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Effects of Methadone on Free Feeding in Satiated Rats

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RUDSKI, J. M., D. W. SCHAAL, T. THOMPSON, J. CLEARY, C. J. BILLINGTON AND A. S. LEVINE. *Effects of methadone on free feeding in satiated rats.* PHARMACOL BIOCHEM BEHAV 43(4) 1033–1037, 1992.—A variety of opioids and opiates are known to increase short-term food intake. In the present study, we evaluated the effects of methadone on free feeding in satiated rats. We assessed the effect of methadone (0, 1.5, 3.0, 5.0, and 10.0 mg/kg) on food intake 1, 2, 4, and 6 h after injection for 3 consecutive days. Two hours after methadone administration, food intake was inversely related to dose, but after 6 h a direct relationship between dose and feeding was obtained. Food intake increased with repeated methadone administration. In Experiment 2, methadone (5.0 mg/kg) was injected and food was made available 0, 1, 2, or 3 h later. Maximal food intake occurred in the third and fourth hours following methadone administration. As in Experiment 1, food intake increased with repeated methadone administration. Increases in food intake following repeated methadone administration may have been due to the development of tolerance to effects of methadone that may interfere with feeding, such as sedation. In Experiment 3, methadone was administered daily or every fifth day, assuming that spacing injections would retard tolerance development. Repeated daily methadone administration was associated with increased food intake earlier in the session, whereas increases in food intake following spaced methadone administration occurred later in the session. These data indicate that methadone increases short-term feeding in satiated rats. This is in contrast to the reported decrease in food-reinforced behavior noted in operant studies. This contrast may be due to sedating or other disabling effects of methadone.

Methadone Opioids Opiates Food intake Eating

DURING the past decade, it has become clear that opioids are involved in the short-term regulation of food intake. Agonists of the opioid receptors have been shown to stimulate short-term feeding, whereas antagonists of these receptors have been shown to decrease food intake (2,10). Associated with such research is the observation that repeated administration of opioid agonists, most notably morphine, results in a more reliable and robust feeding response compared with that observed after a single injection of opioids (11). This "reverse tolerance" could be due to tolerance to some of the opioid effects, such as sedation, that may interfere with feeding.

The synthetic opioid methadone is used extensively in treatment of opioid-dependent individuals (3). Many studies have evaluated the effects of methadone in operant environments where food is used as a reinforcer (1,4,6,7,15). Most of these studies have demonstrated that methadone decreases the rate of responding for food. To our knowledge, methadone's effects on free feeding have not been reported in the scientific literature. In the current study, we evaluated the effects of methadone on free feeding after a single injection or after repeated administration of the drug. We also observed whether spacing methadone administration (every fifth day) would disrupt the development of tolerance to the effects of methadone on feeding. We used body temperature, known to be altered by opiates (12), as a second means of evaluating the effect of spacing of repeated injections on the development of tolerance to an opiate effect.

METHOD

Male Sprague-Dawley rats (Biolab, St. Paul, MN) were individually housed in conventional hanging cages with a 12 L : 12 D photoperiod (lights on at 0700 h) in a temperature-controlled vivarium (21–22°C). Purina certified Lab Chow

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and water were available ad lib except when noted. Methadone HCl (Eli Lilly, Inc., Indianapolis, IN) was dissolved in isotonic saline (0.9%) to obtain a constant injection volume of 1.0 ml/kg. Rats were injected SC with methadone or saline at the start of experimental sessions. Consecutive injection sites were alternated to avoid tissue damage. Satiated rats were used in these studies to more easily demonstrate a drug-induced increase in food intake.

In the first experiment, rats (n = 60, starting weights = 236–320 g) were randomly assigned to one of five groups. Rats were injected with methadone (1.5, 3.0, 5.0, or 10 mg/kg) or saline at 0900 h in their home cages and preweighed food pellets were placed at the base of the cage. Pellets were weighed and replaced 1, 2, 4, and 6 h after injection. Food intake was quantified by calculating the differences between the beginning and ending weights of the food pellets. Spillage was collected and included in the calculations. Experimental food intake sessions were conducted for 3 consecutive days.

