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Methadone and Feeding: Sources of Differences Between Home Cage and Operant Chamber Assessment Procedures

J. M. RUDSKI,* D. W. SCHAAL,§ T. THOMPSON,** J. CLEARY*‡§
C. J. BILLINGTON*†# AND A. S. LEVINE*§¶#[1]

*Research Service, †Medicine, and ‡GRECC, VA Medical Center, Minneapolis, MN 55417
Departments of §Psychology, ¶Psychiatry, and £Medicine, University of Minnesota, Minneapolis, MN 55455
**John F. Kennedy Center for Research on Education and Human Development,
Vanderbilt University, Nashville, TN 37203

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RUDSKI, J. M., D. W. SCHAAL, T. THOMPSON, J. CLEARY, C. J. BILLINGTON AND A. S. LEVINE. *Methadone and feeding: Sources of differences between home cage and operant chamber assessment procedures.* PHARMACOL BIOCHEM BEHAV **49**(1) 143–146, 1994.—Methadone administration is reported to increase food intake in studies examining free feeding and to decrease food reinforced operant responding. In light of this apparent paradox, the present study evaluated methadone's effects on food reinforced operant responding under conditions more typical of free feeding studies than operant studies. The effect of methadone (5 mg/kg) on food intake was examined in rats maintained at 100% of their free feeding weights. Methadone did not increase food intake with food available under a fixed ratio 1 (FR 1) reinforcement schedule. Methadone did not alter response rate when each lever press produced a larger reinforcer (225 mg as opposed to 45 mg), but did increase food intake. When response requirements were changed from lever pressing to interruption of an infrared beam, increases in food intake following methadone administration were observed. Thus, the differences between methadone's effects on free feeding vs. operant chamber food intake may be due to procedural factors such as magnitude of reinforcement and response requirements.

Methadone Opiates Feeding Operant

OPIATES are reported to increase short-term food intake in rats allowed free access to food (for review see [3]), yet produce reductions in food maintained responding under a variety of reinforcement schedules in many species following administration of similar doses (1,5,8,12,18,20). These reported increases in one group of studies (home cages) and decreases in another group (operant chambers) appear paradoxical.

Methadone, a synthetic opiate with mostly *mu* agonist properties, is particularly effective at decreasing food reinforced rats lever pressing or pigeons key pecking behavior (2,4,7,8,14,19). Conversely, methadone increases short-term food intake in rats (15) in a manner similar to other *mu* opioid agonists (see [11] for review). However, these paradoxical results may be superficial.

There are many procedural differences between studies conducted in home cages and those conducted in operant chambers, any of which could account for the discrepancies. These variables include the time following opiate administration over which food intake is measured, and whether or not opiate effects are examined in food satiated or deprived animals. Studies on opiates' effects on free feeding typically examine food intake in satiated animals over 4–6 h postinjection. Studies on opiates' effects in operant chambers are usually conducted with animals maintained at 85% of their free feeding weights, and operant behavior is measured within the first hour and a half postinjection. When free feeding is examined over the time course used in most operant studies, similarities in opiate effects emerge. For example, when intake is measured over the first hour postinjection, morphine has been reported to decrease food intake (9,10,16).

[1] Requests for reprints should be addressed to: Allen S. Levine, Deputy ACOS for Research, VA Medical Center (151), One Veterans Drive, Minneapolis, MN 55417.

Other procedural differences between the two basic paradigms include the amount of food immediately available for consumption, and whether or not experimental sessions are conducted in the home cage environment. Free feeding studies typically use large quantities of food placed on the bottom of the rats' home cage. Responding in operant chambers is reinforced with small quantities of food, and sessions are conducted in an environment different from home cages.

