Pharmacology Biochemistry & Behavior, Vol. 23, pp. 1037–1044, 1985. © Ankho International Inc. Printed in the U.S.A. 0091-3057/85 $3.00 + .00

Buprenorphine Effects on Food-Maintained Responding in Macaque Monkeys

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Received 16 January 1985

MELLO, N. K., M. P. BREE, S. E. LUKAS AND J. H. MENDELSON. *Buprenorphine effects on food-maintained responding in Macaque monkeys.* PHARMACOL BIOCHEM BEHAV 23(6) 1037–1044, 1985.—The effects of acute and chronic administration of buprenorphine, an opioid mixed agonist-antagonist, on food-maintained responding were compared in Macaque monkeys. Low acute doses of buprenorphine (0.01 and 0.03 mg/kg) did not change the number of food pellets earned or response rates on an FR 4 (VR 16:S) schedule of reinforcement from saline pre-treatment levels. Acute administration of 0.10 and 0.30 mg/kg buprenorphine significantly suppressed food-maintained responding ($p<0.01$). Chronic buprenorphine self-administration (0.01–0.10 mg/kg/injection) did not significantly suppress food intake, even at total daily doses that were 3 to 9 times higher than the highest dose (0.03 mg/kg) studied in the acute pre-treatment paradigm. Decreases in daily buprenorphine intake to 30 to 40 percent of control levels were not associated with increased food self-administration. Similarly, chronic heroin self-administration (0.01, 0.05, and 0.10 mg/kg/injection) was not associated with significant changes in food self-administration. These data suggest that during chronic self-administration of buprenorphine, Macaque monkeys developed tolerance to its acute suppressive effects on food-maintained responding.

Buprenorphine Macaque monkeys Food intake

BUPRENORPHINE is an opioid mixed agonist-antagonist that significantly suppresses opiate self-administration by human heroin addicts [21,24] and Macaque monkeys [19]. Unlike opioid agonists, buprenorphine does not produce severe and protracted withdrawal signs and symptoms in man [10,24] and its antagonist component appears to prevent lethal overdose, even at approximately 10 times the analgesic dose [1,13]. Buprenorphine has also been shown to be effective in methadone detoxification [8, 9, 15]. These data suggest that buprenorphine should be a safe and effective pharmacotherapy for opiate dependence [13, 22, 24].

One important characteristic of any drug used for long-term maintenance treatment is relatively low physiological and behavioral toxicity. In man, tolerance to the opiate agonist-like side effects of buprenorphine develops within 2 to 3 weeks [10,24]. Chronic buprenorphine administration over a dose range of 0.5 to 8.0 mg/day, SC did not disrupt operant performance for money [24]. Although nausea and vomiting, a typical opioid agonist side-effect, was reported following both acute [10] and repeated buprenorphine administration [10,24], subjects rarely described changes in appetite, and food intake and weight did not change appreciably over 24 days of buprenorphine administration [24]. The clinical utility of buprenorphine would be greatly diminished if persistent nausea, vomiting and decreased appetite were associated with chronic maintenance treatment.

There is an extensive literature indicating that, in general, opiate agonists increase food intake in several species, whereas opiate antagonists usually suppress feeding behavior (cf. [25, 27, 29] for review). Since buprenorphine is a congener of diprenorphine, a potent opioid antagonist, and etorphine, an opioid agonist [13], it is a unique compound for studying opiate effects on food intake. Relatively little is known about the effects of drugs that have both opiate agonist and antagonist properties on feeding behavior. Butorphanol, an opioid mixed angonist-antagonist, has been shown to stimulate feeding in rats [12,26] but in baboon, acute administration of butorphanol, as well as nalbuphine and pentazocine, produced dose dependent decreases in rate of response for food (unpublished data, S. E. Lukas).

Studies of the basic behavioral pharmacology of buprenorphine and its effect on food self-administration also have yielding conflicting findings. Acute administration of buprenorphine has consistently been shown to disrupt food-maintained responding in several species ([5,11] unpublished data, S. E. Lukas), whereas chronic administration of buprenorphine has not been associated with decreased food self-administration in Macaque monkeys [19,23]. These discrepant findings appear to reflect differences in the dose range of buprenorphine studied as well as differences in the behavioral measures used.

When rate of response was the primary behavioral measure, relatively low acute doses of buprenorphine (0.03–1.0 mg/kg) decreased responding in both components of a multiple Fixed Interval (FI) Fixed Ratio (FR) schedule of food-maintained responding in squirrel monkeys [5]. In pigeon, the acute administration of buprenorphine over a dose range of 0.08 to 5 mg/kg IM, increased rates of responding in the FI component of a multiple schedule, but had no effect on responding in the FR component of a multiple FR 30, FI 5 schedule at doses up to 40 mg/kg [11]. Although a decrement in food intake is suggested by a decrease in the rate of

food-maintained responding, data on actual food intake were not presented (cf. [5,11]).

