Psychoactive Compounds and Their Antibodies: Effect on Self-Stimulation of the Lateral Hypothalamus in Morphinized Rats

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We studied the effect of morphine hydrochloride, brain-specific S100 protein, and antibodies to morphine, S100 protein, and opiate μ-receptors in ultralow doses on self-stimulation of the lateral hypothalamus in morphinized rats. This reaction in morphine-withdrawn rats underwent specific changes after single administration of test preparations. Repeated treatment with preparations in the same dose equalized emotional homeostasis. This effect was especially pronounced after treatment with antibodies to morphine, S100 protein, and opiate μ-receptors. Our findings should be taken into account in developing methods for non-narcotic substitutive therapy of patients with morphine dependence.

Key Words: *self-stimulation; lateral hypothalamus; ultralow doses; morphinized rats*

The brain system of positive reinforcement plays a particular role in the formation of secondary acquired motivations [2,4,7]. The reaction of brain self-stimulation is an adequate model for studies of neurophysiological mechanisms underlying the development of addictions and search for new methods of their prevention. This reaction reflects functional activity of the system for positive reinforcement. Under certain conditions self-stimulation of the brain may be used as a model of endogenous narcotization [4].

The influence of various substances in ultralow doses on brain functions attracts much recent attention. Previous studies showed that ultralow (potentiated) doses of morphine (PM), brain-specific S100 protein (P-S100), and antibodies to these compounds and opiate μ-receptors (PAB-μR) selectively modify emotiogenic brain mechanisms, memory, and sensory processes and produce the adaptogenic effect [5].

Here we studied the effects of substances with different directionality of action on the central nervous system (CNS) and their antibodies on the brain system of positive reinforcement in morphinized rats.

MATERIALS AND METHODS

Experiments were performed on chronically morphinized male outbred albino rats weighing 200-250 g. The rats were morphinized by daily intraperitoneal injections of 1% morphine hydrochloride in increasing doses of 1-10 mg/kg.

The development of morphine addiction was determined by the withdrawal syndrome accompanied by high activity of the brain system for positive reinforcement. To study the effect of single and repeated treatment with test substances the rats were divided into 5 groups of 10 specimens each. These animals perorally received 0.1 ml PM (10^{-2000} wt %), P-S100 (10^{-400} wt %), antibodies to morphine (PAB-M, 10^{-60} wt %), PAB-S100 (10^{-2000} wt %), or PAB-μR (10^{-60} wt %).

Test preparations were synthesized at the "Materia Medica Holding" Research-and-Production Company [3]. Control rats (n=10) perorally received an equivalent volume of distilled water.

Nichrome electrodes in a glass cover were implanted into the lateral hypothalamus according to rat brain coordinates (E. Fifkova and D. Marshal) [7].

Self-stimulation of positive emotiogenic structures in the lateral hypothalamus was performed with rectangular electrical impulses (frequency 100 Hz, 0.5-1 V, pulse duration 0.5 sec) in a Skinner chamber. The rate of self-stimulation (RSS) was recorded on an automatic counter for 60 min before and after administration of preparations. The number of lever presses was evaluated over 5 min.

The results were analyzed by nonparametric Mann-Whitney U test.

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TABLE 1. Changes in RSS Produced by Substances Selectively Affecting CNS and Administered in Ultralow Doses to Morphinized Rats ($M \pm m$, n=10)

Parameter	Baseline level (before morphinization)	Single treatment		Ten-day treatment	
		before	after	before	after
Morphine hydrochloride, 1%	550±11	667±12*	567±7^{+}	739±8^{+}	754±10
PM	584±8	697±8*	636±7^{+}	614±9^{+}	596±8
P-S100	579±5	708±7*	742±8^{+}	623±5^{+}	611±7
PAB-M	549±6	629±7*	679±9^{+}	540±5^{+}	518±7
PAB-S100	617±7	715±6*	641±9^{+}	618±7^{+}	584±7
PAB-μR	540±5	604±5*	556±9^{+}	539±6^{+}	510±7
Water	567±4	673±9*	699±7	636±11	657±7

Note. p<0.05: *compared to the baseline level; $^{+}$compared to parameters before single treatment.

RESULTS

Administration of morphine to control rats did not relieve the withdrawal syndrome. RSS progressively increased with lengthening of treatment.

Before administration of PM, RSS increased compared to the baseline level. Single treatment with PM decreased RSS. During further treatment with PM for 10 days RSS continued to decrease and approached the baseline level (Table 1).

RSS markedly increased after single treatment with P-S100. However, administration of this preparation for 10 days normalized and stabilized RSS, which approached the baseline level (Table 1).

PAB-M significantly increased RSS in morphinized rats (compared to animals with the withdrawal syndrome). Repeated treatment with PAB-M progressively decreased RSS to the baseline level (Table 1).

PAB-S100 significantly decreased RSS, which returned to normal after repeated treatment for 10 days (Table 1).

RSS decreased to the baseline level after single administration of PAB-μR and remained unchanged during repeated treatment (Table 1).

Single and repeated administration of distilled water to control rats was accompanied by a moderate increase in RSS (statistically insignificant, Table 1).

Our results indicate that single treatment with test preparations does not induce a strong nonspecific reaction, but produce the specific effect in rats with the withdrawal syndrome. The withdrawal syndrome was relieved after administration of PM (reinforcement), PAB-S100 (blockade of memory in response to the euphoric effect of morphine), and PAB-μR (blockade of opiate receptors). However, the severity of this syndrome increased after treatment with PAB-S100 (activation of memory in response to positive emotion of morphine-mediated reinforcement) and PAB-M (decrease in the content of endogenous ligands).

Repeated treatment produced similar changes. Activity of the system for positive reinforcement returned to the initial level. Our findings indicate that test preparations possess emotiotropic activity. PAB-M, PAB-S100, and PAB-μR produced a greater normalizing effect on emotional homeostasis than PM and P-S100. It should be emphasized that test preparations produce a prolonged effect without increasing the dose. Therefore, they relieve morphine dependence in a substitutive non-narcotic manner.

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