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BTCP is a potent reinforcer in rats: Comparison of behavior maintained on fixed- and progressive-ratio schedules

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Abstract

N-[1-(2-Benzo[*b*]thiophenyl)cyclohexyl]piperidine (BTCP) is a phencyclidine (PCP) derivative that acts as a potent dopamine (DA) reuptake inhibitor. Earlier studies have shown that BTCP can substitute for the reinforcing effects of cocaine. Therefore, the aim of the study was to further characterize the reinforcing effects of BTCP. The reinforcing actions of BTCP were compared to those of cocaine at equimolar concentrations in drug-naïve rats. Two groups of animals were implanted with jugular catheters and trained to intravenously self-administer BTCP or cocaine (0.25 mg/infusion) on a fixed-ratio five schedule (FR 5) of reinforcement. Both BTCP and cocaine produced comparable inverted U-shaped dose–effect curves on this schedule over doses of 0.03, 0.06, 0.125, and 0.25 mg/infusion. Two doses (0.125 and 0.25 mg/infusion) that produced reliable self-administration in all the animals for cocaine and BTCP were then tested on a progressive-ratio schedule. At each dose, BTCP supported higher breaking points (BPs) than cocaine. The results demonstrate that rats readily acquire responding maintained by BTCP and suggest that BTCP may have greater reinforcing effects than cocaine at equimolar concentrations.

Keywords: Cocaine; BTCP; Dopamine reuptake inhibitor; Self-administration; Fixed ratio; Progressive ratio

1. Introduction

Cocaine is a highly addictive substance that is abused by humans worldwide (Warner, 1993; Higgins, 1997). Cocaine also acts as a potent reinforcer in laboratory animals (Pickens and Thompson, 1968; Koob, 1992; Stolerman, 1992; Woolverton and Johnson, 1992). It is widely accepted that the addictive and reinforcing actions of cocaine are dependent on the drug's ability to block the dopamine transporter (DAT), thereby increasing dopamine (DA) neurotransmission (Kuhar, 1992; Ritz et al., 1987; Parsons et al., 1998a; Woolverton, 1992).

N-[1-(2-Benzo[*b*]thiophenyl)cyclohexyl]piperidine (BTCP) is a phencyclidine (PCP) derivative that has a high affinity for the DAT (Chaudieu et al., 1989; Vignon et al., 1988) but binds to a different site on the transporter than cocaine (Maurice et al., 1991a,b, 1993; Akunne et al., 1994). BTCP, like cocaine, inhibits DA uptake (Chaudieu et al., 1989; Vignon et al., 1988) and is, in fact, one of the most potent inhibitors of DA reuptake known to date (Chaudieu et al., 1989; Deleuze-Masquefa et al., 1997, 2000). Like cocaine, BTCP has a rapid onset of action (Deleuze-Masquefa et al., 2000) and inhibits the transport of serotonin (5-HT) and noradrenaline (Lebel et al., 1994; Rothman et al., 1993). While BTCP is a PCP derivative, it has low affinity for the PCP receptor itself (Chaudieu et al., 1989; Vignon et al., 1988). Moreover, in contrast to the noncompetitive *N*-methyl-D-aspartate (NMDA) antagonists MK-801 and PCP, BTCP does not antagonize NMDA-induced convulsions in mice (Koek et al., 1989). Thus, the pharmacological mechanism of action of BTCP does not seem to be linked to activity at the NMDA receptors as might be inferred from this compound's chemical structure. There is much evidence that inhibition of DA reuptake accounts for the behavioral cocaine-like effects of BTCP (Giros et al., 1996; Hurd et al., 1997; Johanson and Fisch-