In studies of chronic buprenorphine administration where Macaque monkeys were allowed to determine the dose of buprenorphine self-administered each day, food self-administration maintained on a second order FR 3 (VR 16:S) schedule of reinforcement remained stable over a dose range of 0.1 to 2.95 mg/kg/day IV [23]. Similarly, when ascending doses of buprenorphine (0.014 to 0.789 mg/kg/day) were administered over 6 to 8 months, food self-administration remained stable despite concurrent opiate self-administration [19]. Interpretation of these findings is limited by the fact that the maximal dose of buprenorphine studied was relatively low (0.789 mg/kg/day) and the design of the study did not permit clear differentiation of the effects of buprenorphine administration and concurrent opiate self-administration on food-maintained behavior [19]. The purpose of the present study was to reexamine both the acute and chronic effects of buprenorphine on food-maintained responding under conditions where other opiate drugs were not available. The effects of chronic self-administration of this opioid with both agonist and antagonist properties on food self-administration were compared with the chronic effects of an opioid agonist, heroin.

METHOD

Subjects

Nine male Macaque monkeys (*Macaca mulatta* and *Macaca nemistrina*) weighing 4.3 to 8.5 kg were studied. Five monkeys had a history of opiate agonist and mixed agonist-antagonist self-administration (A420, C872, 800B, A389, 814B) and four monkeys (10022, 10067, 762B, 780B) were drug-naive at the beginning of the study. Monkeys were maintained at ad lib weight and given multiple vitamins, fresh fruit and vegetables daily to supplement a banana pellet diet.

Monkeys were surgically implanted with chronic intravenous catheters to permit IV drug self-administration. All surgical procedures were performed under aseptic conditions. Monkeys were anesthetized with either pentobarbital (30 mg/kg IV) or ketamine (25 mg/kg IM) and a double lumen, silicone rubber catheter (inside diameter 0.028″, outside diameter 0.088″) was placed in either a jugular or femoral vein. After surgery, animals were given 200,000 units of longicil IM every other day for a total of 5 injections.

Animal maintenance and research was conducted in accordance with the guidelines provided by the Committee on Laboratory Animals' Facility and Care, the National Research Council Institute of Laboratory Animal Resources. The facility is licensed by the U.S. Department of Agriculture. The health of the primate colony was periodically monitored by a consultant veterinarian from the New England Regional Primate Center.

Apparatus

Monkeys worked at an operant task for food (1 g banana pellet) and for IV drug injections. A custom designed restraining apparatus protected the intravenous catheter and allowed free movement of the arms and legs [20]. The monkey was able to maintain a comfortable natural posture and jump up and down, but could not reach the top of his head, the point of intravenous catheter exit. The restraining apparatus was placed in a well-ventilated experimental chamber equipped with an operant response panel, a water dispenser and an automatic feeder.

Schedules of reinforcement were programmed by silent transistor circuitry (BRS Foringer 200 series). After completion of the scheduled response requirement, one banana pellet or one drug injection was automatically dispensed in a train of pulses. Each pulse dispensed 10 Lambda of fluid. The operation of the injection pump (Model 1302 Lambda Pump®, Harvard Apparatus Co., Inc., Millis, MA) was audible to the monkey.

The conditions of food availability and drug availability and time-out (when responses had no programmed consequence) each were associated with a colored stimulus light (S+), projected on a translucent Plexiglas® response key in the center of the operant panel. When a food pellet or drug injection was dispensed, the 3 vertically-oriented colored stimulus lights below the response key flashed for 1 sec. These stimulus light flashes (S+) were also used to signal the completion of each successive component of the second order schedule response requirement. A more detailed description of this apparatus has been published [20].

Study Designs

Acute effects of buprenorphine on food self-administration. The effects of an acute dose of buprenorphine (0.01–0.3 mg/kg, SC) on food self-administration were examined in 4 drug naive monkeys. These monkeys were initially trained on gradually increasing response requirements on a variable ratio (VR) schedule of food reinforcement in which the number of responses required for each reinforcement varied irregularly. On the final VR schedule (VR 16), an average of 16 responses produced a brief stimulus light (S+) and a 1 g banana pellet. Once behavior was stable, the schedule was changed to a second order schedule. The monkey was required to complete more than one VR 16 response requirement, and each was followed only by a brief stimulus light (S+). The final second order schedule required completion of 4 consecutive VR 16 components before onset of a brief stimulus light (S+) and delivery of a food pellet. The basic schedule was a second order fixed ratio (FR 4) schedule with VR 16 components (FR 4 [VR 16:S]) which required an average of 64 responses for each food pellet.

After food self-administration was stable on the final second order schedule, monkeys were given a single subcutaneous injection of either saline, or buprenorphine at a dose of 0.01, 0.03, 0.1, and 0.3 mg/kg, SC one hour before the 11:00 a.m. food session; the first of four food sessions run each day at 4 hour intervals. Buprenorphine doses were given in an ascending order. Saline and each dose of buprenorphine was repeated twice after a 72 hour interval.

