Neurotropic Compounds and Their Antibodies: Effect on the Brain System of Positive Emotional Reinforcement

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We studied the effects of ethanol, morphine, S100 protein, and antibodies to morphine, S100 protein, and opiate μ-receptors in ultralow doses on self-stimulation of the lateral hypothalamus. The reaction underwent similar changes after single administration of test preparations. Tenfold treatment produced the stimulatory and stabilizing effect, which was related to ambivalent properties of preparations in ultralow doses. Tenfold administration of water did not produce changes in control animals.

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

Much attention is given to mechanisms underlying the action of substances in ultralow doses that differ in the chemical structure and produce various effects on the central nervous system (CNS) [2-7]. This is an urgent problem, since medicinal preparations in standard doses display toxicity, allergic properties, and narcotic activity and cause tolerance and other undesirable effects.

A new class of potentiated preparations was synthesized at the "Materia Medica Holding" Research-and-Production Company. They are used for the therapy of patients with disorders of CNS. These preparations in non-increasing doses stimulate adaptive integrative activity of the brain (*e.g.*, emotiogenic reactions) [7,8].

Here we compared the effects of potentiated substances and their antibodies on the system of positive reinforcement that plays an important role in adaptive reactions of the organism.

MATERIALS AND METHODS

Experiments were performed on 70 adult male outbred rats weighing 200-250 g. The animals were divided into 7 groups of 10 specimens each.

The rats daily perorally received 0.1 ml potentiated ethanol (PE, 10^{-2000} wt %, group 1), potentiated morphine (PM, 10^{-2000} wt %, group 2), potentiated S100 protein (P-S100, 10^{-400} wt %, group 3), and potentiated antibodies to morphine (PAB-M, group 4), S100 protein (PAB-S100, group 5), and opiate μ-receptors (group 6). Test preparations were synthesized at the "Materia Medica Holding" Research-and-Production Company [3]. Nichrome electrodes in a glass cover were implanted into the lateral hypothalamus according to rat brain coordinates (O. Fifkova and D. Marshall) [1].

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.

RESULTS

Single treatment with PE significantly increased RSS of the lateral hypothalamus, which was accompanied by "convenience" behavior. On day 10 RSS before administration of PE in the same dose did not differ from the baseline level. Tenfold treatment with PE tended to decrease RSS compared to the control; the behavioral reaction of positive emotional reinforcement was preserved (Table 1).

Single administration of PM increased RSS and stimulated orientation-and-exploratory activity directed to achieve positive emotions. In rats receiving PM for 10 days RSS decreased compared not only to the control, but also to that observed before treatment (Table 1).

Single and 10-fold administration of P-S100 increased RSS. The baseline level of this reaction remained unchanged (Table 1).

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TABLE 1. Effect of Various Substances and Their Antibodies on RSS in Rats over 5-min Observations ($M \pm m$, n=10)

Parameter	Single treatment		Ten-day treatment	
	before (baseline level)	after	before (baseline level)	after
Distilled water (control)	468±10	511±5	480±7	484±8
PE	511±6	602±6*	502±11	489±11
PM	538±9	618±8*	547±10	525±11
P-S100	444±5	512±5*	444±11	500±16
PAB-M	449±32	518±29	467±28	426±29
PAB-S100	482±5	618±6*	500±8	437±11*
PAB-μR	453±6	499±5*	489±8	500±19

Note. p<0.05: *compared to the baseline level.

Changes in RSS after single and 10-fold administration of PAB-M were statistically insignificant (Table 1). RSS increased after single treatment, but decreased after 10-fold administration of PAB-M (Table 1).

Single and repeated administration of PAB-μR activated the system of positive reinforcement and increased RSS (Table 1).

Our results show that substances with different chemical structure administered in ultralow doses produce the stimulatory effect and activate the system of positive emotional reinforcement. This nonspecific effect is probably associated with the interoceptive exploratory reaction to changes in the internal environment. Biologically, this reaction normalizes homeostasis in the body.

Repeated treatment with test preparations for 10 days produces the specific and differentiated effect on the system of positive emotional reinforcement. PE, PM, and PAB-M slightly decrease RSS and equilibrate the emotional state. PAB-S100 and PAB-μR produce the modulatory effect, maintain RSS at the near-initial level and, therefore, recover emotional homeostasis. These changes are related to ambivalent activity of preparations and realized via the complex mechanism.

Brain-specific S100 protein markedly activates the system of positive emotional reinforcement. Probably, this protein specific for trace processes activates them and improves memory of positive emotions.

It should be emphasized that deprivation of preparations was not accompanied by the withdrawal syndrome. These data indicate that test preparations do not possess narcogenic activity.

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