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Food Deprivation and Motor Activity in Rats: Differences Between Morphine and Clonidine

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BARTOLETTI, M., M. GAIARDI, C. GUBELLINI, A. BACCHI AND M. BABBINI. *Food deprivation and motor activity in rats: Differences between morphine and clonidine.* PHARMACOL BIOCHEM BEHAV 47(4) 969–972, 1994.– The effects of various doses of morphine (0, 1.25, 2.5, 5 mg/kg) and clonidine (0, 1.67, 15, 45 μg/kg) on motility were determined in food satiated and in food deprived rats. Food deprivation failed to change the general activity of rats after saline injections. Nevertheless, food-deprived animals tested under morphine were more active than food satiated ones. Clonidine exhibited slight psychomotor stimulant properties that were not increased by food deprivation. The results are discussed in terms of possible mechanisms of deprivation-related hypermotility.

Morphine Clonidine Food deprivation Locomotor activity Rat

IT has been suggested (14) that motivation has to be viewed as a nonspecific final common response to activation by a wide range of innate and learned stimuli; according to this theory, the most salient stimulus condition at a particular moment in time dominates the motivational state and results in the emergence of responses relevant to that stimulus. Thus, if motivation is flexible rather then rigid in nature, food-deprived rats with no food available are possibly more reactive to many other stimulus. In fact, hungry rats have shown both a marked increase in activity (5,6) and a potentiation of amphetamine-induced arousal (6). In this line, a first purpose of the present experiment was to see whether the motility effect of morphine would interact with deprivation-related motility.

Clonidine behavioral effects are largely reminiscent of morphine ones. Clonidine, like morphine, produces analgesia, suppresses operant behavior, and increases or decreases locomotor activity depending on the dose (4,16). Furthermore, it seems to possess reinforcing properties (1). Thus, a second objective of the work was to examine the possibility that food deprivation could also influence the motility effects of clonidine.

METHOD

Subjects

The subjects were male Sprague-Dawley rats, weighing 400–500 g at the start of the experiment. The animals were housed three to a cage under standard laboratory conditions (lights on 0700–1900 h, temperature 22 ± 1°C). Water and food were freely available for half the rats (FS), the others were food deprived for 72 h before motility tests (FD). The same deprivation schedule has been adopted in a previous study showing an increased sensitivity to the stimulus properties of morphine in food-deprived rats (10). On the other hand, amphetamine-induced psychomotor excitation has been found proportional to the duration of food deprivation, the maximum of the increase being obtained after 96 h (6).

Apparatus and Procedure

Activity was measured using six jiggle cage actometers. The oscillatory movements of the cage were counted by means of solid-state circuits; the sensitivity of the apparatus was adjusted to register mainly gross body movements. The animals were left in the activity cages for 1 h to acclimatize to the apparatus: then they were injected with the test drug and put again into the actometers 15 min later. Motility data were recorded for 2 h, reading being made every hour.

Fed and fasted animals were run in the activity cages after saline, morphine (1.25, 2.5, 5 mg/kg), or clonidine (1.67, 15, 45 μg/kg).

Drugs

Morphine HCl (S.A.L.A.R.S., Italy) and clonidine HCl (Boehringer Ingelheim, Italy) were injected IP in a volume of 2 ml/kg. The drugs were dissolved in saline. Doses are expressed in terms of total salts.

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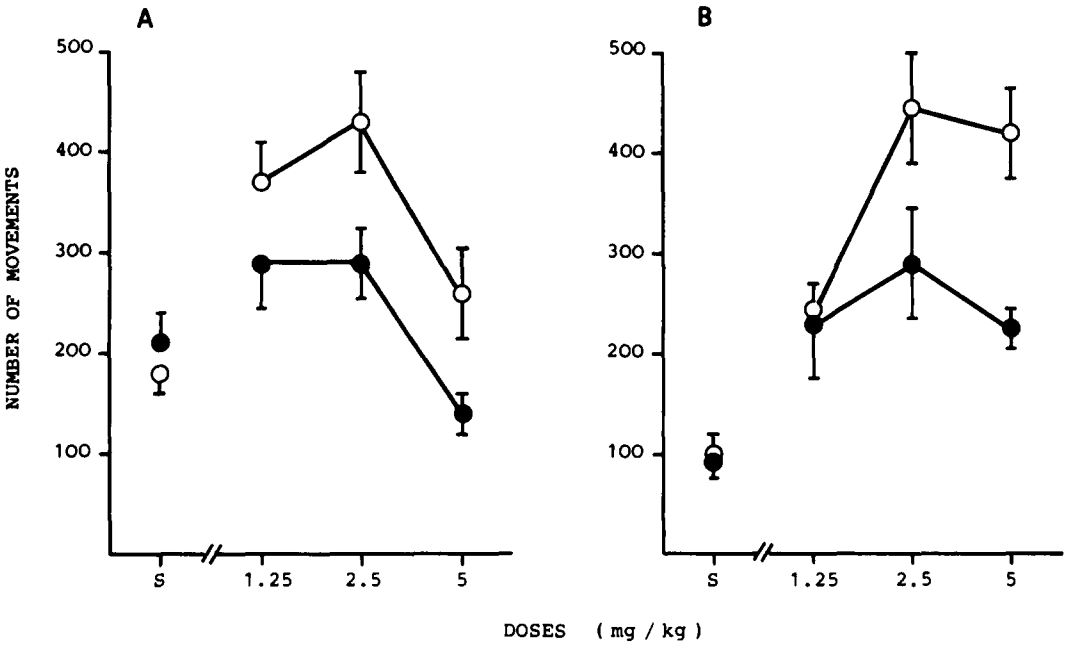