Effects of chronic buprenorphine self-administration on food self-administration. The effects of buprenorphine 0.01–0.1 mg/kg injection) and heroin (0.01–0.1 mg/kg/injection) on food self-administration were examined under conditions where drug self-administration was maintained on a second order schedule and on a progressive ratio schedule. In both conditions, drug and food self-administration were maintained on the same second order schedule of reinforcement for a minimum of 40 sessions over 10 days, or until food and drug self-administration were stable. The basic reinforcement schedule was a second order

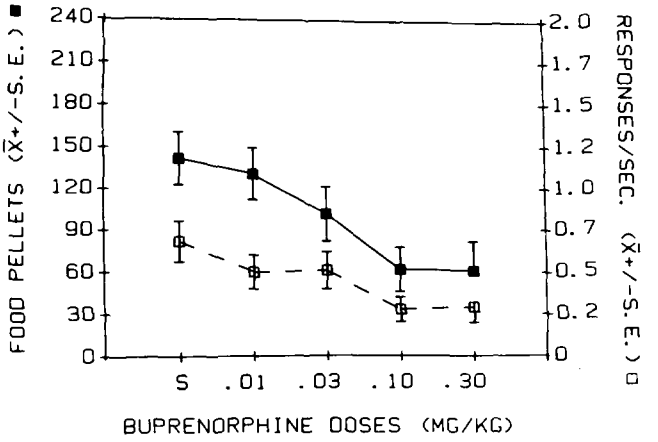

FIG 1. Effects of an acute dose of saline or buprenorphine on food maintained responding. Saline and buprenorphine doses (0.01–0.30 mg/kg) are shown on the abscissa. Average food pellets earned in 4 post-drug food sessions distributed over 20 hours are shown on the left ordinate (black squares). Responses per second are shown on the right ordinate (open squares). Each data point represents an average of 32 food self-administration sessions.

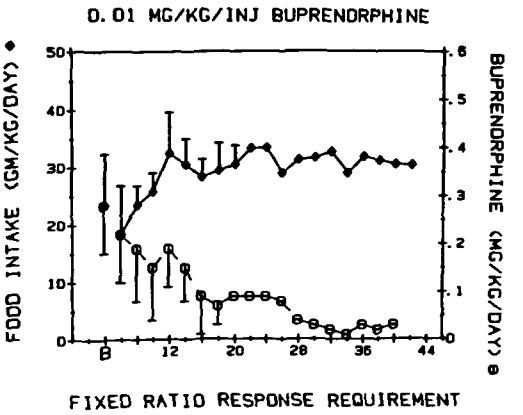

FIG. 2. The effects of chronic buprenorphine self-administration (0.01 mg/kg/injection) on food self-administration. Food intake in g/kg/day is shown on the left ordinate (mean±S.E.). Total daily buprenorphine intake (mg/kg) is shown on the right ordinate (mean±S.E.). Increasing fixed ratio response requirements on a second order FR (VR 16:S) schedule of reinforcement are shown on the abscissa. B denotes a 10 day (40 session) baseline on an FR 4 VR 16:S reinforcement schedule. Each data point up to an FR 18 represents an average of 3 or 4 animals. Each data point without a standard error is an average of 2 animals.

FR 4 (VR 16:S) which required an average of 64 responses for each food pellet or drug injection. An average of 16 responses on a variable ratio schedule (VR 16) produced a brief colored stimulus light (S+) and a drug injection or a food pellet was delivered only after a fixed ratio of 4 (FR 4) of the VR 16 response requirements were completed.

In the progressive ratio studies, food-maintained responding was controlled by an FR 4 (VR 16:S), but the number of responses required for each drug injection was systematically increased [14,18]. The value of the fixed ratio (FR) component of the second order schedule was progressively increased in units of 2, i.e., from FR 4 to FR 6 to FR 8 to FR 10, etc. which increased the average response requirement for each drug injection from 64 to 96 to 128 to 160, respectively. Each increase in the FR schedule component was run for 8 sessions over 2 days. Progressive increases in the response requirement for drug injections were continued until the monkey stopped responding for drug for 2 consecutive days, i.e., the "break-point." The immediately preceding response requirement for a single drug injection was recorded as being the maximum number of responses that the monkey would emit for that dose of that drug [14,18].

Once the "break-point" at a single drug dose was determined, the monkey was returned to the baseline schedule requirement (FR 4 [VR 16:S]) of the same drug dose until drug self-administration resumed. Monkeys were then given access to the next dose of a drug and run at the basic second order schedule response requirement until drug self-administration was stable over 40 consecutive sessions or 10 days. The progressive ratio procedure was then repeated as before. Four doses of buprenorphine over a range of 0.01 to 0.10 mg/kg/injection were studied in five monkeys. All monkeys were not studied at every dose of each drug. Three doses of heroin over a range of 0.01 to 0.10 mg/kg/injection were studied in two monkeys. Monkeys were exposed to an ascending series of doses of buprenorphine and heroin.

Procedures

Daily sequence of conditions. Food and drugs were available 4 times each day, 7 days a week. During the acute dose studies, food sessions began at 11 a.m., 3 p.m., 7 p.m. and 7 a.m. During progressive ratio studies, food sessions began at 11 a.m., 3 p.m., 7 p.m. and 11 p.m. each day and drug sessions began an hour later at 12 noon, 4 p.m., 8 p.m., and 12 midnight. Each food or drug session lasted either one hour or until 65 food pellets or 20 drug injections were delivered. The chamber was dark between 1 a.m. and 7 a.m. each day. Cleaning and weighing were completed in the morning before the 11 a.m. food session.

