Effect of Potentiated Antibodies to Morphine on Behavioral Reactions in Rats with Morphine Dependence

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We studied the effect of potentiated antibodies to morphine (10^{-100} wt %) on self-stimulation of the lateral hypothalamus and behavioral reactions reflecting the severity of withdrawal syndrome in rats with morphine dependence. Repeated treatment with potentiated antibodies to morphine increased the rate of self-stimulation, suppressed active avoidance response, promoted freezing behavior after acoustic stimulation, and decreased tail-flick latency in rats after morphine withdrawal. Distilled water did not produce these changes.

Key Words: *potentiated antibodies to morphine; brain self-stimulation; pain sensitivity; acoustic startle response; morphine abstinence*

We studied the effects of potentiated antibodies to morphine (PAB-M) on behavioral reactions in rats with morphine dependence.

MATERIALS AND METHODS

Experiments were performed on 30 male outbred albino rats weighing 220-240 g (3 series, 10 animals per each).

Series I was performed under general thiopental anesthesia. Nichrome electrodes (diameter 100 μ) were implanted into the lateral hypothalamus according to rat brain coordinates (E. Fifkova and D. Marshal) [1]. Self-stimulation of the lateral hypothalamus was performed with rectangular electrical impulses (25-100 μA, 100 Hz frequency, 0.5 sec pulse duration) in a Skinner box for 60 min. The rate of self-stimulation was recorded for 5 min on an automatic counter.

In series II the effect of PAB-M on startle response to supraphysiological acoustic stimuli (110 dB, 10 kHz, duration 20 sec) were studied. The response was scored using a 3-point scale (1 — freezing; 2 — startle; and 3 — avoidance). In series III the effect of PAB-M on nociceptive threshold was estimated by tail-flick latency during thermal stimulation [2].

Experimental morphinism in rats was induced by daily intraperitoneal injections of 1% morphine hydrochloride for 10 days. The dose of morphine gradually increased from 1 to 10 mg/kg.

PAB-M in a concentration of 10^{-100} wt % were obtained from the "Materia Medica Holding" Research-and-Production Company and given perorally 3-4 times a day (2 drops). Control rats received distilled water.

The results were analyzed using Excel software.

RESULTS

In series I we observed a significant increase in the rate of self-stimulation in rats with morphine abstinence (Table 1). The first treatment with PAB-M also slightly increased this parameter. Administration of PAB-M for 8 days after morphine withdrawal was followed by progressive increase in the average rate of self-stimulation. These data indicate that PAB-M increase functional activity of the positive reinforcement system.

In series II the startle response in intact rats corresponded to 1.5 points, no avoidance reaction was observed, while the startle response was most pronounced, which reflected adequate orientation and exploratory activity in response to supraphysiological acoustic stimuli in intact animals. In animals with morphine abstinence the pattern of the acoustic startle response was different and the reactivity of these rats increased. The first administration of PAB-M produced no changes (Table 1). At latter terms the severity of the withdrawal syndrome increased with predominance of the avoidance reaction. Repeated treatment with PAB-M attenuated active avoidance response and enhanced freezing behavior.

In series III nociceptive thresholds increased to 47.1 sec during chronic morphinization ($p<0.01$). In

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0007-4888/03/supp-0034$25.00

TABLE 1. Effect of PAB-M on Rats with Morphine Abstinence (Mean Values)

Parameter	Intact	Morphinization	Treatment with PAB-M during abstinence			
			single		7-day course	
			control (water)	experiment	control (water)	experiment
Rate of self-stimulation, pressings over 5 min	449	—	513	530	560	617
Startle response, points	1.5	—	1.7	1.45	2.4	0.5
Tail-flick latency, sec	17.5	47.1	11.4	24.8	7.8	8

rats with withdrawal syndrome the tail-flick latency decreased to 11.4 sec ($p<0.01$ compared to animals receiving morphine, Table 1). The first administration of PAB-M to rats with morphine abstinence increased nociceptive threshold, but after 1 h this parameter slightly decreased. Long-term treatment with PAB-M decreased the tail-flick latency in rats with morphine deprivation. In these animals the tail-flick latency was lower than in intact rats.

Our results indicate that PAB-M increase functional activity of the positive reinforcement system in rats with withdrawal syndrome. Repeated treatment with PAB-M modifies the startle response to suprathreshold acoustic stimuli, activates passive defense reactions, and suppresses active avoidance response, i.e. emotional components are preserved, but are transformed into the passive defense behavior.

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