NEUROANATOMICAL DISSOCIATION BETWEEN REINFORCING AND ANALGESIC EFFECTS OF MORPHINE

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A previous investigation demonstrated the role of the ventral tegmental region (VTR) in the realization of the reinforcing, but not the analgesic effect of opiates [2]. To continue the study of morphological and functional coupling of these two most important effects a further investigation was made of the antinociceptive and emotionally positive properties of morphine when injected into the same zone of the brain. Structures connected with the reinforcement system (lateral hypothalamus, nucleus accumbens of the septum [8]) and structures belonging to the integrative centers of the antinociceptive system (periventricular gray matter – PGM – and dorsomedial hypothalamus [1, 5, 6]) were analyzed.

EXPERIMENTAL METHOD

Experiments were carried out on 40 male albino rats. Under pentobarbital anesthesia a guide cannula was inserted unilaterally into one of the chosen brain structures of the

TABLE 1. Changes in Pain Response Induced by Electrical Stimulation of Base of Rat Tail under the Influence of Microinjections of Morphine (5 μg) into Brain Structures (frequency of appearance of sign given as a percentage of control, taken as 100%)

Sign of pain response	Time after microinjection, min			
	0	5	15	30
Dorsomedial hypothalamus				
Squeaking	100	100	100	87,5
Biting electrode	100	87,5	75	62,5
Turning (escape)	100	75	50	25*
Crying	100	62,5	37,5*	12,5*
Chewing electrodes	100	62,5	25*	12,5*
Lateral hypothalamus				
Squeaking	100	100	100	80
Biting electrode	100	100	80	60
Turning (escape)	100	100	100	60
Crying	100	100	80	60
Chewing electrodes	100	100	100	80
Nucleus accumbens				
Squeaking	100	100	100	100
Biting electrode	100	100	100	100
Turning (escape)	100	100	100	100
Crying	100	84	84	84
Chewing electrodes	100	92	92	92

Legend. Here and in Tables 2 and 3: *$p < 0.05$.

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TABLE 2. Changes in Vocalization Threshold Caused by Mechanical Compression of Base of Rat Tail under Influence of Microinjections of Morphine (5 μg)

Brain structure	Threshold level of tail pinching or vocalization threshold (conventional points) after microinjection			
	0 min	5 min	15 min	30 min
Dorsomedial hypothalamus	2,25	2,48	2,50	3,0*
Lateral hypothalamus	2,10	2,20	2,20	2,30
Nucleus accumbens	2,33	2,45	2,45	2,45

TABLE 3. Results of Study of Secondary Reinforcing Properties of Morphine (5 μg) on Intracerebral Injection

Brain structure	Nucleus accumbene	Change in length of stay in preferred compartment (in sec) after pharmacological conditioning	Number of animals (in %) with effect of pharmacological conditioning
Lateral hypothalamus	12	+42,1+19,6	8,3
Nucleus accumbens	10	+170,0+58,9*	50
Periventricular gray matter	10	+37,6+10,2	0
Dorsomedial hypothalamus	13	+20,0+5,8	0

animals, taking coordinates from the atlas [7]. After 4-6 days the antinociceptive action of morphine was investigated on a model of mechanical (pinching the base of the tail, evaluated by the vocalization threshold) and electrical stimulation [4] in the course of 30 min after microinjection. The secondary reinforcing effects of morphine injected into the same point, were then assessed by the conditioned place preference formation method [3].

Morphine (5 μg) was injected in a volume of 0.5 μl over a period of 1 min. After the end of the series of experiments the brain was investigated histologically. Data obtained on animals with confirmed location of the chemical electrodes were analyzed. Statistical assessment was by the use of parametric and nonparametric tests.

EXPERIMENTAL RESULTS

A short-latency antinociceptive effect was obtained after microinjection on two (PGM and the dorsomedial hypothalamus) of the five structures studied. Diminution of the pain response to electrical stimulation of the tail, manifested as disappearance of the emotional-affective components of the generalized response and an increase in the force of crushing of the base of the tail required to produce vocalization, took place within the first 5 minutes after microinjection. The powerful analgesic effect of the drug was maintained throughout the 30-min recording period.

The antinociceptive effect in rats with chemical electrodes located at a higher level, in the ventrolateral PGM, also was manifested in both models for 5 min after injection of morphine and had a tendency to "deepen" after 15 and 30 min.

The analgesic action of morphine was accompanied by a characteristic set of behavioral manifestations: reduced response to handling, hyperactivity (jumping, running away) in response to tactile and acoustic stimuli.

The analgesic action of morphine after microinjection into the dorsomedial hypothalamus also had a short latent period (Tables 1 and 2). The pain response tested on both models was reduced 5 min after injection of the drug, with a tendency toward a further significant decrease after 15 and 30 min of observation. Microinjections of morphine into the lateral hypothanamus and into the nucleus accumbens did not lead to any significant changes in the pain response.

A study of the secondary reinforcing effects of morophine revealed a significant increase in the length of stay in the unpreferred compartment only after microinjection into the nucleus accumbens (Table 3). The emotionally positive properties of morphine were expressed much more weakly in this case than after its injection into the ventral tegmental region [2]. Only in five of the 10 animals was a significant pharmacological conditioning effect observed. The study of the conditioned response of place preference following injection of morphine into PGM, and the dorsal and lateral hypothalamus, revealed no positive reinforcing effects of the opiate.

The results are further proof of the morphological and functional dissociation of the analgesic and emotionally positive effects of morphine. The dose of the opiate used was

large enough to create conditions for massive activation of opiate-sensitive neurons in the zone of infusion. Despite this fact, selective analgesic (PGM, dorsomedial hypothalamus) and secondary reinforcing (VTR, nucleus accumbens—weaker) responses were obtained from different structures, evidence of the neuroanatomical heterogeneity of the trigger zones for these effects of morphine.

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CLONIDINE-INDUCED AGGRESSION IN MICE: ROLE OF GENOTYPE AND DOMAPMINERGIC SYSTEM

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Administration of the α-adrenoreceptor stimulator clinidine in large doses to mice leads to the appearance of characteristic manifestations of intraspecific aggressiveness (attacking, biting, assuming the side position). Investigation of the neurochemical mechanisms of clonidine-induced aggression has shown that it is manifested as a result of stimulation of postsynaptic α-adrenoreceptors [8, 9]. Meanwhile, it has been shown that certain neuroleptics and, in particular, spiperone, inhibit clonidine-induced aggressiveness in mice [8]. This suggests that the dopaminergic system is involved in the effects of clonidine. However, no investigations of this aspect of the action of clonidine have been undertaken.

It is not yet clear how characteristic of clonidine is that induced aggressiveness, for this phenomenon has been discovered virtually in only one strain of mice. There are good reasons to investigate this aspect of the problem because marked dependence of the reaction to amphetamine [13], a dopaminergic apomorphine agonist [2, 6] on genotype has been observed.

The aim of this investigation was to study genotypic differences in the role of the dopaminergic system in aggressiveness induced in mice of various strains by the Soviet preparation clofelin, which is identical to clonidine.

EXPERIMENTAL METHOD

Experiments were carried out on male inbred BALB/c, C57BL/6, CBA/Lac, DD, A/He, C3H, CC57BR, and DBA/1 mice aged 3-4 months and weighing 22-35 g. The mice were kept under standard animal house conditions, eight to a cage.

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