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man, 1989; Silvia et al., 1997). Like cocaine, BTCP increases extracellular DA levels in the striatum and the nucleus accumbens (Martin-Fardon et al., 1996; Maurice et al., 1992), stimulates locomotor activity in rats (Slimani et al., 1988) and mice (Ilagouma et al., 1993; Koek et al., 1989), and produces locomotor sensitization in rats (Martin-Fardon et al., 2000). BTCP also substitutes for cocaine in drug discrimination studies (Koek et al., 1989), can substitute for cocaine in a self-administration test (Martin-Fardon and Weiss, 2000), and produces similar breaking points (BPs) compared to cocaine on a progressive-ratio schedule of reinforcement in rats previously trained to self-administer cocaine (French et al., 1995). These earlier findings led to the hypothesis that BTCP and cocaine exert similar rewarding and reinforcing effects and, therefore, that BTCP can substitute for some of cocaine's behavioral actions. Such a profile would identify this compound as a possible agonist pharmacotherapeutic candidate for the treatment of cocaine addiction (Rothman, 1990; Kreek, 1997). However, the behavioral and reinforcing profiles of BTCP have not yet been fully characterized, especially with regard to its intrinsic abuse liability and, in particular, in animals that do not have any stimulant experience. The goal of the present study was, therefore, to investigate whether BTCP and cocaine have differential reinforcing actions using fixed- and progressive-ratio schedules of reinforcement in drug-naïve rats.

2. Methods

2.1. Subjects

Thirteen male Wistar rats (Beckman Laboratories, The Scripps Research Institute, La Jolla, CA) weighing 200–250 g upon arrival were used. The rats were group-housed (two to three per cage) in a temperature- and humidity-controlled vivarium on a 12/12-h light/dark cycle (lights off at 6:00 p.m.) with ad libitum access to food and water, except during operant training for food reinforcement (see Self-administration training). All animals were handled once daily for 5 min during the first week after arrival. At the beginning of the dose–response evaluation, the animals weighed 447.6 ± 10.8 g ($N = 13$), and at the beginning of the progressive-ratio test, they weighed 512.0 ± 11.1 g ($N = 12$). All procedures were conducted in strict adherence to the National Institutes of Health Guide for the Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985) and approved by the Institutional Animal Care and Use Committee of The Scripps Research Institute.

2.2. Drugs

BTCP was a gift from Dr. Jean-Marc Kamenka (CNRS UPR 1086, ENSCM, Montpellier, France). It was dissolved in sterile saline and filtered sterile with 0.22-μm filters (Fisher Scientific, Pittsburgh, PA). Cocaine was obtained from the National Institute on Drug Abuse and was dissolved in sterile physiological saline and filtered sterile. All BTCP solutions were prepared fresh each day.

2.3. Surgery

Rats were prepared with chronic silastic jugular catheters under halothane anesthesia (1.5–2.0%) as previously described (Caine et al., 1993). Briefly, the catheters consisted of silastic tubing (length 14 cm) fitted to a guide cannula bent at a right angle, encased in dental cement, and anchored with 2.5 cm^2 durable mesh. The tubing was passed subcutaneously from the animal's back to the right external jugular vein, which was punctured with a 25-gauge needle. Silastic tubing (3.7 cm) was inserted into the vein and gently tied with suture thread. All the animals were allowed to recover for a minimum of 10 days and were treated with antibiotic (TICAR 20 mg, iv) during the first 5 days postsurgery. Catheter patency was maintained by flushing with 0.1 ml of sterile heparin/saline solution (30 USP units/ml) before and after each self-administration session. Rats with compromised catheters were implanted with a new catheter in the contralateral jugular vein when possible, or excluded from the experiment.