The present study examined which factors might contribute to the discrepancy between home cages and operant chambers in opioid-induced changes in food intake. Although all animals were run in operant chambers, the current study differed from previous operant research in several ways. First, rats were not food deprived. Second, intake over a time period more similar to that used in home cage studies (i.e., 4 h) was measured. Third, rats were housed in the operant chambers so that they could only obtain food via one method both during and following experimental sessions. To examine whether the operant response of lever pressing is responsible for reported differences in methadone's effects on food intake between operant chamber and home cage experiments, the lever pressing requirement was completely removed for rats in group 3. The operant response consisted of disrupting an infrared beam. To examine whether the amount of the immediately available food contributes to methadone's effects on food intake, rats in group 2 received five pellets following each lever press instead of only one.

METHODS

Subjects

Seventeen experimentally naive male Sprague-Dawley rats (Harlan Sprague-Dawley, Madison, WI), starting weights 285–330 g, were used. Rats were housed individually in conventional operant chambers (see below) enclosed in an isolation cubicle with a 12 h light/12 h dark photoperiod (lights on at 0700). Tap water was freely available in the chamber at all times. Food was available 23 1/2 h per day. The control and recording apparatus attached to the operant chambers were shut down for one-half hour, 1 1/2 h after the start of the light cycle (0830), at which time data were collected and chambers were cleaned. All rats were maintained at 100% of their free feeding weights.

Apparatus

Experimental sessions were conducted in six commercially available small animal operant chambers (Model E10-10TC, Coulbourn Instruments, Inc., Allentown, PA). Each chamber was enclosed in an isolation cubicle (Model E10-20, Coulbourn Instruments, Inc.) to attenuate outside noise. Chambers were equipped with two operant levers on opposite sides of the front panel of the chamber. The left lever was used exclusively throughout the experiment, except for group 3 (see below). The house light, located in a top-central position, was illuminated during sessions. Forty-five milligrams dustless precision pellets (Bioserv Holton Industries, Frenchtown, NJ) could be delivered to a pellet trough between the levers. When a pellet was delivered, a 4-W light above the pellet trough was illuminated for 3 s. For group 3, chambers were equipped with infrared photocell beams (model DIG-723-M, MED Associates, VT) mounted 1.9 cm from the front of the pellet troughs. A light beam was detected by a photoelectric detector mounted directly across from it. When the rat poked his head into the food trough, the photoelectric beam was interrupted and a single 45-mg food pellet was delivered. Only one pellet was delivered following each photoelectric beam interruption. A Zenith computer (Zenith Computer systems, Glenview, IL) immediately adjacent to the chambers controlled experimental conditions, and displayed and recorded data.

Drug Preparation and Administration

Methadone hydrochloride (Eli Lilly, Inc., Indianapolis, IN) was dissolved in isotonic saline (0.9%) at room temperature and administered in a constant injection volume of 1.0 ml/kg. Rats were injected SC with saline during baseline sessions or with methadone (5.0 mg/kg) immediately preceding experimental sessions (0900). Location of injections were varied to avoid tissue damage. Methadone injections were given for 10 consecutive days.

Procedure

Lever pressing was acquired by reinforcing successive approximations with a 45-mg food pellet. For rats in group 1 (n = 6), food was available under a fixed ratio 1 reinforcement schedule (i.e., FR 1-1 pellet). Methadone treatment began when food intake showed no trends as judged by visual inspection of the data (10–25 days of baseline). Rats in group 2 (n = 5) responded under an FR 1 reinforcement schedule in which each lever press produced five 45-mg food pellets (i.e., 225 mg) delivered over 2 1/2 seconds (FR 1-5 pellets). For rats in group 3 (n = 6), food troughs were equipped with infrared photocell beams, and pellets were delivered when rats interrupted the beam under an FR 1 reinforcement schedule (nosepoke-1 pellet).

To control for handling and repeated injections, methadone administration in groups 2 and 3 progressed according to a repeated baseline design. Under this design, a particular treatment (i.e., in this experiment, administration of 5.0 mg/kg methadone) is applied in sequence (i.e., over a time lag) across subjects presumably exposed to similar environmental conditions. As the same treatment variable is applied to successive subjects, the baseline (i.e., number of saline injections) for each subject increases in length. Thus, this baseline can be used a control for number of injections (i.e., by staggering the beginning of methadone treatment, each subsequent rat served as a control for those preceding it in treatment). The decision of which rat in the multiple baseline would subsequently receive methadone was made by choosing the subject with the least variability in its baseline food intake on the preceding 5 days, as assessed by visual inspection of the data.