In the second experiment, rats (n = 64, starting weights = 275–325 g) were assigned to one of eight groups, four receiving methadone and four receiving saline. Rats were injected with methadone (5.0 mg/kg) or saline at 0900 h in their home cages. The first two groups received food immediately after injection of methadone or saline. The next six groups received food 1, 2, or 3 h after injection of methadone or saline. Food intake was then quantified, as stated above, for a 1-h period in each group.

In the third experiment, rats (n = 40, starting weights = 260–310 g) were assigned to one of four groups. In the first two groups, rats were injected with saline or methadone (5.0 mg/kg) every day (0900 h), followed by measurement of food intake at 1, 2, 4, and 6 h. In Groups 3 and 4, food intake was measured every fifth day. In Group 3, methadone was injected every fifth day and saline was administered on the intervening days. In Group 4, saline was injected daily. Food intake was again measured at 1, 2, 4, and 6 h. A subgroup of rats (n = 4) was selected from each group to study the effect of methadone on temperature. Thermocouples were inserted 6 cm into the rectum of each rat and core body temperature was recorded 60 s later on a YSI telethermometer (model 43 TF, Yellow Springs, Inc., Yellow Springs, CO). Temperatures were measured immediately before methadone or saline injection and 0.5, 2, and 4 h after injection on those days in which food intake was measured.

All data are represented as mean ± SEM. Main effects were evaluated by analysis of variance (ANOVA) and significance levels adjusted with a Bonferroni correction. Means were compared by a Tukey's honest significant different test.

RESULTS

Methadone administration resulted in an increase in food intake during h 2–6 after repeated administration (Fig. 1). There was a main effect of dose at the 2-h, $F(4, 55) = 10.54$,