Drugs. Buprenorphine HCl and heroin (3,6-diacetyl morphine HCl) were obtained from the National Institute on Drug Abuse (Rockville, MD). Buprenorphine HCl was dissolved in water and adjusted to pH 4 with HCl to make an 0.30 mg/ml solution. Heroin HCl was dissolved in normal saline. Solutions were diluted to the appropriate concentration for individual monkeys and passed through a Millipore filter to remove pyrogens before IV administration. Doses are expressed as the hydrochloride salts. Solutions were checked daily to ensure that no precipitate had formed. Fresh solutions were prepared every 7 to 10 days.

Data analysis

Analysis of variance for repeated measures was used to evaluate changes in food self-administration at each buprenorphine dose per injection [17]. When significance between treatment groups was detected, LSD (least squares or weighted squared difference), followup tests were performed to identify specific data points that were significantly different [17]. Changes in food self-administration in comparison to the drug-free baseline after acute administration of buprenorphine was examined with *t*-tests for two means (one tailed) [16].

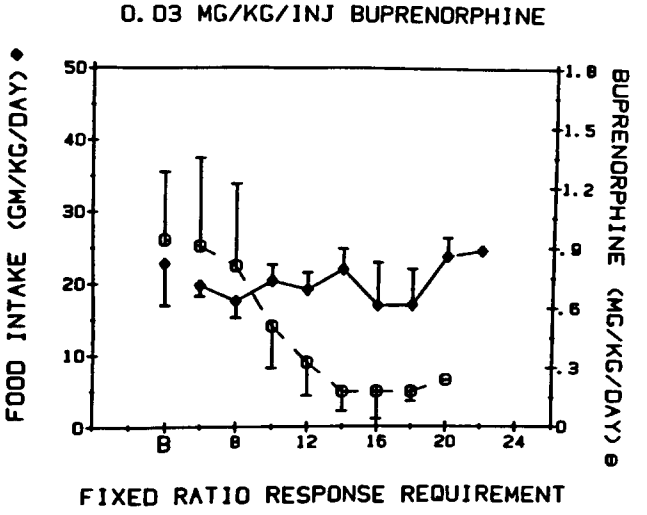

FIG 3. The effects of chronic buprenorphine self-administration (0.03 mg/kg/injection) on food self-administration. Food intake in g/kg/day is shown on the left ordinate (mean±S.E.). Total daily buprenorphine intake (mg/kg) is shown on the right ordinate (mean±S.E.). Increasing fixed ratio response requirements on a second order FR (VR 16:S) schedule of reinforcement are shown on the abscissa. B denotes a 10 day (40 session) baseline on an FR 4 VR 16:S reinforcement schedule. Each data point up to an FR 18 represents an average of 3 or 4 animals. Each data point without a standard error represents a single monkey.

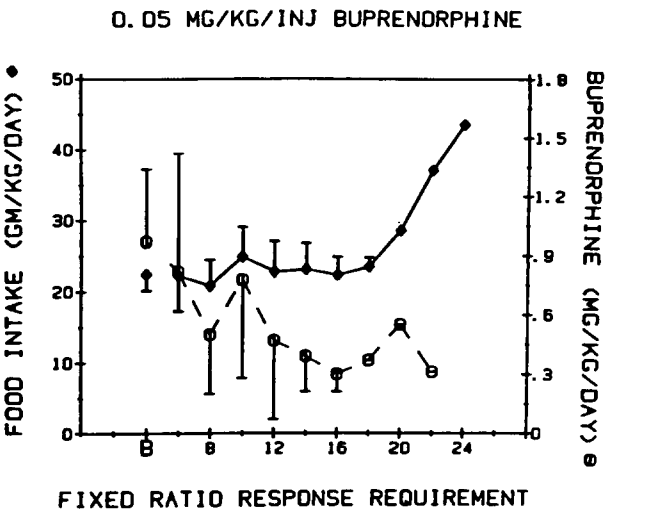

FIG 4. The effects of chronic buprenorphine self-administration (0.05 mg/kg/injection) on food self-administration. Food intake in g/kg/day is shown on the left ordinate (mean±S.E.). Total daily buprenorphine intake (mg/kg) is shown on the right ordinate (mean±S.E.). Increasing fixed ratio response requirements on a second order FR (VR 16:S) schedule of reinforcement are shown on the abscissa. B denotes a 10 day (40 session) baseline on an FR 4 (VR 16:S) reinforcement schedule. Each data point up to an FR 16 represents an average of 3 or 4 animals. Each data point without a standard error represents an average of 2 animals.

RESULTS

Effects of Acute Buprenorphine Administration on Food Maintained Responding

The effects of acute buprenorphine administration on food pellets earned and rate of food-maintained responding are shown in Fig. 1. There were no significant changes from saline control levels in either the number of food pellets earned or response rates after buprenorphine doses of 0.01 and 0.03 mg/kg. Food pellets earned declined gradually from an average of 142 (±19) after saline pre-treatment to an average of 102 (±21) after pre-treatment with 0.03 mg/kg of buprenorphine. Response rates decreased from 0.68 (±0.12) resp/sec after saline pre-treatment to 0.51 (±0.10) resp/sec after pre-treatment with 0.03 mg/kg of buprenorphine.

Pre-treatment with higher doses of buprenorphine (0.10 and 0.30 mg/kg), significantly suppressed food pellets earned in comparison to saline control levels ($p<0.01$). The average number of food pellets earned after 0.10 and 0.30 mg/kg of buprenorphine were equivalent, 62.5 (±16) and 61.2 (±21) respectively. The rate of food-maintained responding also declined significantly from saline control levels after acute buprenorphine administration ($p<0.01$).

