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BRIEF COMMUNICATION

Changes in Food-Maintained Progressive-Ratio Responding of Rats Following Chronic Buprenorphine or Methadone Administration

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MACENSKI, M. J., D. W. SCHAAL, J. CLEARY AND T. THOMPSON. *Changes in food-maintained progressive-ratio responding of rats following chronic buprenorphine or methadone administration.* PHARMACOL BIOCHEM BEHAV 47(2) 379–383, 1994.—Seven rats lever pressed under a progressive ratio 3 (PR 3) schedule of food presentation; the number of responses per reinforcer systematically increased during each session. Break point (i.e., the number of responses in the last completed ratio before session termination) was measured under daily methadone (4.5 mg/kg and 3.0 mg/kg) or buprenorphine (0.3 mg/kg) administered prior to experimental sessions. Both drugs initially eliminated rats' food-maintained progressive-ratio responding. Break points during chronic methadone did not return to baseline levels after 80 drug sessions and a dose reduction. In contrast, break points during chronic buprenorphine administration were considerably above baseline control levels for two rats and returned to baseline levels for the third.

Buprenorphine Methadone Progressive ratio Food reinforcement Chronic opioid Tolerance Rats

METHADONE is a μ-receptor agonist that is orally effective as an analgesic. Methadone reduces opioid withdrawal and is used for treating opioid dependency (17). Buprenorphine is a partial μ-receptor agonist, sharing pharmacological properties with both μ-receptor agonists like methadone and μ-receptor antagonists like naloxone (25). Buprenorphine may be a useful substitute for methadone maintenance in treating opioid dependence (11) and is a potential pharmacotherapy for cocaine dependence (19). Acute methadone reduces operant responding in a variety of species and under various reinforcement schedules (18,21,34). Following chronic methadone administration, initially reduced operant response rates typically return to levels from 75% below baseline to complete recovery of baseline values (3,14,20,36). Recovery of baseline response values following initial response rate reductions has also been observed with other μ-receptor agonists (23,38,43).

Acute buprenorphine administration reduces operant responding by rats, squirrel monkeys, and rhesus monkeys (3, 6,29,34), while buprenorphine appears to have no effect on the response rates of patas monkeys (33,34). Additionally, in pigeons acutely administered buprenorphine has been reported to increase (20), have no effect on (20), or decrease response rates (9,24). Monkeys self-administering buprenorphine daily show complete recovery of or increases in schedule-controlled food intake (22,29,30). Monkeys given concurrent access to drug reinforcers and food also exhibit complete recovery of or increases in schedule-controlled food intake, while concurrent drug-reinforced responding is reduced (31, 32). Studies examining buprenorphine's effects on food-maintained schedule-controlled behavior after daily administration have produced mixed results. Squirrel monkeys did not recover food-maintained baseline response rates after 17 daily

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buprenorphine (0.01 mg/kg) injections (8). Food-maintained response rates have also been reported to return to baseline (3) and to increase above baseline values (23).

The current study further examined effects of daily administered buprenorphine and methadone on food-maintained operant behavior. Opioids play a role in feeding (35) and differentially affect the organism's physical ability to produce a given behavior (i.e., "motoric effects") and the ability of the reinforcer to support behavior (i.e., "motivational effects") (9). Rats' lever pressing was maintained under a progressive ratio (PR) schedule. PR schedules require an increasing number of responses for each successive reinforcer delivery. This schedule allows assessment of reinforcer or motivational strength, as break point has been shown to correlate with changes in deprivation level, reinforcer magnitude (15,16), and drug dose (13,41).

METHOD

Subjects

Seven adult male Wistar rats weighing from 440 to 525 g served as subjects. Four rats (R1, R2, R3, R4) had previously received a series of acute methadone injections (0.5–4.5 mg/kg) and three rats (R5, R6, R7) had received acute buprenorphine injections (0.056–3.0 mg/kg). All rats had experience responding under PR and fixed-ratio (FR) food reinforcement schedules. Rats were maintained at 80% of their free-feeding weights throughout the experiment via postsession feeding of their complete food allotment. Rats' weights did not change during the study. Tap water was available in their home cages at all times. Rats lived in individual 18 × 20 × 25-cm stainless steel cages located in a colony room maintained at 24°C and were under constant illumination.

Apparatus

Experimental sessions were conducted in three commercially available small animal operant chambers (Model E10-10, Coulbourn Instruments, Inc., Allentown, PA). Each chamber was enclosed in a sound-attenuating cubicle, and white masking noise was continuously present. Chambers were equipped with two operant levers; the right lever was used exclusively throughout the experiment. Forty-five-milligram pellets (Bio-Serve Holton Industries, Frenchtown, NJ) could be delivered to a food tray positioned between the levers. When a pellet was delivered a 4-W white light above the food tray was illuminated for 5 s. Electromechanical equipment located in an adjacent room controlled experimental conditions and recorded data.

