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Effects of Naloxone and Naltrexone on Locomotor Activity in C57BL/6 and DBA/2 Mice

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CASTELLANO, C. AND S. PUGLISI-ALLEGRA. *Effects of naloxone and naltrexone on locomotor activity in C57BL/6 and DBA/2 mice*. PHARMAC. BIOCHEM. BEHAV. **16**(4) 561–563, 1982.—Administration of naloxone or naltrexone in DBA/2 (DBA) mice was follwed by dose related depressant effects. The locomotor activity of the C57BL/6 (C57) mice injected with naltrexone was also depressed. Low doses of naloxone induced a decrease in activity in the C57 strain. This effect gradually disappeared at intermediate doses and recurred again at higher doses. The results are discussed in terms of differences in type number and/or distribution of the receptors influenced by naloxone and naltrexone in the two strains of mice tested.

Naloxone Naltrexone Locomotor activity Inbred mice

RECENTLY a number of researchers, have considered the behavioral effects of opiate antagonists. In particular, locomotor activity and motility increments or decrements following naloxone treatment have been observed, depending on dose and route of administration [5, 7, 12]. Differences in the ability of naloxone and naltrexone to antagonize the decrement of duration of anaesthesia which is evident in amphetamine injected mice have recently been demonstrated. This suggests the existence of a difference in their mechanisms of action [6]. In addition, some studies have shown that naloxone can also display opiate agonist activity. An example is seen when considering analgesic reaction in humans with postoperative pain, in rats (hot plate test), or in mice (acetic acid induced writhing), (for review see Sawynok *et al.* [15]).

The purpose of the present research was to assess the effects of naloxone and naltrexone on motor activity in mice.

The inbred strains of mice C57BL/6 (C57) and DBA/2 (DBA), are characterized by differences in some functions of the endorphin system and in the behavioral effects of opiates and opiate antagonists [1, 2, 4, 14]. These differences have been explained in terms of endogenous opiate receptors and of dopaminergic and noradrenergic responses [14]. In the present research possible differences in the effects of naloxone and naltrexone on locomotor activity were investigated in these strains of mice.

METHOD

Male naive mice belonging to the strains C57BL/6 and DBA/2 (River Lab., Como, Italy), weighing 23–25 g at the beginning of the experiments, were used throughout. Upon their arrival in the laboratory (2 weeks before the experiments) all mice were maintained in groups of 8 in clear plastic pens with food and water available ad lib. In all experiments the animals were tested only once.

Locomotor activity was measured as previously described [10]. The mice were tested in Plexiglas toggle-floor boxes (24.5×9.0 cm). The number of crossings from one side of the box to the other was automatically recorded by means of a microswitch connected to the tilting floor of the box, and constituted the score of the mouse. Circuitry was arranged so that whenever the mouse crossed the cage, a cumulative counter was advanced. A light located 1.5 m above the top of the boxes was the source of illumination (0.25 ft-c., at the cage floor level).

Different groups of 8 mice from each strain were injected with different doses of naloxone or naltrexone and tested in the toggle box 5 min after treatment for a single 60 min session. Their performances were compared with those of groups of 8 saline injected mice. The doses of naloxone injected were: 0.1, 0.25, 0.5, 1.0, 2.5, 5.0, 10.0, 20.0 and 40.0 mg/kg for the C57 mice, and 0.025, 0.05, 0.1, 0.25, 0.5, 1.0, 2.5, 5.0, 10.0, 20.0 and 40.0 mg/kg for the DBA mice. The doses of naltrexone injected were: 0.5, 1.0, 2.5, 5.0, 10.0, 20.0 and 40.0 for the C57 mice, and 0.05, 0.1, 0.25, 0.5, 1.0, 2.5, 5.0, 10.0, 20.0 and 40.0 for the DBA mice.

Naloxone (HCl) and Naltrexone (HCl) (ENDO, Garden City, NY) were dissolved in 0.9% NaCl and injected intraperitoneally at the volume of 4 ml/kg. 0.9% NaCl (4 ml/kg) was used for control injections. The results were statistically evaluated by ANOVA [3]. Student's *t*-tests and post hoc analyses were carried out, in order to compare individual treatments.

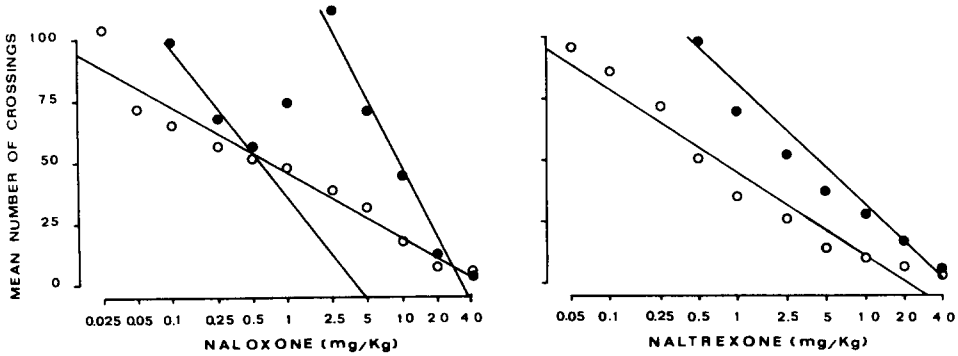

FIG. 1. Regression of naloxone (left) and naltrexone (right) treatment on locomotor activity in C57BL/6 mice (full circles) and DBA/2 mice (open circles). Abscissae: doses (log scale). Ordinates: percent differences between the number of crossings of naloxone, or naltrexone, and saline injected mice. The comparison between two regression coefficients gave the following results: Naloxone (C57) (range doses: 0.1 to 0.5 vs 2.5 to 40 mg/kg: $t=1.9373$, $p<0.05$. Naloxone (C57) (range doses: 0.1 to 0.5 mg/kg) vs naloxone (DBA): $t=2.3438$, $p<0.05$. Naloxone (C57) (range doses: 2.5 to 40 mg/kg) vs naloxone (DBA): $t=8.2375$), $p<0.001$. Naltrexone (C57) vs naltrexone (DBA): $t=1.5919$, $p>0.05$.