2.4. Behavioral testing apparatus

Self-administration training and testing were conducted in standard $29 \times 24 \times 19.5$ cm operant conditioning chambers located inside ventilated sound-attenuating cubicles (BRS/LVE, Laurel, MD). The chambers were equipped with a retractable lever positioned 4 cm above the grid floor on the right side of the front panel with a white cue light located 6 cm above the lever. A counterbalancing arm fitted with a single-channel liquid swivel (Model 375, Instech Labs, Plymouth Meeting, PA) was suspended above the operant chamber. The inlet of the liquid swivel was connected with polyethylene tubing to a 10-ml syringe containing the drug solution, and the liquid swivel outlet was connected via a cannula connector (C313G-5UP, Plastics One, Roanoke, VA) to the chronic jugular catheter on the rat's back. Intravenous infusions were administered by activation of a syringe pump (Razel Scientific Instruments, Stamford, CT) located outside the sound-attenuating boxes. Behavioral testing protocols and data collection were controlled by an IBM-compatible microcomputer.

2.5. Self-administration training

Prior to implantation of intravenous catheters, rats were food restricted for 24 h and then maintained on 20 g standard laboratory chow per day. During this period, the animals were trained to lever-press for 45 mg food pellets (PJ Noyes, Lancaster, NH) to a fixed ratio 5 (FR 5), time-out 20 s (TO 20) schedule. Operant training for food-maintained

behavior was continued until a criterion of at least 50 completed ratio requirements per 30-min session over three consecutive days was reached. All house lights and stimulus lights were off during the food and cocaine self-administration sessions, except after the completion of each ratio requirement which resulted in delivery of a food pellet and illumination of the cue light above the lever for 20 s. The animals were then returned to ad libitum food availability and, 2–3 days later, surgically implanted with chronic jugular catheters.

Ten days after recovery from surgery, cocaine or BTCP self-administration began in daily 2-h sessions conducted 5 days per week. Self-administration sessions were initiated by administration of two noncontingent intravenous drug infusions (0.25 mg/0.1 ml/infusion, delivered over 4 s), which signaled the start of each session. During the dose–response study and the progressive-ratio tests, these two free injections signaled the start of the session as well as the dose of cocaine or BTCP available. Subsequently, the right lever was extended into the operant chamber at which time cocaine or BTCP (at the training dose of 0.25 mg/0.1 ml) was made available on an FR 5 schedule of reinforcement. The completion of each ratio requirement resulted in an infusion of cocaine or BTCP and concurrent illumination of the white cue light for a 20-s period. During this 20-s time-out period, the lever remained inactive to prevent accidental overdosing. Food and water were provided ad libitum in the operant chambers only during the progressive-ratio tests. Testing began once all rats reached stable baselines of responding, defined as no more than 10% variation of the mean of the total number of drug infusions over three consecutive sessions.

The 0.25-mg training dose for BTCP was selected on the basis of its molecular weight to permit comparison of the effects of this compound with those of cocaine. More specifically, since BTCP and cocaine have highly similar molecular weights (335.5 g/mol for BTCP and 339.8 g/mol for cocaine), choice of the 0.25-mg dose of BTCP provided for equimolar concentrations of the training doses for cocaine and BTCP ($\approx$7.4 mM).

It has been described earlier that under conditions of limited access to cocaine, rats maintain a highly constant level of cocaine intake over long periods of time, despite increases in the animal's body weight (Ahmed and Koob, 1998). This body weight-independent stability in cocaine intake has been interpreted as reflecting a constant "hedonic set point" in limited access cocaine self-administration models (Ahmed and Koob, 1998). Based on this earlier observation, the dose of cocaine and BTCP was held constant throughout the present experiment.

2.6. Behavioral testing procedures

2.6.1. Fixed-ratio dose–response curve

All experiments for the determination of the dose–response curve were conducted in 2-h limited-access self-administration sessions on an FR 5 schedule of reinforcement. Dose–effect functions for BTCP or cocaine-maintained responding were established by determining the total number of cocaine or BTCP infusions per 2 h session obtained by rats during self-administration of each of four different concentrations (0.03, 0.06, 0.125, and 0.25 mg/infusion). Eight animals were used to establish the BTCP dose–effect curve and five animals for the cocaine dose–response curve. To control for order effects, the animals were tested with the four different doses in a random sequence. A stability criterion of three consecutive self-administration sessions with less than $\pm$10% variation of the mean of the total number of infusions was established for each drug dose, and the total number of infusions was calculated for the last session that defined the baseline criterion. After completion of the dose–response tests, the rats again were given daily access to the training dose of BTCP or cocaine (0.25 mg/infusion) until stable baselines of self-administration were reestablished. Subsequently, the reinforcing effects of BTCP and cocaine (0.25 and 0.125 mg/infusions) were determined using a progressive-ratio schedule.