Behavioral Procedure

Rats were trained to press the right lever by reinforcing successive approximations. Initially, a 45-mg food pellet was delivered immediately following each lever press. The number of lever presses required per food pellet was gradually increased from 1 to 10 (i.e., FR 1 to FR 10). Under these conditions a pellet was delivered immediately following every 10th lever press. After several sessions of lever pressing under the FR 10, the contingency was changed to a PR 3 schedule with an 8-min termination criterion. Under this schedule, following each food pellet earned the number of lever presses was increased by 3 and a clock was reset to 8 min. The initial ratio was 9; thus a pellet was delivered after the 9th, 12th, 15th lever presses, and so on. Sessions ended when a ratio was not completed within 8 min. The number of responses in the last completed ratio prior to session termination was defined as the break point. Sessions began with houselight illumination and initiation of the PR 3 schedule contingency. Number of food pellets delivered (i.e., ratios completed), largest ratio completed (i.e., break point), cumulative lever presses, and total session time were recorded during each session. When the termination criterion was met, the houselight was extinguished and lever presses had no further scheduled consequences.

Drug Preparation and Administration

Methadone HCl (Eli Lilly, Chicago) and buprenorphine HCl (Burroughs Wellcome, Research Triangle Park, NC) were dissolved in isotonic saline (0.9%) at room temperature. All solutions are expressed in terms of the salt and were mixed to be delivered in a volume of 1.0 ml/kg. Single, daily injections of methadone or buprenorphine were administered IP 10 min prior to sessions, and rats were returned to their home cages during the injection-session interval. Methadone (4.5 mg/kg) and buprenorphine (0.3 mg/kg) were chosen because initial testing in our laboratory indicated that they were approximately equally effective (i.e., these were doses which, after acute injections, completely eliminated responding in three of four rats responding under a PR 3 schedule; see Table 1). The methadone dose was subsequently reduced to 3.0 mg/kg/injection. The rats were rank-ordered according to baseline PR break point values, and successive pairs of rats were randomly assigned to receive methadone or buprenorphine.

Rats received neither drugs nor injections for at least 30 days prior to the start of this experiment. Initially, rats were injected with 0.9% saline. When responding was stable, rats were injected with methadone (4.5 mg/kg) or buprenorphine (0.3 mg/kg) as appropriate to group. After over 30 daily methadone injections, the daily methadone dose was reduced to 3.0 mg/kg. After cessation of opioid injections, several sessions were completed with no presession injections given. Doses used and days of injections are presented in Table 2.

TABLE 1

BREAKPOINT AFTER ACUTE OPIOID INJECTIONS

	Methadone Dose (mg/kg)			
Rat	Saline	2.5	3.0	4.5
R1	72	42	12	0
R2	74	66	12	33
R3	96	0	0	0
R4	72	0	0	0
Mean	78.3	27.0	6.0	8.25
	Buprenorphine Dose (mg/kg)			
Rat	Saline	0.17	0.3	1.0
R5	69	30	0	0
R6	110	39	0	0
R7	66	0	27	0
R8*	66	0	0	0
Mean	77.8	17.25	6.75	0

*Rat 8 was not used during chronic injections due to illness.

TABLE 2

DRUG ADMINISTRATION REGIMEN (DAYS UNDER EACH CONDITION)

Methadone-Treated Rats				
Rat	Saline	4.5 mg/kg	3.0 mg/kg	No Drug
R1	1-13	14-45	46-78	79-88
R2	1-13	14-45	46-78	79-88
R3	1-13	14-45	46-78	79-88
R4	1-13	14-45	46-78	79-88

Buprenorphine-Treated Rats			
Rat	Saline	0.3 mg/kg	No Drug
R5	1-13	14-62	63-71
R6	1-13	14-62	63-73
R7	1-13	14-59	60-70

RESULTS

Figure 1 shows the effects of daily methadone administration on break point. Three of four rats displayed no lever pressing the first day of methadone administration, and none of the rats lever pressed on the second day. After 32 daily 4.5-mg/kg methadone injections, the means of the last six break points (as percent saline control) were 27.3, 82.2, 62.5, and 34.5% for rats R1, R2, R3, and R4. Lever pressing break point values increased after the first 3.0-mg/kg injection for all animals. After 32 daily 3.0-mg/kg methadone injections, the means of the last six break points (as percent saline control) were 73.3, 75.8, 67.6, and 61.0% for the same rats. Daily methadone injections were discontinued and break points returned to saline control levels within the first few days. Mean break points over the last six days were within 7% of the mean break points following saline administration for all rats.

