magnus raphe differs in character in different types of analgesia.

It was accordingly decided to compare the role of the nucleus magnus raphe in the mechanisms of different types of analgesia.

EXPERIMENTAL METHOD

Experiments were carried out on 40 male albino rats weighing 200-250 g. Rats of the experimental group were anesthetized with chloral hydrate and a platinum–iridium electrode was inserted at coordinates AP −2.4, VD −6.2, L ± 0.5 mm [9], through which electrical stimulation of the nucleus magnus raphe with a current of 5 mA was applied for 20 sec. Animals of the control group (19 rats) underwent a mock operation without destruction of the nucleus magnus raphe. The experiments were carried out 12-15 days after the operation. Nociceptive sensitivity was estimated by measuring the latent periods (LP) of the tail withdrawal reaction (TWR) before and after the action of the analgesics. Analgesia was induced by intraperitoneal injection of M in a dose of 5 mg/kg, by electrodermal stimulation of the paws (2.5 mA, 60 Hz, 5 min), and by cold stress (CS; swimming in water at a temperature of 4°C for 2.5 min). After the experiments the animals of the experimental group were killed and sections 60 μ thick were cut from pieces of the brain tissue after fixation in neutral formalin, and

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TABLE 1. Time Course of LP of TWR (in sec) before and after injection of M in Rats with Destruction of the Nucleus Magnus Raphe and in Control (M ± m)

Group of animals	Initial data	Time after injection, min		
		15	30	45
Control (n=6)	3,9±0,4	0,9±0,3*	1,4±0,5**	2,3±0,5**
Experimental (n = 6)	3,2±0,4	0,1±0,4***	1,6±0,6*	0,9±0,3**,***

Legend. *p_T < 0.05, **p_T < 0.01 after injection of M, ***p_U < 0.05, for comparison between control and experiment.

TABLE 2. Duration of LP of TWR (in sec) before and after Electrodermal Nociceptive Stimulation and Cold Shock of Rats with Destruction of Nucleus Magnus Raphe and in Control (M ± m)

Procedure	Initial data, sec	Time after injection, min			
		0	5	10	20
EDNS					
Control	3,2±0,2	7,0*	5,7±0,4*	—	3,8±0,3
Experiment	3,3±0,2	7,0*	4,4±0,3**	—	3,7±0,4
CS					
Control	2,8±0,2	6,9±0,1*	6,7±0,3*	5,0±0,5*	4,8±0,5*
Experiment	2,7±0,3	7,0*	6,6±0,4*	6,7±0,3**	5,5±0,5*

Legend. *p_U < 0.05 between initial LP and LP after procedure, **p_U < 0.05 between LP in experimental and control groups.

the location of the zone of destruction was verified. The results were subjected to statistical analysis by nonparametric tests (Wilcoxon's or the Mann–Whitney test).

EXPERIMENTAL RESULTS

The lesion produced by electrolytic destruction was located in the region of nucleus magnus raphe; analysis of layer by layer sections shows that virtually the whole extent of the nucleus was destroyed. Such extensive blocking of this brain structure had no significant effect on the background value of LP in rats of the experimental group compared with the control (3.1 ± 0.2 and 3.3 ± 0.2 sec respectively), in full agreement with data obtained by the writers previously [4] and in the experiments [10]. Meanwhile, there is experimental evidence that destruction of the nucleus magnus raphe is accompanied by a decrease in the basic duration of LP of TWR [11, 14]. The reasons for this disagreement between the results are not yet clear.

The results of the study of the time course of changes in LP following intraperitoneal injection of M are given in Table 1. They show that M induced an increase in LP in the control group throughout the experiment. LP rose by 23% (p_T < 0.05), 36% (p_T < 0.01), and 59% (p_T < 0.01) compared with its initial level, after 15, 30, and 45 min respectively. In the experimental group lengthening of LP was observed at the 30th minute to 50% (p_T < 0.05) and at the 45th minute by 28% (p_T < 0.01). Comparison of LP in the control and experimental groups showed that these parameters were lower in rats with destruction of the nucleus magnus raphe on the 15th (p_T < 0.05) and 45th (p_T < 0.05) minutes of the experiment, whereas at the 30th minute no differences were found in LP.

The results indicate that the function of nucleus magnus raphe in the mechanisms of acute analgesia due to M has activity which is cyclic in character. This conclusion is confirmed by the results of the next experiments (Table 2). In rats of both groups unavoidable electrodermal nociceptive stimulation (EDNS) and CS caused significant (p < 0.05) lengthening of LP compared with the background values. Statistical analysis between animals of the control and experimental groups showed that LP was shorter in rats with destruction of the nucleus magnus raphe at the 5th minute of the experiment (p < 0.05) but there was no difference after the other time intervals. This result must be interpreted as evidence that the nucleus magnus

raphe is involved in the formation of antinociceptive responses to EDNS, not for the whole duration of the experiment, but only during certain time intervals. It must accordingly be concluded that the functional role of the nucleus magnus raphe and of other brain structures during EDNS and after injection of M changes with time. Our previous experiments [4] and those of other workers [7] on animals, in which specific blocking of serotonin neurons of the nucleus magnus raphe was induced, showed no changes in analgesia after EDNS, evidence of the unimportant role of serotonin mechanisms in this type of analgesia. Comparison of these results with reduction of the analgesic activity after EDNS, discovered in the present investigation, leads to the conclusion that other neurochemical mechanisms participate in the regulation of analgesia during EDNS. These may include noradrenergic systems, for it has been shown that injection of the α-adrenergic antagonist phentolamine into the nucleus magnus raphe induces the development of hypoalgesia, which depends on the noradrenalin level in the spinal cord [12].

Comparison of the duration of LP in the experimental and control groups of rats after CS revealed stronger analgesia in rats with destruction of the nucleus, which was 34% higher ($p < 0.05$) at the 10th minute of investigation. It can accordingly be concluded that the nucleus magnus raphe also plays a role in suppression of nociceptive sensitivity during CS at certain times in the course of the experiment. However, in the case of analgesia during CS the nucleus magnus raphe plays an inhibitory role, whereas in EDNS and during the action of M its role is activating.

The significant lengthening of LP found in rats of the experimental group after analgesic procedures suggests that the development of analgesia is realized through the participation both of the nucleus magnus raphe and of other brain structures.

The data described above thus lead to the conclusion that the functional role of the nucleus magnus raphe in mechanisms of different types of analgesia changes dynamically with time, and its functional role is determined by the character of the acting stimulus.

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