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Naloxone Potentiates Shock-Induced Aggressive Behavior in Mice

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PUGLISI-ALLEGRA, S. AND A. OLIVERIO. *Naloxone potentiates shock-induced aggressive behavior in mice.* PHARMAC. BIOCHEM. BEHAV. 15(3) 513–514, 1981.—Naloxone (0.025 to 0.05 mg/kg IP) potentiates shock-induced aggressive behavior in C57BL/6 mice but not in DBA/2 mice which do not fight in absence of drug. This effect is not related to pain sensitivity since the doses used in this experiment do not lower tail-flick threshold in C57BL/6 mice. These findings are discussed in terms of the role of the endorphin system and of catecholamine related sensory attention in a number of social interactions in the mouse.

Naloxone Shock-induced aggressive behavior Endorphins Inbred mice

ENDOGENOUS opioids (enkephalins and endorphins) are involved in a number of behavioral patterns and social activities connected to emotionality. Animals treated with naloxone, a drug which antagonizes the effects of endorphins, are characterized by increased locomotor activity, different signs of social discomfort and enhanced sexual behavior (for review see Panksepp *et al.* [5]).

These behavioral patterns were described in different species ranging from birds to rodents and the functions of the endogenous analgesic systems have been interpreted in terms of adaptive species-specific mechanisms. Differences in the function of the endorphin system and in the behavioral effects of opiates have been described and interpreted in terms of different types of receptors and of their cerebral distribution [9]. In particular morphine or other opiates exert a stimulating effect on the activity of some strains of mice such as C57BL/6 (C57), while they depress or induce freezing responses in other strains such as DBA/2 (DBA); these differences have been explained in terms of endogenous opiate receptors and of dopaminergic and noradrenergic responses [2]. C57 and DBA mice are also characterized by different levels of aggressive behavior in a number of tests in response to pharmacological and environmental manipulations [6,10]. In the present study these strains of mice were injected with naloxone in order to assess whether or not an inhibition of endogenous opiates results in an increased shock-induced aggressive behavior.

METHOD

Male C57BL/6 (C57) and DBA/2 (DBA) mice (Charles River, Como, Italy), 11–12 weeks old were used. Shock-induced aggressive behavior was measured in an apparatus in which the bites between two mice are recorded through a counter [7]. The apparatus consists of an experimental chamber (9×9×14 cm). Two holes (1 cm diameter at 1 cm above the grid floor) allow the tails to extend out of the chamber on two opposite walls. A threaded bush previously glued on each tail by means of Bostik is fixed by a nut in the center of a ball bearing, so that the mouse can move freely with no danger to the tail. The two ball bearings work as slip rings for a contact detector. A low current (2 μA) passing through both mice during biting is amplified by the contact detector so that all bites, but no other body contact, can be recorded by a digital counter. Aggressive behavior was induced by shocking simultaneously both mice. The electric shock (0.25 mA) was applied by means of two electrodes to the part of the tail available between the hole and the ball bearing.

In our experiments each treatment group consisted of ten pairs of mice per strain. Each session lasted for four minutes in which shocks of 0.5 sec duration were delivered every 3 sec. Prior to each encounter the mice were placed in opposite halves of the experimental cage, separated by a sliding door. After a 60 sec adaptation period the sliding door was raised, and shocks were delivered. The experimental cage was cleaned between sessions in order to remove odors. Mice of each pair came from different breeding groups. To study pain sensitivity the tail-flick method was used.

Naloxone hydrochloride was injected intraperitoneally 10 minutes before testing at different doses. Control mice were injected with saline.

Data were analyzed statistically by single-factor analysis of variance (ANOVA; independent). Further analysis for individual between-group comparisons was carried out by employing the error term of the overall analysis of variance.

RESULTS

Saline-injected C57 mice are characterized by very low levels of aggressive responses: Figure 1 shows that naloxone

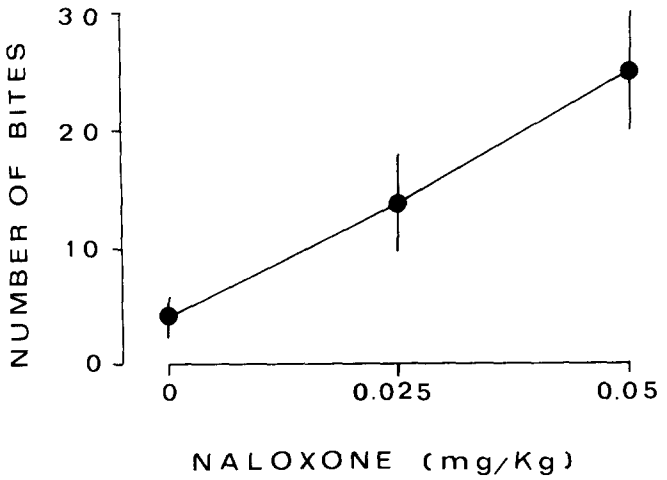

FIG. 1. Effects of naloxone hydrochloride on shock-induced aggressive behavior in C57BL/6 mice. Data were analyzed statistically by single factor analysis of variance (ANOVA; independent). The analysis was performed on number of bites between couples of mice. Further analysis for individual between-group comparisons was carried out by employing the error term of the overall analysis of variance. The overall analysis showed significant naloxone main effects, $F(2,27)=7.52$, $p<0.01$. Individual between-group comparisons showed that the dose of 0.025 mg/kg was not significantly different from saline, $F(1,27)=3.26$, $p>0.05$, while the dose of 0.05 mg/kg differed from saline with statistical significance, $F(1,27)=15.02$, $p<0.001$. Moreover the two doses of naloxone were statistically different, $F(1,27)=4.27$, $p<0.05$.

(0.025 and 0.05 mg/kg) induces a dose-related increase of the mean number of bites per session. The effects of naloxone became evident after 5 minutes and faded 30 minutes after the injection. On the contrary the same doses of naloxone do not modify the aggressive responses of DBA mice, $F(2,27)=0.60$, $p>0.05$. It must be pointed out also that lower (0.015) or higher (0.1, 0.5, 1.0, 2.0, 5.0, 10.0, 15.0 and 20.0) doses of naloxone did not modify the behavior of DBA mice. Saline-injected C57 mice did not significantly differ in their tail-flick latencies from mice injected with 0.05 mg/kg of naloxone, $F(1,10)=0.59$, $p>0.05$.

DISCUSSION

The present findings indicate that a clear increment of shock-induced aggressive behavior is evident after blocking the endorphin system in C57 but not in DBA mice. It must be pointed out that naloxone induces a slight depression of locomotor activity in both C57 and DBA mice [2]. As for other behavioral tasks naloxone was effective at low systemic doses and ineffective at high doses; this effect has been explained in terms of the distribution of receptors occupied by different doses of naloxone [3]. The effects of naloxone on aggressive behavior of other species of animals have been interpreted in terms of freezing and pain sensitivity [1]; however, our findings indicate that potentiation by naloxone of shock-induced aggression takes place when pain sensitivity is not modified. In addition, the failure of naloxone in inducing potentiation of the shock-induced aggressive response in DBA mice may be ascribed to the differences in the reactivity to opiates and to the function of endorphine system in these strains [9].

The facilitating effect of naloxone on different behaviors ranging from copulatory behavior to social interactions have been interpreted in terms of its ability to block opiate-induced inhibition of dopamine release in specific brain areas; it is possible that an enhancement of neostriatal sensory attention mechanisms which play a role in aggressive behavior is responsible for the effects of naloxone in C57 but not in DBA mice, as suggested by opiate-induced differences in dopaminergic function [8] in these strains.

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