Analysis of the immediate (same-day) effects of buprenorphine on food acquisition during the first food session, one hour after buprenorphine, showed dose dependent suppression of food-maintained responding. After low doses of buprenorphine (0.01 and 0.03 mg/kg), monkeys worked for food in 4 of 8 and 6 of 8 sessions respectively. After high buprenorphine doses (0.10 and 0.30 mg/kg), monkeys worked for food in only 2 or 3 of a possible 8 sessions. These suppressive effects of buprenorphine were greatly attenuated by the start of the second food session, five hours after buprenorphine administration. Monkeys worked for food in 6 or 7 of the 8 sessions after all doses of buprenorphine.

The delayed (next-day) effects of buprenorphine on food-maintained responding were also dose dependent. After pre-treatment with low doses of buprenorphine (0.01 and 0.03 mg/kg), food-maintained responding remained slightly depressed for 48 hours, but it was not significantly different from baseline levels. After an acute dose of 0.10 mg/kg of buprenorphine, the total number of pellets earned were within 4 percent of the saline control baseline within 48 hours after buprenorphine administration. However, after pre-treatment with an 0.30 mg/kg dose of buprenorphine, food-maintained responding was suppressed for up to 72 hours. The persistent suppressive effects of this dose of buprenorphine significantly reduced both food intake ($p<0.02$) and rate of food-maintained responding ($p<0.05$).

Effects of Chronic Buprenorphine Self-Administration on Food Self-Administration

The effects of chronic buprenorphine self-administration on food intake during the progressive ratio studies are shown in Figs. 2 through 5. Baseline buprenorphine self-administration increased from less than 0.3 mg/kg/day to over 2.8 mg/kg/day as the dose per injection increased from 0.01 to 0.10 mg/kg/injection. However, food intake during the 10 day baseline periods was equivalent at each dose of buprenorphine and ranged from 22.39 (±5.62) to 23.44 (±9.3) g/kg/day.

During the 10 day baseline of buprenorphine (0.01 and 0.03 mg/kg/injection) self-administration on the FR 4 (VR 16:S) schedule, monkeys self-administered an average of 0.28 (±0.07) and 0.94 (±0.22) mg/kg/day of buprenorphine and 23.44 (±9.3) and 22.83 (±5.85) g/kg/day of food (Figs. 2

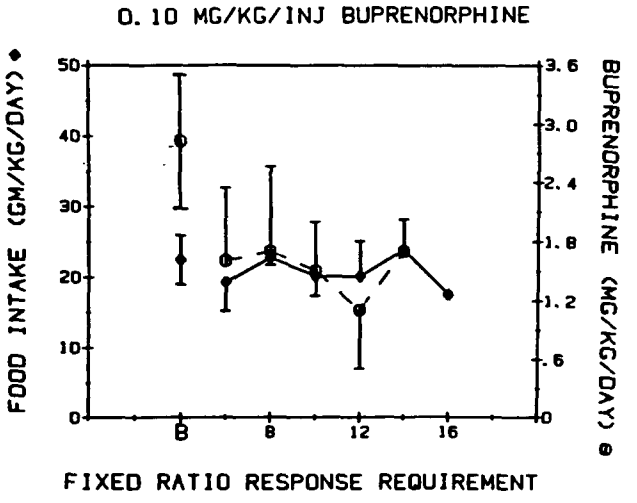

FIG 5. The effects of chronic buprenorphine self-administration (0.10 mg/kg/injection) on food self-administration. Food intake in g/kg/day is shown on the left ordinate (mean±S.E.). Total daily buprenorphine intake (mg/kg) is shown on the right ordinate (mean±S.E.). Increasing fixed ratio response requirements on a second order FR (VR 16:S) schedule of reinforcement are shown on the abscissa. B denotes a 10 day (40 session) baseline on an FR 4 (VR 16:S) reinforcement schedule. Each data point up to an FR 14 represents an average of 3 monkeys. The FR 16 data point is an average of 2 monkeys.

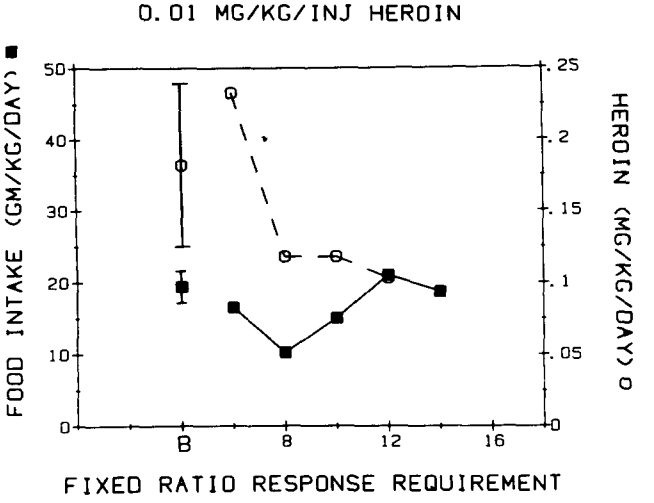

FIG 6. The effects of chronic heroin self-administration (0.01 mg/kg/injection) on food self-administration. Food intake in g/kg/day is shown on the left ordinate (mean±S.E.). Total daily heroin intake (mg/kg) is shown on the right ordinate. Increasing fixed ratio response requirements on a second order FR (VR 16:S) schedule of reinforcement are shown on the abscissa. B denotes a 10 day (40 session) baseline on an FR 4 (VR 16:S) reinforcement schedule. Each data point represents an average of two monkeys.

and 3). Although daily buprenorphine intake gradually declined as the progressive ratio response requirement for each buprenorphine injection increased, food self-administration increased slightly (Fig. 2) or remained relatively stable (Fig. 3). Evaluation of these data with analysis of variance showed no significant changes in food self-administration through time.