2.6.2. Progressive-ratio schedule

Under this schedule, the response requirement (i.e., the number of lever presses or ratio required to obtain a drug infusion) was increased in the following manner: for each of the first eight cocaine or BTCP infusions the ratio was increased by 1; for each of the next eight infusions the ratio was increased by 2; for each of the next eight cocaine or BTCP infusions the ratio was increased by 4; thereafter, the ratio was increased by 8 for each drug infusion (Caine and Koob, 1995). A 20-s time-out period followed all infusions during which the lever presses were recorded but had no scheduled consequences. The progressive-ratio sessions started at a ratio of 5 (i.e., the same ratio used in the fixed-ratio dose–response curve). Sessions were terminated when more than 1 h elapsed since completion of the last response requirement resulting in an infusion of cocaine or BTCP. The BP was defined as the highest ratio achieved in a session resulting in the delivery of a drug reinforcer. The time to reach the BP was defined as the total time elapsed since the beginning of the session to obtain the final infusion of cocaine or BTCP. The self-administration of 0.125 and 0.25 mg/infusion of cocaine or BTCP was examined using a within-subject design and was randomized between animals. The animals were the same as those used for the FR 5 dose–response determination. One rat in the BTCP group was lost because of catheter failure, reducing the number of animals to seven. Before changing cocaine or BTCP doses, animals had to meet a baseline criterion of three consecutive self-administration sessions with less than $\pm$10% variation of the mean of the total number of infusions, and the BP for each dose level was then systematically defined as the animal's performance on the third session.

2.7. Data analysis

Dose-dependent differences in the total number of infusions per 2-h session as well as the time course (per 10-min interval) were analyzed by two-way within-subjects ANOVA followed by Newman–Keuls and simple effects post hoc tests. For the progressive-ratio experiment, the dependent measure was the total number of infusions obtained per session, and this value was calculated for the last session that defined the baseline criterion. These values were then used for statistical analysis using a Student's *t* test between different doses. Although the BP (i.e., the highest ratio achieved) has been used as the dependent variable in progressive-ratio studies (Hodos, 1961), this measure can be difficult to analyze statistically because of the violation of the assumption of homogeneity of variance (e.g., Depoortere et al., 1993; Richardson and Roberts, 1996). The number of infusions earned per session is a natural logarithmic function of the highest completed ratio and, thus, this value does not violate the assumption of homogeneity of variance. Nonetheless, the BPs for cocaine and BTCP self-administration are presented also in the Results and figures as a qualitative measure of behavior, but were not used for statistical comparisons.

3. Results

3.1. Analysis of body weights between cocaine- and BTCP-trained animals

At the beginning of the dose–response study, the mean (±S.E.M.) body weight of the rats in the cocaine group was 437.2±19.4 g, and 519.6±22.5 g at the end of the experiment (i.e., after the progressive-ratio test). The mean (±S.E.M.) of the rats' body weight for the BTCP group was 454.1±13.3 g at the beginning of the dose–response study, and 533.0±26.3 g at the end of the study.

Comparison of the body weights of rats assigned to the cocaine vs. BTCP conditions during the dose–response study did not reveal any differences between groups nor an interaction between the four doses tested and the body weights of the two groups of animals.

As observed during the dose–response study, no significant weight differences existed between the two groups during the progressive-ratio tests, nor was there an interaction between the two doses tested and the weights of the two groups of animals. Therefore, the body weight range of the animals in the cocaine and BTCP groups was similar throughout the experiment.

