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The Effects of Methadone on the Social Behavior and Activity of the Rat

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PLONSKY, M. AND P. R. FREEMAN. *The effects of methadone on the social behavior and activity of the rat.* PHARMAC. BIOCHEM. BEHAV. **16**(4) 569–571, 1982.—Pairs of 80-day-old female rats were given SC injections of either 0, 1, 2.5, or 4 mg/kg of methadone hydrochloride on each of 6 days. Both animals of the pair received the same dose. One hour postinjection, each pair was observed in a circular arena for a five minute period during which the following dependent measures were recorded: total time in contact, latency to initial contact, frequency of aggressive grooms, and locomotor activity. The results indicated that the rats treated with methadone spent less time in contact, took longer to contact, and aggressively groomed each other less frequently than rats treated with a saline vehicle. Also, the results suggested that the disruption of social behavior produced by methadone was not a reflection of decreased activity levels.

Methadone Opiates Social behavior Aggression Locomotor activity Rat

METHADONE is an opiate drug commonly used for the treatment of heroin addicts. Although the purpose of administering methadone to heroin addicts is to rehabilitate them both physically and socially, relatively little is known about its effects on social behavior. There is some suggestion, however, that it may decrease sociability in humans. In one study using ex-addict volunteers and a self-administration procedure, Babor *et al.* [1] found that the percentage of waking time subjects spent in social isolation was greater when receiving methadone than when given no drug.

While studies of methadone's effects on the social behavior of humans are important, there is much information to be gained from examining the effects of methadone on the social behavior of animals, primarily because there are numerous variables which cannot be manipulated in humans for ethical and/or practical reasons. Crowley *et al.* [2] worked with a small group of Bonnet macaques and administered a dose of about 10–20 mg/kg/day orally. They found that "the overall total of associative behaviors, including proximity, contact, grooming, and clasping, fell during methadone administration" (p. 139). In addition, they noted that "a net increase in motor activity occurred despite intermittent drowsy nodding" (p. 141). Therefore, the possibility exists that the observed decreases in social behavior were a result of the altered motor activity, rather than being specific effects of the drug.

Thus, the present study was designed to investigate the effects of methadone on the social behavior and activity of the rat. In an effort to dissociate the effects of methadone on social behavior from its effects on activity, we used several doses of methadone which were expected to influence activity in opposite directions. A low dose was expected to stimulate activity [3], and a higher dose to suppress activity (the latter had been observed during pilot work). If social behavior is influenced in a similar fashion when activity is both stimulated and depressed, then it would be difficult to attribute the alterations produced in social behavior to changes produced in activity.

METHOD

Subjects

Seventy-two naive female Wistar rats approximately 80 days old at the time of testing were used. They were obtained from Royalhart Laboratory Animals, Inc. (New Hampton, NY) in 2 squads of 36 each, separated by a 21 day interval. After an initial analysis of each dependent measure revealed no significant differences between squads, the squad data were combined for the final analyses. Animals were maintained on a 12:12 hr light-dark cycle. Purina lab chow and water were available ad lib.

Apparatus

The apparatus was a circular arena consisting of a six beam photoactivity cage (BRS/LVE, PAC001; Fogelsville, MD) measuring 38 cm (height) × 61 cm (diameter). The inside of the apparatus was finished flat black and a 25 watt light bulb in a conical shield was hung 61 cm above the floor. The testing room was supplied with white noise (50 dB) and the only light in the room was that of the apparatus.

Procedure

After extensive handling, the animals were housed individually for 8 days prior to, as well as during, the 6 days of testing. Prior to experimental manipulations, the animals were randomly assigned permanent partners and these pairs of animals were then randomly assigned to one of four drug

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treatment conditions (0, 1, 2.5, or 4 mg/kg). Both members of the pair received the same drug treatment. According to group assignment, methadone hydrochloride (Eli Lilly, Indianapolis, IN), dissolved in 0.9% saline, or saline alone was administered daily by subcutaneous injections (in a volume of 1 ml/kg) to each pair of rats during each day of the 6 days of testing. All injections were administered one hour prior to testing and were performed between 9:30 a.m. and 12:30 p.m., with the order randomized each day within this period. On the first day of injections, one animal of each pair was stained with red ink on its tail for purposes of identification.