Figure 4 shows data for four monkeys that self-administered 0.97 (±0.25) mg/kg/day of buprenorphine at a dose of 0.05 mg/kg injection. Analysis of variance showed that food intake changed significantly over the time of observation ($p<0.01$). Food increased considerably over baseline levels at fixed ratio response requirements of 22 and 24 when daily drug intake averaged 0.62 and 0.31 mg/kg/day. However, these points represent data from only two monkeys.

Figure 5 shows data for three monkeys that self-administered 0.10 mg/kg/injection of buprenorphine. During the 10 day baseline, buprenorphine intake averaged 2.82 (±0.85) mg/kg/day and food intake averaged 22.39 (±5.62) g/kg/day. At progressive ratio values of FR 6 to FR 14, food intake remained relatively stable although drug intake fell below 2.0 mg/kg/day. Analysis of variance showed no significant changes in food intake over time.

Effects of Chronic Heroin Self-Administration on Food Self-Administration

The effect of chronic heroin self-administration on food intake during progressive ratio studies are shown in Figs. 6–8. Analysis of variance showed no statistically significant changes in food self-administration over time. Daily heroin intake gradually decreased as progressive ratio response requirements increased, but this was not accompanied by changes in food self-administration. For example, monkeys shown in Fig. 6 self-administered an average of 0.18 (±0.175) mg/kg/day of heroin (0.01 mg/kg/injection) during the baseline and total daily dosage fell to 0.10 mg/kg/day with no significant change in food self-administration. Figure 7 shows monkeys that self-administered 1.12 (±0.54) mg/kg/day of heroin (0.05 mg/kg/injection) during baseline. Total daily heroin dosage increased to above 1.5 mg/kg, then fell to 0.59 mg/kg with relatively constant food self- administration levels. Figure 8 shows monkeys that self-administered 1.79 (±0.62) mg/kg/day of heroin during baseline and daily dosage fell to 0.55 mg/kg/day with no significant change in food self-administration across 20 days of observation.

DISCUSSION

Effects of Acute Buprenorphine Administration on Food-Maintained Responding

Low doses of buprenorphine (0.01 to 0.03 mg/kg) had no significant effect on food-maintained responding but after high buprenorphine doses (0.10 and 0.30 mg/kg), both number of food pellets earned and rate of response were significantly depressed (Fig. 1). These findings are consistent with previous studies of the acute effects of buprenorphine on food-maintained responding, however, the dose required to effectively suppress food-maintained responding differs among species. In squirrel monkeys, buprenorphine doses as low as 0.003 mg/kg decreased response rates maintained under a multiple FR FI schedule of food presentation [5]. A buprenorphine dose (0.03 mg/kg) that had no significant effect on food-maintained responding in rhesus monkeys, completely eliminated responding in squirrel monkeys [5]. Baboons and Macaque monkeys both were considerably

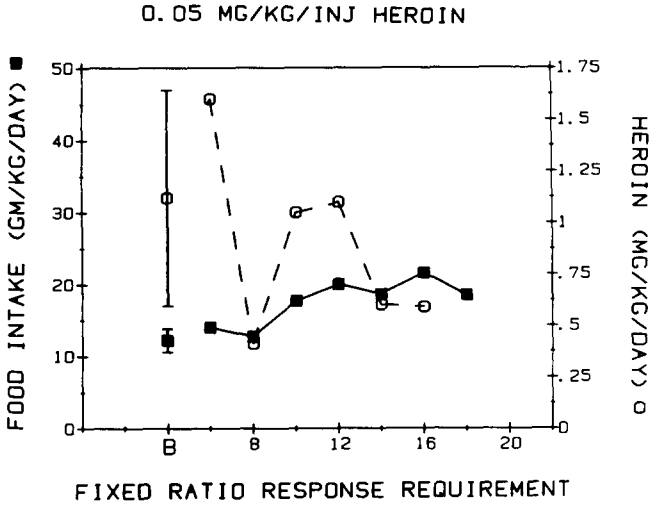

FIG 7. The effects of chronic heroin self-administration (0.05 mg/kg/injection) on food self-administration. Food intake in g/kg/day is shown on the left ordinate (mean±S.E.). Total daily heroin intake (mg/kg) is shown on the right ordinate. Increasing fixed ratio response requirements on a second order FR (VR 16:S) schedule of reinforcement are shown on the abscissa. B denotes a 10 day (40 session) baseline on an FR 4 (VR 16:S) reinforcement schedule. Each data point represents an average of two monkeys.