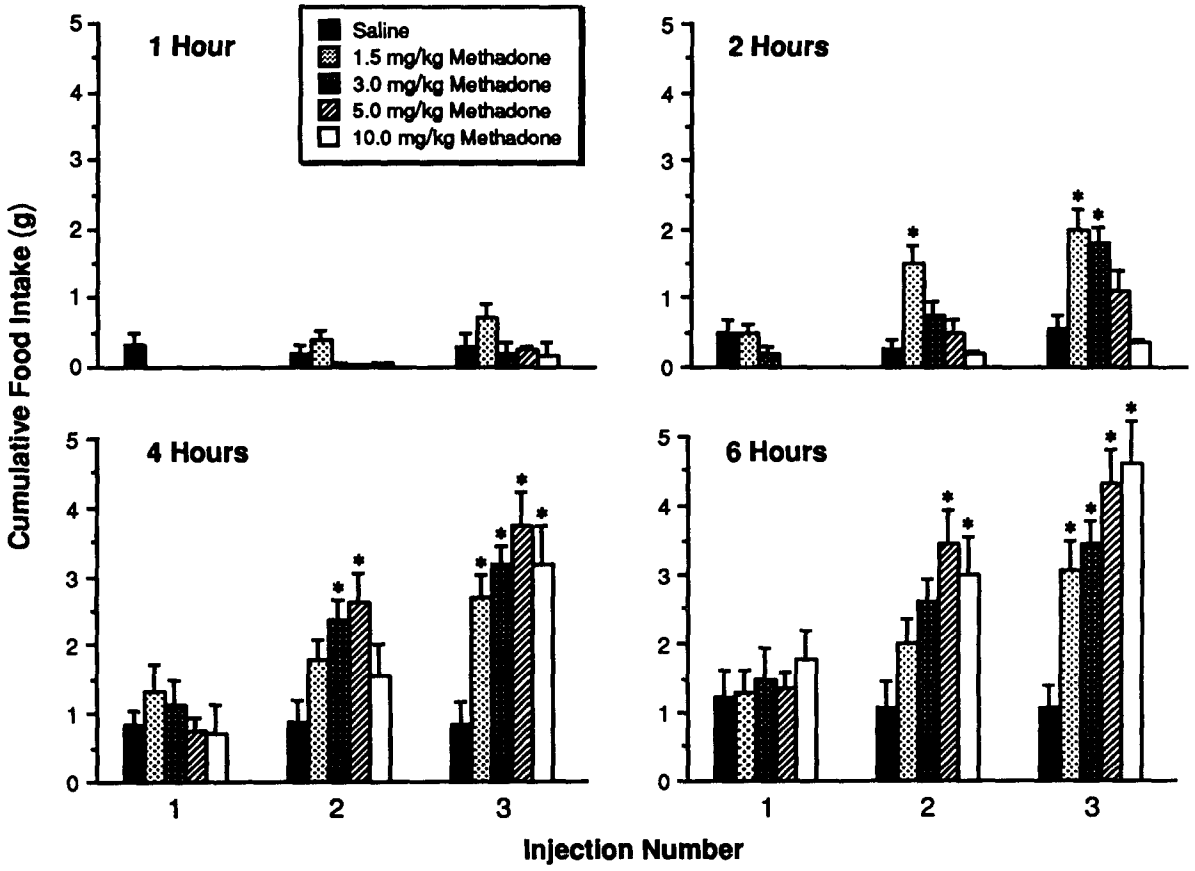

FIG. 1. Effect of repeated methadone administration (0, 1.5, 3.0, 5.0, and 10.0 mg/kg) on food intake in satiated rats. *p < 0.05 compared to saline controls.