Sessions began with house light illumination. Number of food pellets eaten were recorded. Intake was assessed from 0900–1300 h. Pellets consumed following the final 5 baseline days, the first 5 days, and the last 5 days of methadone administration were compared by a two factor repeated measures analysis of variance (RMANOVA) for each group. Post hoc comparisons were compared with paired t-tests.

RESULTS

When each lever press produced one food pellet (group 1), food intake was not increased by methadone (5.0 mg/kg) administration [$F(2, 8) = 1.56, p > 0.05$] (Fig. 1, top panel). However, when a lever press produced five pellets (group 2), methadone produced an increase in food intake (Fig. 1, middle panel) [$F(2, 8) = 7.13, p < 0.05$], although this effect

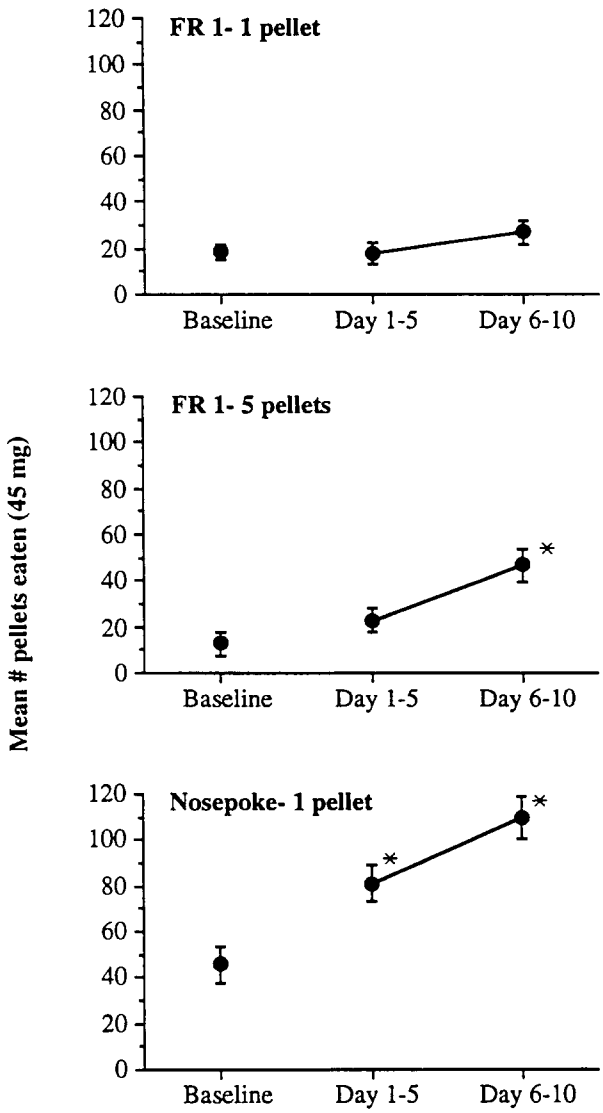

FIG. 1. Comparison of the mean number of pellets (45 mg) eaten following the final five baseline, first five, and last five methadone (5 mg/kg) injections. Group 1 rats (top panel) responded under an FR 1-1 pellet reinforcement schedule. Group 2 rats (middle panel) responded under an FR 1-5 pellets reinforcement schedule. Group 3 rats (bottom panel) had pellets delivered when an infrared photolectric beam was interrupted (i.e., nosepoke). *$p < 0.05$.

was not significant over the first 5 days of methadone treatment. However, there was no change in response rate between the first and second groups. Thus, rats may have eaten more food simply because more pellets were delivered after each lever press.

When response requirements were changed so that pellets were produced by a rat poking his nose through an infrared beam (group 3), significant increases following methadone administration were also observed [$F(2, 8) = 12.32$, $p < 0.05$] (Fig. 1, bottom panel). Furthermore, such a contingency produced a relatively immediate increase (i.e., observable over days 1–5 of methadone treatment) ($F(1, 5) = 6.70$, $p < 0.05$).