TABLE 1

MEAN NUMBER OF CROSSINGS (±SEM) IN THE TOGGLE BOX OF DIFFERENT GROUPS OF EIGHT C57 AND EIGHT DBA MICE FOLLOWING TREATMENT WITH SALINE, NALOXONE OR NALTREXONE

C57				DBA			
Group mg/kg		Group mg/kg		Group mg/kg		Group mg/kg	
Saline	98.0 ± 9.9	Saline	98.0 ± 9.9	Saline	81.1 ± 2.0	Saline	81.1 ± 2.0
Nalox. 0.1	97.0 ± 8.1	Naltrex. 0.5	96.8 ± 3.9	Nalox. 0.025	84.6 ± 4.2	Naltrex. 0.05	77.7 ± 2.6
Nalox. 0.25	67.5 ± 3.5†	Naltrex. 1.0	68.7 ± 3.7†	Nalox. 0.05	58.2 ± 3.0†	Naltrex. 0.1	69.7 ± 2.0*
Nalox. 0.5	56.2 ± 3.6†	Naltrex. 2.5	51.6 ± 4.3†	Nalox. 0.01	52.8 ± 2.8†	Naltrex. 0.25	58.1 ± 1.8†
Nalox. 1.0	73.5 ± 4.8*	Naltrex. 5.0	37.5 ± 3.1†	Nalox. 0.25	45.8 ± 2.5†	Naltrex. 0.5	41.0 ± 4.0†
Nalox. 2.5	110.1 ± 5.9	Naltrex. 10.0	28.3 ± 2.3†	Nalox. 0.5	41.6 ± 1.5†	Naltrex. 1.0	28.6 ± 3.7†
Nalox. 5.0	70.1 ± 2.8†	Naltrex. 20.0	17.2 ± 1.9†	Nalox. 1.0	38.7 ± 1.9†	Naltrex. 2.5	21.2 ± 1.6†
Nalox. 10.0	44.1 ± 3.8†	Naltrex. 40.0	6.2 ± 0.7†	Nalox. 2.5	31.2 ± 1.8†	Naltrex. 5.0	11.5 ± 0.9†
Nalox. 20.0	13.1 ± 2.1†			Nalox. 5.0	25.6 ± 2.3†	Naltrex. 10.0	8.2 ± 0.9†
Nalox. 40.0	4.3 ± 0.9†			Nalox. 10.0	14.3 ± 1.3†	Naltrex. 20.0	5.2 ± 0.5†
				Nalox. 20.0	6.0 ± 1.2†	Naltrex. 40.0	2.5 ± 0.5†
				Nalox. 40.0	4.7 ± 1.0†		

*$p<0.01$; †$p<0.001$, in comparison with saline (ANOVA).

RESULTS AND DISCUSSION

The results of the present research indicate that (a) the opiate antagonists naloxone and naltrexone exert depressant effects on locomotion in both C57 and DBA mice; (b) these effects are evident in the DBA strain following the administration of doses ineffective in the C57 strain (0.05 mg/kg of naloxone, and 0.1 mg/kg of naltrexone); and (c) in both strains naloxone is more powerful than naltrexone in decreasing locomotor activity. Moreover, in the C57 mice naloxone depressed activity at low doses (0.25 and 0.5 mg/kg). This effect gradually disappeared at intermediate doses (1 and 2.5 mg/kg), and at higher doses (from 5 to 40 mg/kg) again became evident (see Fig. 1 and Table 1). Finally, it must be noted that visual inspections did not reveal the occurrence of other behavioral symptoms, in addition to the motility depression, in either naloxone or naltrexone treated mice.

Differences in the ratios of μ and δ receptors have been postulated in order to explain the strain differences observed in the analgesic and motor responses to opiates administration when C57 and DBA mice are considered [14]. Thus, differences between C57 and DBA mice in type, number and/or distribution of the receptors involved may also account, at least in part, for the biphasic effects observed in our study. Experiments in which the influence of naloxone on memory [9] or aggressive behavior [13] was considered, have shown that the effects of this drug may disappear with the increasing dosages. These dose-related effects have been

explained in terms of possible differences in the populations and distribution of receptors which might be occupied by the different concentrations of naloxone. Such an hypothesis could perhaps also explain the effects observed following naloxone administration in C57 mice in the present research. Moreover, differences in number type and/or distribution of the receptors influenced could explain the different effects of naloxone and naltrexone in C57 mice [14].

However, it must be taken in account that recent experiments have shown that naloxone may have pharmacological actions unrelated to opiate blockade [15]. Possibly, the differences between naloxone and naltrexone effects observed in C57 mice, in the present research, might be attributed also to some of these actions.

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