Each pair of animals were tested in the circular arena using a paradigm developed by Latane [6]. This procedure involves placing the animals at opposite sides of the arena and allowing them to interact freely for a period of five minutes. During this five minute period, locomotor activity (interruptions of the photocell beams) was recorded electronically. Social behavior was recorded by experimentally blind observers using telegraph keys hooked up to standard relay apparatus in an adjoining room. Three measures of social behavior were recorded: (1) latency to initial contact, (2) total time spent in contact, and (3) aggressive grooms. Contact was timed whenever one rat touched another, except for tail-to-tail touching. Aggressive grooms were scored when one animal of the pair oriented itself at approximately a 90 degree angle to the other and vigorously groomed the other on the back or neck [4]. Interobserver reliabilities for these measures, established during pilot studies, were all above 0.85.

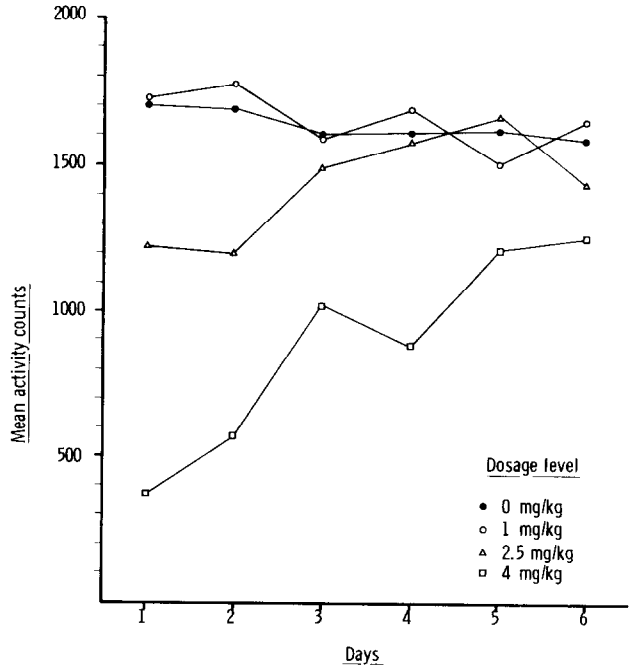

FIG. 1. The effects of methadone on the locomotor activity of the pairs of rats during the six days of testing (N=9 pairs per group).

RESULTS

Figure 1 shows the effects of methadone on the locomotor activity of the pairs of rats. Analysis of the data, with dose as a between subject factor and day as a within subject factor, revealed a significant interaction between dose and day, $F(15,160)=6.35$, $p<0.001$. As can be seen in Fig. 1, this interaction is due to the 0 and 1 mg/kg groups maintaining constant activity levels over days, while the 2.5 and 4 mg/kg groups increased their activity levels over days. Analysis of the simple main effects of dose at each day revealed that there were significant differences between the groups on all days (all $Fs(3,192)>2.70$, all $ps<0.05$). Post hoc comparisons using the Newman-Keuls method (experimentwise error rate of 0.05) further revealed that on days 1 and 2 all groups were significantly different from each other, except the 0 and 1 mg/kg groups. On days 3 and 4, the 4 mg/kg group had significantly lower activity than all the other groups. And finally, on days 5 and 6 the 4 mg/kg group had significantly lower activity than the 0 and 2.5 mg/kg groups and 1 mg/kg group, respectively.

Figure 2 shows the effects of methadone on the time the rats spent in contact. Analysis of the data demonstrated only main effects of dose, $F(3,32)=38.90$, $p<0.001$ and day, $F(5,160)=5.22$, $p<0.001$. As can be seen in Fig. 2, time in contact generally increased over days. All comparisons between treatment groups (for all days combined) were significant, indicating that time in contact was significantly reduced by all methadone doses and that higher doses reduced time in contact more than lower doses.

A reciprocal transformation was performed on the latency to contact measure due to its extreme skew. Analysis of the data demonstrated only main effects of dose, $F(3,32)=5.47$, $p<0.001$ and day, $F(5,160)=8.52$, $p<0.001$. Latency to initial contact decreased over days. Comparisons between the treatment groups (for all days combined) revealed that the 4 mg/kg group took significantly longer to their initial contact than did any of the other groups (which did not differ among themselves).

The mean number of aggressive grooms per testing session for the 0, 1, 2.5, and 4 mg/kg groups was 1.15, 1.00, 0.22, and 0.04, respectively. Since aggressive grooms occurred so infrequently, the data were collapsed across days. A one-way ANOVA was then performed, which demonstrated a significant main effect of dose, $F(3,32)=5.38$, $p<0.01$. Newman-Keuls post hoc comparisons revealed that the 2.5 and 4 mg/kg groups aggressively groomed each other less frequently than the 0 or 1 mg/kg groups. The 2.5 and 4 mg/kg groups did not differ from each other, nor did the 0 and 1 mg/kg groups.