3.2. Fixed-ratio dose–effect functions for cocaine self-administration

The mean (±S.E.M.) number of sessions required to reach the training criterion for cocaine self-administration (0.25 mg/infusion) on an FR 5, TO 20 schedule of reinforcement was 12.2±0.9. The animals then developed a regular pattern of intake throughout the 2-h self-administration session, characterized by densely spaced infusions at the beginning of the session (loading phase) followed by regular interinfusion intervals (maintenance phase) (Fig. 1A, inset). This typical self-administration pattern was reflected by a main effect for time [$F(11,77)=2.6$, $P<.05$] and confirmed by a significant difference between the number of infusions during the first 10 min (loading phase) and the rest of the session (maintenance phase) (Fig. 1A, inset; Newman–Keuls, $P<.05$).

Cocaine self-administration produced a characteristic inverted U-shaped dose–effect function (Fig. 1A, left panel) confirmed by a main effect for cocaine dose [$F(3,12)=7.8$; $P<.01$]. The mean (±S.E.M.) number of sessions to reach the baseline criterion at each dose of cocaine was the following: 0.03 mg/infusion, 5.4±0.9 sessions; 0.06 mg/infusion, 8.0±1.8 sessions; 0.125 mg/infusion, 4.2±0.8 sessions; 0.25 mg/infusion, 4.4±1.4 sessions. No statistical difference was found between the number of sessions required to meet the baseline criterion at each dose.

The two lower doses of cocaine (0.03 and 0.06 mg/infusion) available in the dose–response tests (Fig. 1A, left panel) did not maintain reliable self-administration. Self-administration of these doses was characterized by substantial variability of cocaine intake among rats during the loading phase as well as the rest of the session. At the 0.03-mg dose, responding was consistently low and randomly scattered throughout the 2-h session in all five rats with a mean (±S.E.M.) total number of infusion of 4.4±1.5 in 2 h (Fig. 1A, left panel). At the 0.06-mg/infusion dose, even greater variability between animals was observed. At this particular dose, different types of response patterns were observed such as response bursts during the first 10 min of the session followed by termination of responding in one rat (extinction-like pattern with early termination of responding), intermittent bursts of responding in one rat, and negligible responding in three rats (i.e., two infusions in 2 h). The mean (±S.E.M.) total number of infusions in this group was 21.8±15.9 (Fig. 1A, left panel).

In contrast, during the dose–response determination with the two higher doses of cocaine (0.125 and 0.25 mg/infusion; Fig. 1A, left panel), all rats maintained a reliable and consistent intake of cocaine and earned a mean (±S.E.M.) total number of infusions of 55.0±4.0 at the 0.125-mg dose and 30.0±2.4 at the 0.25-mg dose (Fig. 1A, right panel). Thus, reduction of the cocaine dose from 0.25 to 0.125 mg/infusion increased the total number of cocaine infusions obtained in a 2-h session (Fig. 1A, left panel; $P<.05$) by decreasing the interinfusion intervals (shown as the slope of the cumulative number of reinforcers obtained per unit of time in Fig. 1A, right panel) and revealed