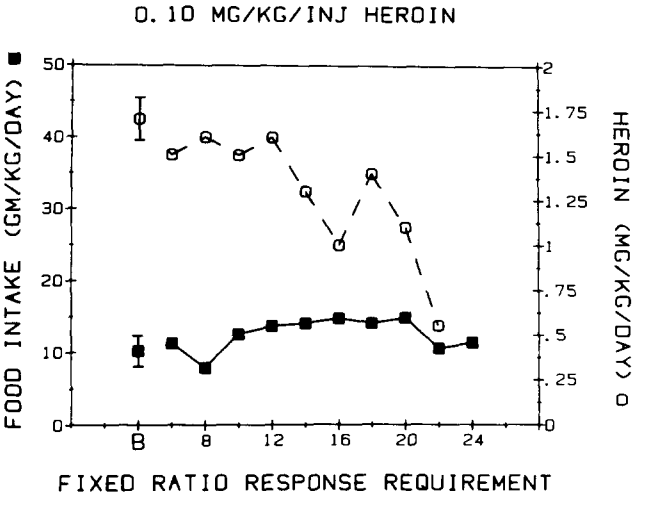

FIG 8. The effects of chronic heroin self-administration (0.10 mg/kg/day) on food self-administration. Food intake in g/kg/day is shown on the left ordinate (mean±S.E.). Total daily heroin intake (mg/kg) is shown on the right ordinate. Increasing fixed ratio response requirements on a second order FR (VR 16:S) schedule of reinforcement are shown on the abscissa. B denotes a 10 day 40 session) baseline on an FR 4 (VR 16:S) reinforcement schedule. Each data point represents an average of two monkeys.

more resistant to the acute effects of buprenorphine than squirrel monkeys. A buprenorphine dose of 0.10 mg/kg was the lowest buprenorphine dose that suppressed food intake in both Macaque monkeys and baboons (unpublished data, S. E. Lukas). In baboons, acute administration of 0.10 mg/kg of buprenorphine, suppressed response rates for food on an FR 50 schedule by 75%. However, at higher buprenorphine doses (1.0 to 3.2 mg/kg) response rates remained between 50 and 70 percent of control. An acute buprenorphine dose of 10 mg/kg suppressed response rates to about 85% of control levels in baboon (unpublished data, S. E. Lukas).

The duration of buprenorphine-induced suppression of food-maintained responding also differed among species. In squirrel monkeys, buprenorphine doses of 0.10 to 1.0 mg/kg suppressed food-maintained responding for 2–3 days [5]. In the present study, acute high doses of buprenorphine rapidly suppressed food-maintained responding but these effects did not persist. These findings are consistant with the pharmacokinetic profile of buprenorphine [2,28]. In humans, peak buprenorphine levels were reached within 1 to 5 minutes after intravenous and intramuscular administration [2]. In rhesus monkey, peak plasma levels of buprenorphine (1.0 mg/kg) were observed within one hour after subcutaneous administration and the half-life was 1.12 hours for the first phase and 4.789 hours for the second phase [28]. The recovery of food-maintained responding by the day after buprenorphine administration is also consistent with these pharmacokinetic data. Yet Bullingham and co-workers [2] noted that the analgesic effects of buprenorphine far outlast measurable levels in plasma.

Effects of Chronic Buprenorphine Self-Administration on Food Self-Administration

In contrast to the dose dependent suppression of food-maintained responding observed after acute buprenorphine administration (Fig. 1), there were no significant effects of chronic buprenorphine self-administration on food self-administration (Figs. 2–5). The average daily doses of buprenorphine self-administered at 0.03 to 0.10 mg/kg/injection were initially three to nine times higher than the highest dose studied in the acute buprenorphine administration paradigm (Figs. 3–5). When buprenorphine intake fell to 30 or 40 percent of baseline levels, food self-administration remained constant. Daily buprenorphine intake fell from over 0.9 mg/kg during baseline to approximately 0.30 mg/kg/day with no corresponding changes in food intake (Figs. 3 and 4). Food intake increased significantly in two monkeys when buprenorphine self-administration (mg/kg/day) was equivalent to or double the acute dose that significantly suppressed food intake (cf. Fig. 1 and Fig. 4). At higher doses per injection (0.10 mg/kg/injection), total daily buprenorphine intake decreased from over 2.5 mg/kg/day to approximately 1.5 mg/kg/day with no corresponding changes in food intake (Fig. 5). In one monkey, buprenorphine doses as high as 5 mg/kg/day did not suppress food intake and gradual decreases in buprenorphine self-administration were not accompanied by increased food self-administration.

Stable food-maintained responding during chronic buprenorphine self-administration is consistent with previous reports from this laboratory and in baboon (unpublished data, S. E. Lukas). In 1981, we reported that self-administration of buprenorphine up to a dose of 2.95 (±0.24) mg/kg/day had no appreciable effect on food self-administration maintained on an FR 4 (VR 16:S) reinforcement schedule [23]. In 1983, we reported that a single daily injection of buprenorphine over a range of 0.14 to 0.789 mg/kg IV had no significant effect on food self-administration maintained under the same second-order schedule [19]. Similarly, in baboon, buprenorphine self-administration (0.01 to 1.0 mg/kg/injection) at average daily doses of 0.52 (±0.02) to 78.8 (±35) mg/kg did not change

food self-administration (g/kg) significantly from control levels. The mixed agonist-antagonists, butorphanol and nalbuphine, also did not suppress food intake over a dose range of 0.001–0.1 mg/kg/injection. Buprenorphine (3.2 mg/kg/injection) significantly suppressed food self-administration in baboons at an average daily dose of 18.6 (±2.7) mg/kg (unpublished data, S. E. Lukas).