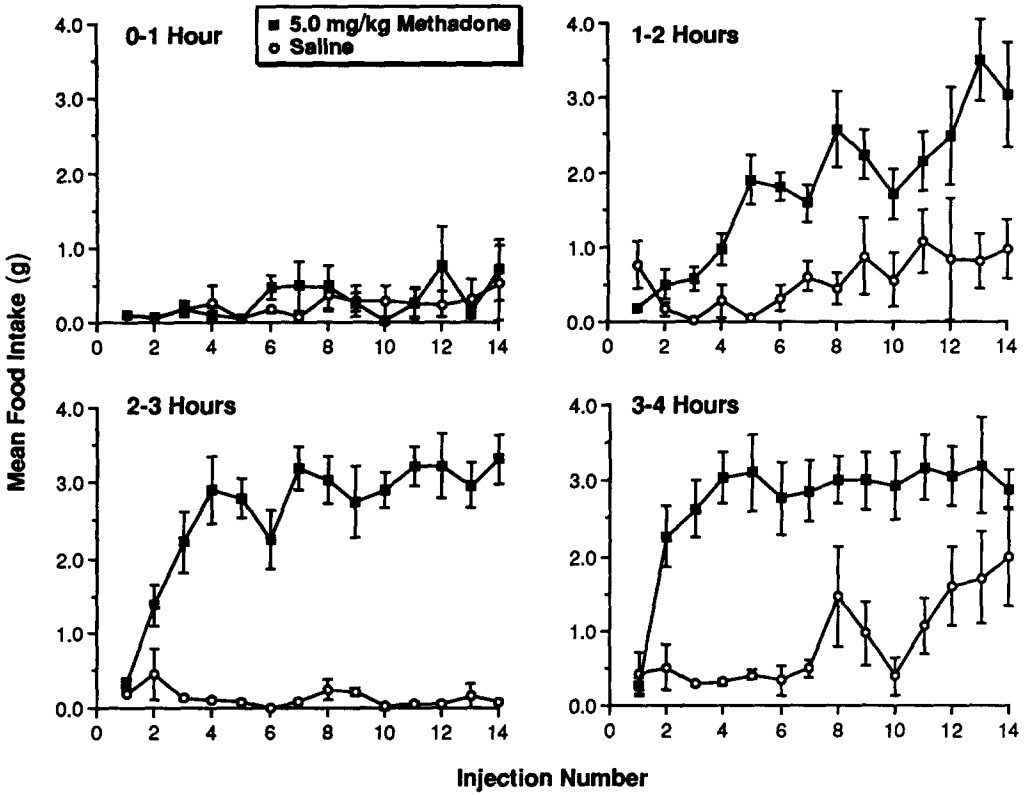

FIG. 2. Effect of repeated methadone administration on 1-h food intake (0–1, 1–2, 2–3, and 3–4 h after drug administration) in satiated rats.

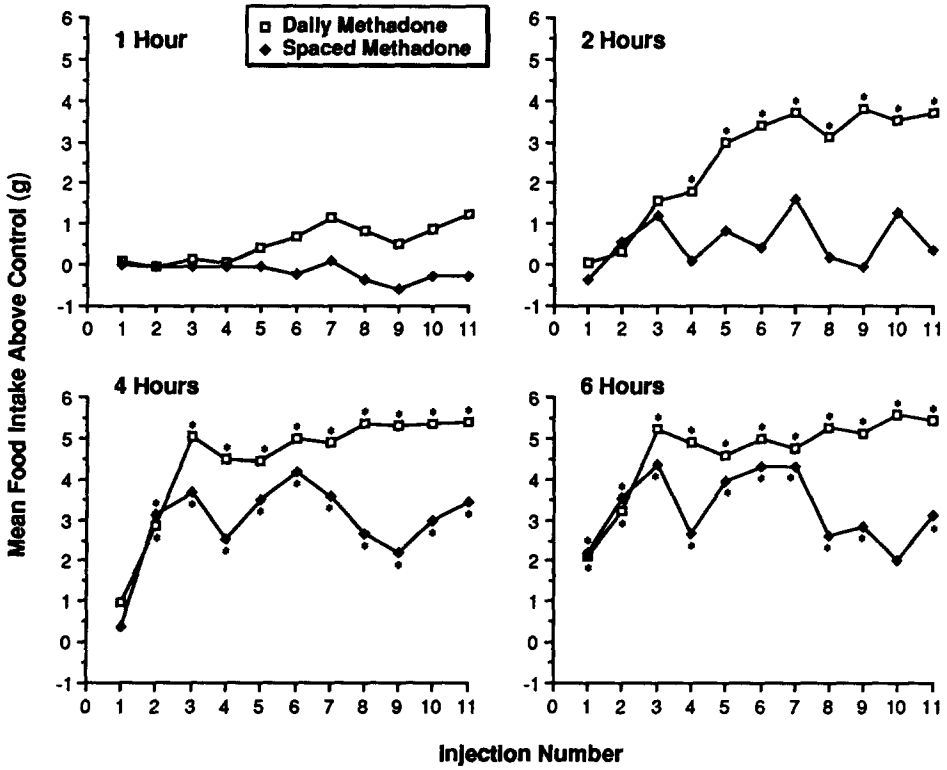

FIG. 3. Effect of repeated methadone administration on food intake in satiated rats when methadone was administered either daily or every 5 days. *$p < 0.05$ compared to saline controls for groups injected daily or every fifth day.

$p < 0.0001$, 4-h ($F = 4.28$, $p < 0.005$), and 6-h ($F = 6.36$, $p < 0.005$) time points. Repeated methadone presentation resulted in increased food intake at each time point [1-h $F(2, 110) = 10.17$, $p < 0.0001$; 2-h $F = 41.07$, $p < 0.0001$; 4-h $F = 47.68$, $p < 0.01$; 6-h $F = 45.76$, $p < 0.0001$]. At the 2-h time point, food intake was inversely related to dose. By the third day of injection, all doses potently increased feeding at the 4- and 6-h time points.