Repeated saline administration did not increase food intake in any of the groups.

DISCUSSION

The present study assessed methadone's effects on food intake in light of the discrepancy between opioid-induced increases in food intake under free access conditions and decreases in lever-press or key peck contingent delivery. Differences in procedures typically used for each of these types of studies were examined to determine which factors contribute to these disparate results.

Results from the current study suggest that the differences in methadone's observed effects in free feeding and operant chamber paradigms are not due to procedural differences involving the level of food deprivation of the rats, the time course over which methadone's effect on food intake is measured, or whether experimental sessions occurred in the same or different environment as where the rats were housed. As is typical of home cage studies, rats in group 1 (FR 1-1 pellet) were not food deprived, the environment and contingencies for food acquisition were the same both during and following experimental sessions, and intake was measured over an extended period of time (i.e., 4 h). Despite all these factors being similar to home cage studies, a dose of methadone (5.0 mg/kg) that produces robust increases in free feeding (15) did not increase intake contingent upon a reinforcement schedule as lenient as an FR 1. Methadone's effects were also different from those previously observed in operant chambers. Equipotent doses are reported to decrease food maintained operant responding (2,7,8,14,19). However, this may have been an artifact of the low food intake levels during baseline, resulting in a floor effect.

Responding can be increased by increasing the quantity of a reinforcer (6), and subsequent drug effects may also depend upon reinforcer size (17). Studies in home cages typically involve rats approaching relatively large (e.g., 15 g) amounts of food, whereas studies in operant chambers typically involve responding that produces a small (e.g., 45 mg) food pellet. Increasing the amount of available food following each lever press (group 2) resulted in methadone-induced increases in food intake. However, the increase in food intake seems to have occurred due to the presence of more food in the hopper, rather than a change in response rate. This result is consistent with the observation that methadone increases free feeding (15). Thus, the amount of food immediately available for consumption might contribute to reported differences between methadone's effects in home cage and operant chamber settings. The effect of magnitude of reinforcement does not produce identical increases following methadone administration in the current study as those reported in home cages. Increases in 4-h intake are observable after the third methadone injection in home cage studies, whereas the increase in operant-dependent food obtained with rats in group 2 (FR 1-5 pellets) was not evident until days 6–10 of methadone administration.

When response requirements for food acquisition were changed to having food produced by breaking an infrared beam (group 3), methadone-induced increases in food intake similar to those occurring in free feeding studies (i.e., similar in magnitude of effect and in the number of injections necessary to produce such increases) were observed. Thus, differences between methadone's effects on free feeding and in operant chambers may likely result from their differences in response requirements for food. Whereas both home cage and operant chamber settings involve approaching the food and

the consummatory responses of seizing, chewing and swallowing, the operant situation also requires the emission of another response (e.g., pressing a lever or pecking a key) to produce the food before approach can occur. Under these conditions, increased food intake following methadone was not observed unless the magnitude of reinforcement was increased (group 2). Methadone's motivational effects appear similar to those reported following ventromedial hypothalamus (VMH) lesions. Miller et al. (13) reported that VMH lesions produced differential effects on food intake depending on the amount of work required. Food intake was increased when response requirements were lax and decreased when response requirements were difficult by VMH lesions.

In all operant chamber studies (including the current one), a contingency between the rats behavior and food availability exists. There is no such contingency in home cage studies. Reported differences in methadone's effects in these two paradigms might reflect differences in this contingency. However, methadone-induced food intake increases similar to those reported in home cages were observed in the current study when food was produced by breaking an infrared beam. Thus, methadone can increase intake of response-contingent food.

In sum, the differences between methadone's effect on free feeding vs. operant chamber food intake may be due to procedural factors such as magnitude of reinforcement and response requirements. By making conditions in operant chambers more similar to those used in home cage studies, methadone-induced increases in food intake are possible.

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