DISCUSSION

The results of this study indicate that rats given acute methadone treatment demonstrate disrupted social behavior as compared to rats treated with a saline vehicle. Methadone treated rats spent less time in contact, took longer to contact, and aggressively groomed each other less frequently than control rats.

Contrary to our expectations, methadone failed to stimulate locomotor activity at any of the dosage levels used. As noted previously, Davis and Bristar [3] reported an increase in locomotor activity using a dose of 2.5 mg/kg. The failure of the present study to replicate this stimulation in activity may be due to the differences in the routes of injection (Davis and Bristar used the intraperitoneal route) or to other procedural differences.

The pattern of our findings suggests that the disruption of social behavior in the methadone treated rats did not reflect decreased activity levels. Although the 1 mg/kg group dem-

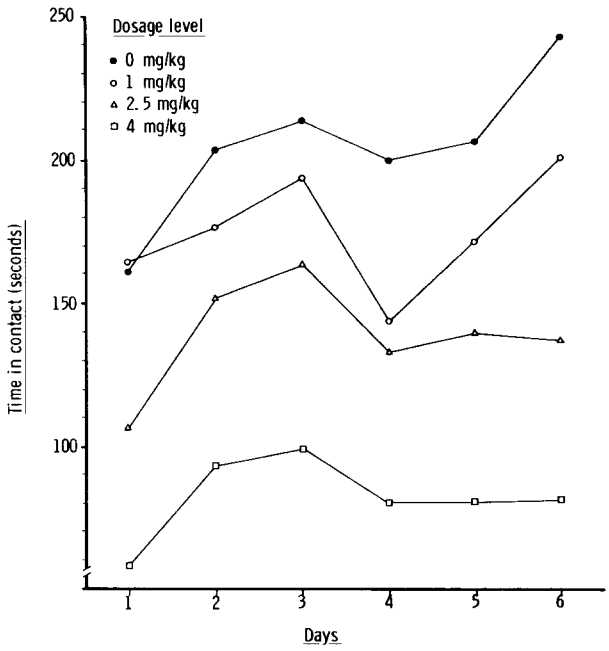

FIG. 2. The effects of methadone on the time the pairs of rats spent in contact during the six days of testing (N=9 pairs per group).

onstrated disrupted social behavior (i.e., decreased time in contact) as compared to the 0 mg/kg group, no differences in activity levels between these two groups were observed. In addition, correlations between activity and time spent in social contact were computed for each dosage level at each day of testing. This analysis failed to reveal any consistent pattern of correlations. Finally, although there was a significant interaction between dose and day on the activity measure, this interaction failed to reach significance with any of the social behavior measures. This suggests that tolerance developed to the decreases in activity produced by methadone, but failed to develop (within the 6 days of testing) to the disruptions of social behavior. Taken together, these findings clearly suggest that the effects of methadone on social behavior were not a consequence of its effects on activity levels.

The present finding that low doses of methadone disrupt the social behavior of rats is consistent with data from morphine studies [8]. Panksepp *et al.* [8] note that "the effect is not readily explicable by reduced arousal, since the effect was apparent in the absence of decreased activity . . . as well as during hyperactivity produced by concurrent treatment with amphetamine" (p. 132). Similarly, the results of the present study suggest that the decreased social behavior produced by methadone does not reflect altered activity levels.

The work of Panksepp and co-workers (e.g., [5, 7, 8]) may also provide a mechanism for the methadone-induced alterations of social behavior observed in the present study. They have proposed that brain endorphins may play an important role in the mediation of intraspecies social bonds. In support of this they report that opiates, such as morphine, are very powerful in reducing isolation-induced distress vocalizations in young puppies, guinea pigs, and chicks, while opiate antagonists, such as naloxone, increase distress vocalizations [7]. In addition they report that infant/maternal proximity-maintenance time in guinea pigs [5], as well as social cohesion in rats [8], are reduced by administration of low doses of morphine. Thus the interaction of methadone with the endogenous opiate system might possibly be the basis of the decreased social behavior observed in the present experiment and reported previously in monkeys [2] and humans [1].

In conclusion, the present findings suggest that methadone disrupts the social behavior of rats, and that this disruption of social behavior is not a reflection of altered activity levels. These results extend previous reports of a disruption of social behavior produced by morphine in rats [8] to methadone and also extend previous reports of a disruption of social behavior produced by methadone in monkeys [2] and humans [1] to rats.

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