In the second study, rats were given access to food for a 1-h period either 0, 1, 2, or 3 h after methadone administration. There was a main effect of time, $F(7, 55) = 30.42$, $p < 0.0001$, and day of injection, $F(13, 715) =$ a 18.15, $p < 0.0001$, on food intake and a significant interaction between these factors, $F(91, 715) = 30.42$, $p < 0.0001$. Immediately after injection, only a small amount of food was ingested (Fig. 2). Significant increases in intake occurred at the 1- to 2-, 2- to 3-, and 3- to 4-h time points. During h 1–2, daily methadone injections resulted in an incremental increase in food intake over the 14-day period. At the 2- to 3- and 3- to 4-h time points, food intake reached an symptote by about the fourth day of injections.

In the third experiment, we evaluated the effect of daily or spaced methadone injections on food intake (Fig. 3). There was a significant main effect of drug treatment (2-h $F = 22.33$, $p < 0.01$; 4-h $F = 52.95$, $p < 0.0001$; and 6-h $F = 41.0$, $p < 0.0001$) and injection number [1-h $F(10, 360) = 10.28$, $p < 0.0001$; 2-h $F = 18.56$, $p < 0.0001$; 4-h $F = 25.24$, $p < 0.0001$; 6-h $F = 22.90$, $p < 0.0001$] on food intake. Those rats receiving daily methadone injections ate significantly more than their controls during the 2-h time point after 4 days of injections (Fig. 3). In contrast, when the methadone injections were spaced 5 days apart no effect was noted during h 2, even after 11 injections. Rats in both groups increased their food intake above control levels of intake 4 h and 6 h after methadone injection. The increase in intake during h 4–6 was noted even after a single injection of methadone.

We also evaluated the effect of repeated injections, either daily or spaced 5 days apart, on core body temperature. There was a significant main effect of methadone [2-h $F(3, 12) = 13.13$, $p = 0.0004$; 4-h $F = 32.00$, $p < 0.0001$] and day of injection [½-h $F(10, 120) = 4.57$, $p < 0.0001$; 2-h $F = 12.87$, $p < 0.0001$] on temperature. Methadone increased body temperature in both groups during the first 2 h of the study (Fig. 4). In the group injected daily with methadone, temperature returned to baseline by the fourth hour after injection. In contrast, the temperature of rats injected every fifth day failed to return to baseline by the last measurement (4 h).