Figure 2 shows the effects of daily buprenorphine administration on break point. For two of three rats, no lever pressing occurred on the first day of buprenorphine injections; break point for the third was reduced by 75%. Break point values returned to within 75% of saline values in 4 to 10 days and to within 1 SE of saline values after 10 (R5) to 16 (R6) days of buprenorphine administration. After 15-20 days of buprenorphine injections, break points of rats R6 and R7 were consistently above saline baseline break points. The break point for rat R7 increased more than 150%. However, R6's break points declined to near baseline levels. When buprenorphine injections were discontinued, all rats' break points decreased within the first few days; the break points of some rats increased above saline levels before returning to saline control levels. The mean break points of the last six days were within 7% of mean saline break points for two rats and 37% for the third.

DISCUSSION

Methadone initially eliminated or substantially reduced lever pressing by all rats, which is consistent with previous reports of the acute response rate-reducing effects of methadone in rats as well as other species (4,7,10,27,42). The elimination or reduction of responding observed in this study is also consistent with reports of acutely administered buprenorphine in rats. However, buprenorphine is contrasted with

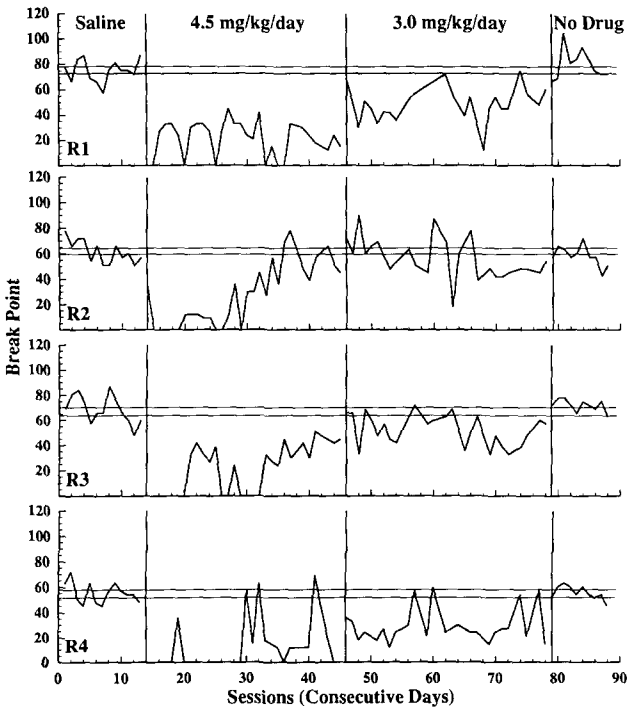

FIG. 1. Break point as a function of days for individual rats responding under a progressive ratio 3 (PR 3) schedule of food presentation. Rats received daily methadone injections as indicated. Horizontal lines represent ± 1 SE above and below the mean of 13 saline baseline days.

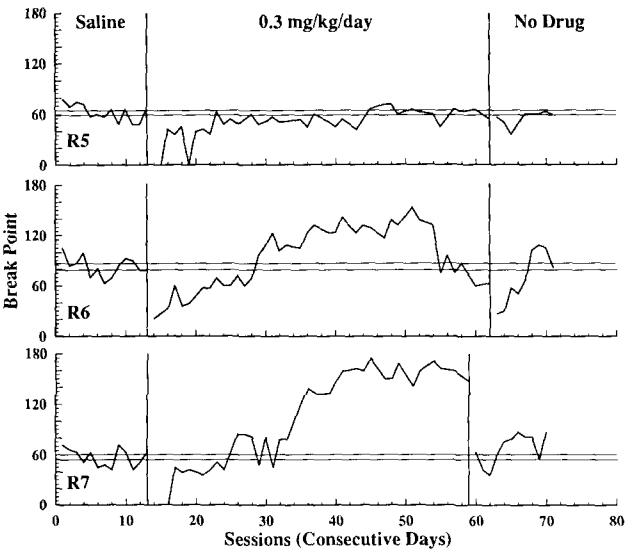

FIG. 2. Break point as a function of days for individual rats responding under a progressive ratio 3 (PR 3) schedule of food presentation. Rats received daily buprenorphine injections as indicated. Horizontal lines represent ± 1 SE above and below the mean of 13 saline baseline days.

methadone as reductions in responding are not reliably observed in some other species (e.g., pigeons, patas monkeys).