The lack of robust effects of buprenorphine on food intake during chronic administration could be due to (1) changes in buprenorphine's pharmacokinetics during chronic exposure, (2) differences in effective drug dose during acute and chronic drug administration studies or (3) tolerance to buprenorphine's direct, disruptive effects. The first two hypotheses cannot adequately explain the differences between the acute (Fig. 1) and chronic data (Figs. 2–5). Changes in buprenorphine's pharmacokinetics during chronic exposure probably cannot account for the lack of effect on food-maintained responding, since repeated administration of buprenorphine to rhesus monkey (1.0 mg/kg q 6 hr for 4 weeks) increased the biological half-life of buprenorphine by threefold [28]. Moreover, the difference between a single bolus dose of buprenorphine, and distribution of the total daily dose between 4 drug self-administration sessions over 24 hours does not seem sufficient to explain the differences between the acute and chronic buprenorphine exposure data. For example, a single acute dose of 0.10 mg/kg of buprenorphine significantly suppressed food-maintained responding (Fig. 1), but 4 times that dose (0.40 mg/kg/day) during chronic drug self-administration had no effect on food-maintained responding (Figs. 3–4). Similarly, acute administration of 0.30 mg/kg of buprenorphine significantly suppressed food-maintained responding (Fig. 1) whereas over 4 times that dose (1.2 mg/kg) did not affect food-maintained responding during chronic drug self-administration conditions (Fig. 5).

The most parsimonious hypothesis to account for the differences between acute and chronic effects of buprenorphine on food-maintained responding appears to be the development of tolerance to buprenorphine's effects. This interpretation is necessarily inferential since this study was not designed to measure tolerance per se. But this hypothesis is consistent with our clinical observations that tolerance to the opioid agonist-like side effects of buprenorphine developed within 21 days [24]. However, this hypothesis is not consistent with observations in squirrel monkey where repeated administration of 0.01 mg/kg/day of buprenorphine for 17 days continued to suppress food-maintained rates of responding [5]. The development of tolerance to opioid mixed agonist-antagonist drugs may differ in higher primates with convoluted brains (humans and Macaque monkeys) and lower primates such as squirrel monkeys which have lissencephalic brains. The dose-time parameters required to induce tolerance to buprenorphine in Macaque monkeys remain to be determined. The mechanism of tolerance to buprenorphine is unknown, but it is possible that continuous occupation of the receptor decreases buprenorphine's agonist effects and increases its antagonist effects. This notion is consistent with the agonist "ceiling effect" of buprenorphine reported in several systems [10,13].

Heroin Effects on Food-Maintained Responding

Chronic heroin self-administration also had no significant effects on food self-administration. Abrupt increases in total daily heroin dose from 0.18 to 0.23 mg/kg/day (Fig. 6) and from 1.12 to 1.60 mg/kg/day (Fig. 7) were not associated with an increase or a decrease in food self-administration. Moreover, decreases in daily heroin self-administration from high levels of 1.79 to 0.550 mg/kg/day also were not associated with changes in food self-administration (Fig. 8). These data are inconsistent with recent studies indicating that opioid agonists have a facilitatory effect on feeding behavior [25, 27, 29]. The present findings are also inconsistent with previous reports that opiate agonist administration was associated with a suppression of food intake [3, 4, 7]. It appears that monkeys in the present study also became tolerant to the effects of heroin since food self-administration remained constant over a wide range of heroin doses.

Relative Role of Agonist and Antagonist Effects on Food-Maintained Behaviors

Although opioid agonists are usually associated with increased food intake and antagonists with decreased food intake [25,27], it is unclear whether opioid agonist or antagonist effects were primarily responsible for suppression of food-maintained responding after acute buprenorphine administration (Fig. 1). Diprenorphine is the antagonist component of buprenorphine [13] and it has been shown to suppress rates of food-maintained responding [5] and body weight [6] in squirrel monkeys but comparable data are not available for rhesus monkey. If the acute suppression of food-maintained responding by buprenorphine does reflect predominately antagonist effects, a more protracted suppression of food-maintained responding would be expected. Behavioral and physiological measures suggest that the opioid agonist effects of buprenorphine persist for at least 6 hours while its opioid antagonist effects persist for up to 72 hours [10,13]. Further studies will be necessary to clarify the relative contribution of the agonist and antagonist components of opioid mixed agonist-antagonist drugs to effects on food-maintained behavior.

ACKNOWLEDGEMENTS

This research was supported in part by Grants DA02519, DA00101 and DA00064 from the National Institute on Drug Abuse, ADAMHA, and Grant RR05484 awarded to McLean Hospital by the Biomedical Research Support Program, Division of Research Resources, NIH. We thank Andrea Baughn and Mario Spinelli for excellent technical assistance in the conduct of these studies. We are grateful to Dr. Prabhat Sehgal for veterinary consultation.

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