FIG. 1. Effects of various doses of morphine on the locomotor activity of food satiated (●) and food deprived (○) rats at the first (A) and at the second (B) hour of registration. Each point represents the mean of 9–10 values ± SE.

Statistical Analysis

Both morphine and clonidine data were analyzed according to a three factor (deprivation, dose, time) ANOVA.

RESULTS

The results relative to morphine are represented in Fig. 1. Morphine exhibited the characteristic pattern of effects repeatedly described (2): excitatory actions at low doses (1.25 and 2.5 mg/kg) and biphasic actions at higher doses (5 mg/kg). The analysis of variance yielded a treatment, $F(3, 142) = 23.14$, $p < 0.01$, and a deprivation, $F(1, 142) = 20.52$, $p < 0.01$, but not a time ($F < 1$) effect. The difference between FS and FD rats varied from treatment to treatment [treatment × deprivation interaction: $F(3, 142) = 4.53$, $p < 0.01$]. FS and FD animals did not differ following saline ($F < 1$). FD rats that received 2.5 and 5 mg/kg of morphine had substantially greater activity scores than FS rats; only a tendency to a greater locomotor activity was observed in these animals after 1.25 mg/kg. In fact, the difference between FS

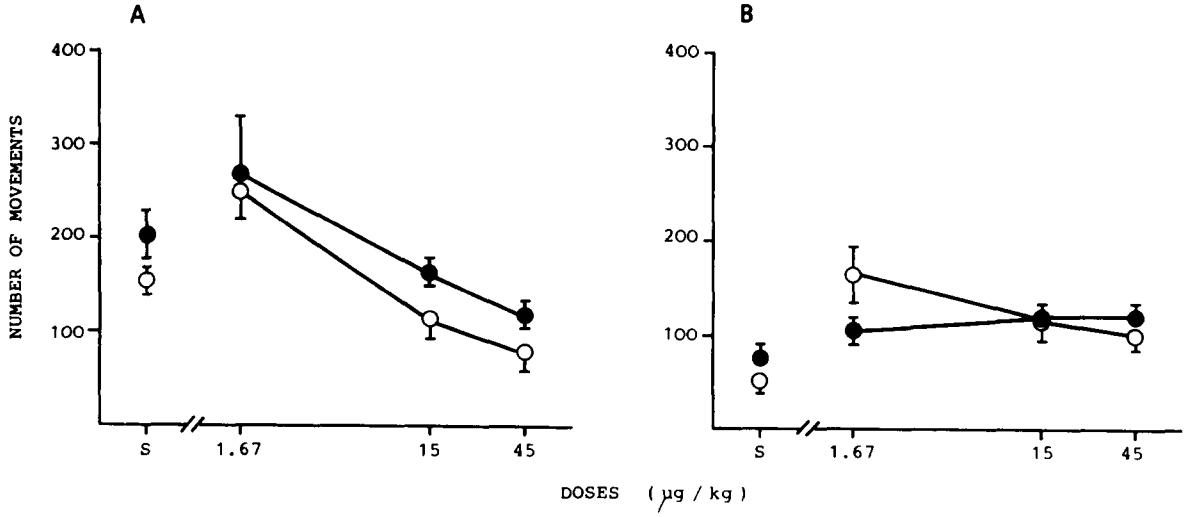

FIG. 2. Effects of various doses of clonidine on the locomotor activity of food satiated (●) and food deprived (○) rats at the first (A) and at the second (B) hour of registration. Each point represents the mean of 8–11 values ± SE.

and FD animals was significantly greater than control one at 2.5 mg/kg, $F(1, 142) = 8.50$, $p < 0.01$, and 5 mg/kg, $F(1, 142) = 18.65$, $p < 0.01$, but not at 1.25 mg/kg, $F(1, 142) = 1.128$, p = NS. No deprivation × time or treatment × deprivation × time interaction was found ($F < 1$).