Daily methadone administration (4.5 mg/kg) caused cessation of lever pressing for 3 to 16 days, and baseline break points did not recover to baseline levels after 32 days of methadone administration. The dose was subsequently reduced to 3.0 mg/kg for an additional 32 days, and under these conditions break points increased to slightly below saline baseline levels. Likewise, previous studies revealed that response measures during chronic methadone administration often fail to completely return to baseline levels [e.g., (5,14,39)]. Similar results are obtained when *levo*-α-acetylmethadol (LAAM) or other μ-receptor agonists, such as morphine, are chronically administered (2,26,38). In the current study, after extended administration of methadone complete recovery from methadone's effects on food-maintained schedule-controlled behavior did not occur.

In contrast to methadone's effects, two of three rats exhibited break points consistently above baseline levels during daily buprenorphine administration (0.3 mg/kg); the third rat maintained responding at baseline levels. These data are congruent with several studies showing increases in food-maintained responding both during daily concurrent buprenorphine self-administration (29,30) and during daily buprenorphine treatment when drug and food reinforcers are concurrently available (31,32). In addition to species differences, opioid self-administration was the main concern of the former studies; thus daily buprenorphine dose was not constant. The latter studies focused on the effects of buprenorphine on other self-administered drugs; thus the monkeys received other drugs, and in amounts that were not constant, making direct comparisons with the current study questionable.

Studies examining buprenorphine's effects on food-maintained schedule-controlled behavior after daily administration have produced mixed results. Dykstra (8) reported persistent reductions in the lever pressing of squirrel monkeys over 17 daily 0.01-mg/kg buprenorphine injections. Maintenance dose and treatment duration are determinants of behavioral recovery (1). Lack of behavioral recovery may be due to a low dose and insufficiently long treatment period. Rats maintained under a fixed-ratio schedule of food delivery tended to respond at rates higher than those observed during baseline conditions (3). However, a protocol calling for systematic increases in the dose administered obviated robust rate increases. Lukas et al. (23) observed increases in food-maintained operant behavior of macaque monkeys after 20 days of 1.0-mg/ml buprenorphine injections. Rate increases in the current study were not observed until day 25 of the chronic injection regimen. When differences in unit dose and treatment time are taken into account, the current study as well as previous studies examining the effects of chronic buprenorphine administration show that chronic buprenorphine treatment can potentiate food-maintained operant responding.

Differences in behavioral recovery after drug administration may be due to the nonequivalence of the methadone and buprenorphine doses. However, doses of both drugs were sufficient to eliminate responding initially (see Table 1). Likewise, in studies where these drugs have been acutely administered to rats the doses used were in the range of those shown to be the lowest required to eliminate operant behavior completely [e.g., (3,27,37,40,42)]. Additionally, baseline response levels could not be reestablished, despite a 35% reduction in the methadone dose. Thus, it is unlikely that a substantial difference in the effects of original opioid doses can account for the differences in the present data.

A more likely explanation of the observed differences between methadone and buprenorphine is the pharmacokinetics of the two opioids. Methadone's effects are short lasting (3–5 h), though methadone's extended ability to control withdrawal symptoms in opioid-dependent individuals is an exception (17). Thus, the methadone injection regimen may not have been appropriate to produce full behavioral tolerance. In contrast, behavioral effects of a single buprenorphine injection have been reported to persist for two days in both pigeons (20) and primates (8). Previous studies have shown interinjection interval to be a major determinant in tolerance development, with no tolerance developing when single daily opioid injections are used (12,28). The methadone injection regimen used in the present study may have caused acute behavioral effects during the experimental session, but did not allow for full recovery of baseline response rates.

The pharmacokinetics of these two opioids may explain differences in baseline recovery; however, pharmacokinetics cannot explain the increase in break point values observed in two of the three buprenorphine-treated rats. Opioid agonists increase food intake and play a role in the initiation of feeding (35). Additionally, opioids have differential effects on motoric function and motivation (9). Increases in food-maintained responding may be related to differences in buprenorphine's and methadone's efficacy at the μ-receptor. Regardless, it is clear that the buprenorphine-induced lever-press rate increases are not simply tolerance. Though the present data do not identify a mechanism of action, they suggest that buprenorphine may have advantages over methadone in that neither motoric function nor motivation were irreversibly reduced.

The current data show that after daily methadone administration complete tolerance did not develop. In contrast, the data from the buprenorphine-treated animals suggest tolerance developed in all three rats. However, rate increases above saline baseline values suggest an additional effect different from tolerance to opioid-induced rate-reducing effects; buprenorphine-induced increases in food-maintained operant behavior merit further investigation.

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