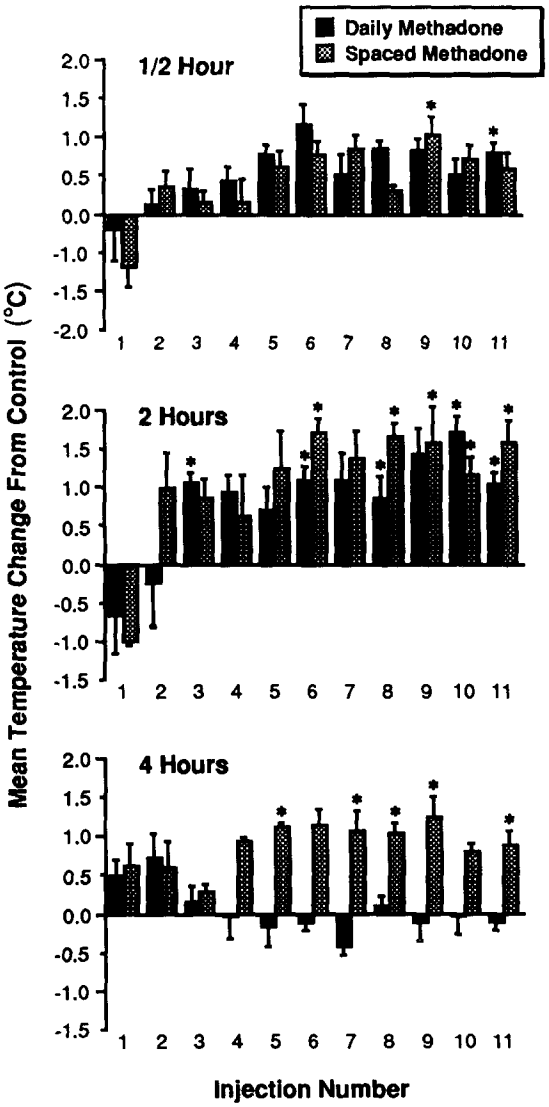

FIG. 4. Effect of repeated methadone administration on core body temperature when methadone was administered either daily or every 5 days. *$p < 0.05$ compared to saline controls for groups injected daily or every fifth day.

DISCUSSION

We found that methadone increased food intake after repeated administration in a manner similar to that observed with other opiates. Leshem (8,9) noted that morphine administration decreased food intake during the first hour and increased food intake 1–4 h after drug administration. Morley et al. (13) found that repeated injection of morphine increased food intake more reliably and vigorously than in rats injected only once. In our study, methadone failed to increase food intake during the first hour of the experimental sessions, even after 14 days of injection. Injecting methadone daily steadily enhanced second-hour food intake over 14 days. Food intake reached an symptote 4 days after initial injection of methadone in the third and fourth hours following methadone administration.

Repeating methadone administration with a 5-day hiatus between injections failed to increase food intake as potently as following daily methadone injections. The rate at which tolerance to the effects of opiates develops is reported to be a function of the dose and frequency of administration (5). The shorter the interdose interval, the more rapid is the development of tolerance. Thus, spacing methadone injections by 5-day intervals should have retarded the development of tolerance.

While these data clearly show methadone's ability to enhance feeding, especially late in the session and after repeated injections, other effects of this opiate may actually interfere with food intake. For example, casual observation indicates that rats injected with methadone are sedated. Clearly, an extremely sedated rat would not be able to ingest food. Methadone might have other effects that also disable the rat and

interfere with eating. It is well known that opiates and opioids can cause cataplexia, which would interrupt feeding behavior. With repeated injection, the rat appears to become tolerant to many effects of methadone. For example, we found that methadone-injected rats eventually became tolerant to the well-described effects of opiates on temperature (12). Spacing of the methadone injections obstructed the development of tolerance to the hyperthermic effect. The spacing of methadone injections decreased its ability to induce robust feeding, suggesting that the lack of daily injections hindered the development of tolerance to sedation or other effects of methadone that may have interfered with feeding behavior. It should be noted that it is possible that repeated injection of methadone also increases ingestive behavior, independent of its effects on sedation or and other disabling behaviors.

In contrast to the effects we observed on free feeding, methadone has been reported to reduce food-reinforced operant behavior (1,4,6,7,15). This paradox may be due to a variety of factors. Studies of food-reinforced operant behavior usually measure response rate of food-deprived rather than satiated rats. Sanger and McCarthy (14) found that morphine decreased food intake in 24-h food-deprived rats but increased intake in nondeprived rats. In addition, the opiate effects in the operant environment are usually evaluated immediately or shortly after injection of drugs and only for brief periods of time (1 h or less). Thus, studies evaluating opiate effects on food-reinforced operant behavior need to be reevaluated over longer periods of time to allow for the diminution of possible disabling properties of opiates. Sedated rats certainly would have difficulty repeatedly pressing a bar to obtain food, even if they were "hungry."

In conclusion, we found that methadone induces feeding in a reliable and relatively robust fashion after repeated administration. At higher doses, methadone appeared to disable rats from engaging in feeding behavior unless the food was presented to rats 2 h or more after drug administration. The enhanced feeding that occurs with repeated methadone injection may be due to the development of tolerance to some effect of the drug that interferes with the rat's ability to eat.

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