The results relative to clonidine are shown in Fig. 2. The analysis of variance yielded a treatment, $F(3, 128) = 11.49$, $p < 0.01$, and a time, $F(1, 128) = 30.12$, $p < 0.01$, effect and a treatment × time interaction, $F(3, 128) = 30.12$, $p < 0.01$. Further analysis indicated that, during the first hour of recording, the lowest dose of clonidine (1.67 μg/kg) induced a significant excitatory effect, $F(1, 128) = 12.32$, $p < 0.01$. By increasing the dose the stimulant effect was no more present, but after the highest dose (45 μg/kg) a depressant effect was obtained, $F(1, 128) = 12.89$, $p < 0.01$. During the second hour, all the doses tested induced a significant but very slight excitatory effect [1.67 μg/kg: $F(1, 128) = 9.64$, $p < 0.01$; 15 μg/kg: $F(1, 128) = 6.50$, $p < 0.05$; 45 μg/kg: $F(1, 128) = 4.87$, $p < 0.05$]. The analysis of variance yielded neither deprivation effect, $F(1, 128) = 2.71$, p = NS, nor treatment × deprivation, $F(3, 128) = 1.28$, p = NS, nor treatment × deprivation × time interaction ($F < 1$). Thus, FS and FD rats did not significantly differ following clonidine at any dose and at any time.

DISCUSSION

Increased behavioral arousal during food deprivation has been reported (5,6). Under the present experimental conditions food deprivation failed to change the general activity of rats after saline injections. This is actually not unexpected, because deprivation makes animals more excitable (see the introductory paragraphs), not necessarily more excited. So if there is little external stimuli, a food-deprived animal would not be very active. In fact, food-deprived animals tested under morphine (an arousal stimulus) were more active than food satiated one. Thus, the morphine effect was sensitized (see the nonsignificant deprivation effect and the significant treatment × deprivation interaction). Food deprivation could have potentiated the motility effect of morphine setting the occasion for low doses of the drug to function like high doses. However, considering the characteristic motor effect of morphine in rats (hypermotility at low doses and hypomotility followed by hypermotility at higher doses) (2), the present results seem not attributable to a shift in the morphine dose-effect curve. On the contrary, these findings could be the consequence of two different changes in the morphine response: a decrease in the depressant effect of the drug and/or an increase of the excitatory one. Because low doses of morphine have been used, a real increase of the excitatory component of the action of morphine seems likely. Thus, as predicted, food-deprived rats with no food available, but treated with morphine increase their activity, apparently approaching the most salient objects in the environment.

The excitatory effect of clonidine was different from the morphine one first of all from a quantitative point of view; in fact, the increase in motility was significant but very slight. Similar results have been obtained in a previous work (4). Furthermore, food deprivation did not change the motility effects of clonidine. The results suggest that the stimulant effect of clonidine is not morphine-like in nature and confirm previous data obtained in morphine-dependent and postdependent animals. In fact, clonidine induced only slight hyperactivity when substituted for morphine in dependent rats, and this effect did not seem to undergo the long-lasting cross-sensitization that has been reported for morphine-like drugs (3). To sum up, food-deprived rats with no food available increase their activity if treated with morphine, but not with clonidine.

Many studies have demonstrated that injection of opiates into the ventral tegmental area or into the nucleus accumbens produces a behavioral hyperactivity that is dopamine dependent and independent respectively (15,19). The injection of clonidine, too, into the nucleus accumbens produces a behavioral hyperactivity, 60–120 min after drug administration (17); however, the mechanism by which the drug affects locomotor activity is not well known and possibly involves the noradrenergic and cholinergic systems (16). On the other hand, amphetamine-induced arousal is potentiated by starvation (6), and both amphetamine (20) and severe or repeated exposure to a stressor (12,13) increase dopamine release and metabolism in mesolimbic terminals. In conclusion our data suggest that deprivation-induced hypermotility is dopamine mediated and can be potentiated by drugs capable of activating the mesolimbic dopamine system.

Considering that positive reinforcing properties seem to be predicted from the ability of drugs to induce psychomotor activation (20) and that food deprivation increases the reinforcing effects of addicting drugs (7), the present results should suggest that clonidine differently from morphine has, at best, a very low reinforcing efficacy. In this regard it is worth noting that clonidine has been demonstrated to provide relief of withdrawal signs and symptoms in human opiate addicts, but not to induce euphoria and to be abused by man (11). Some animal experiments revealed that clonidine possess reinforcing properties (1), but others suggested that this drug may be a relatively weak positive reinforcer (8,18); furthermore, it has been reported (9) that clonidine, unlike morphine, supports self-administration in morphine abstinent but not in morphine dependent rats.

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