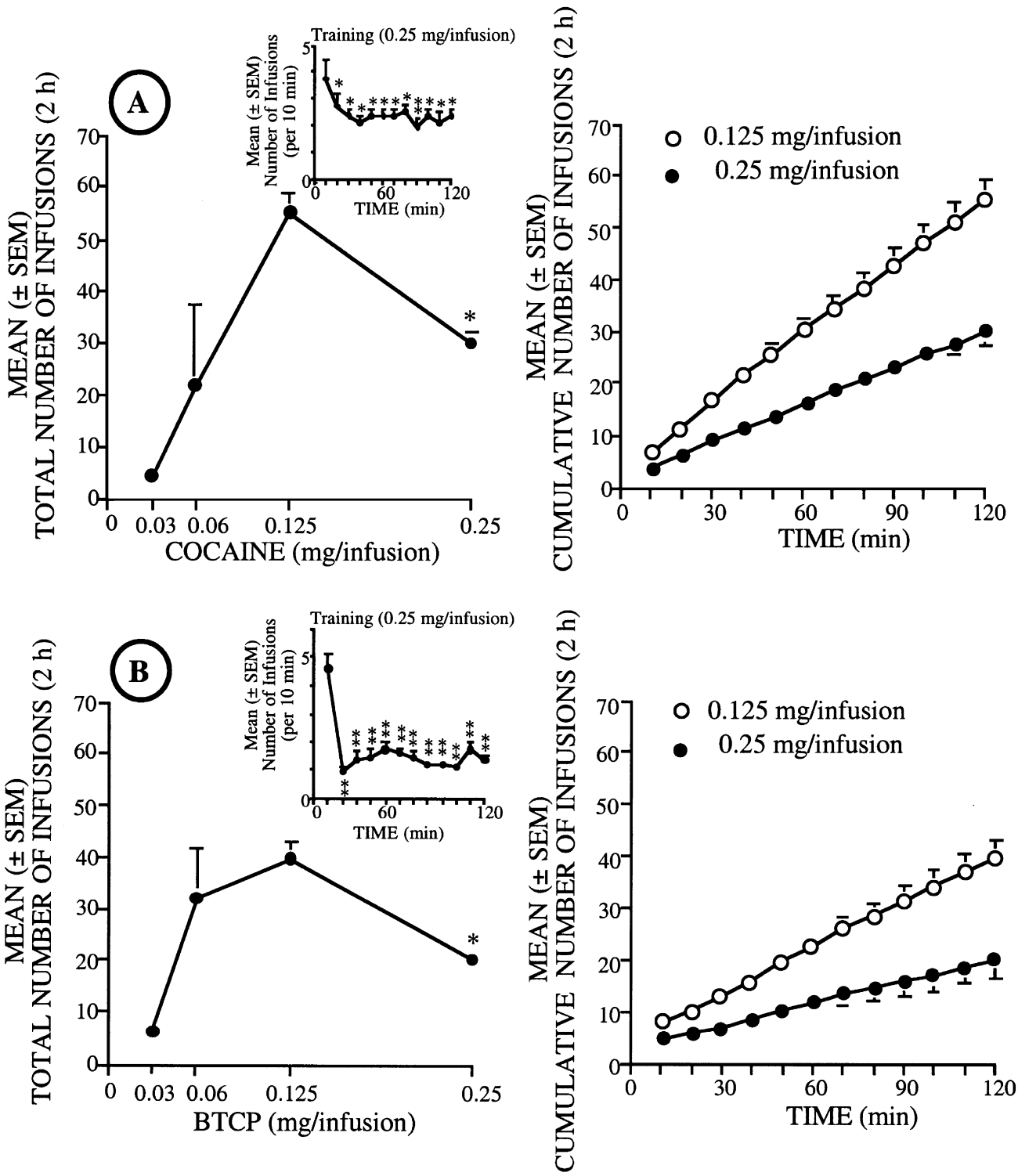

Fig. 1. Self-administration of either cocaine ($n=5$) or BTCP ($n=8$) on an FR 5, TO 20 schedule of reinforcement. (A) Cocaine dose–effects are expressed as the total number of infusions at each dose during the 2-h self-administration session (left panel), and cumulative number of infusions (right panel) per 10-min interval of two doses of cocaine (0.125 and 0.25 mg/infusion) that maintained reliable self-administration in this particular cocaine dose–response determination. (B) BTCP dose–effects are expressed as the total number of infusions at each dose during the 2-h self-administration session (left panel), and as the cumulative number of infusions (right panel) per 10-min interval of two doses of BTCP (0.125 and 0.25 mg/infusion) that maintained consistent intake of BTCP in this dose–response determination. ($*P<.05$ vs. 0.125 mg/infusion; see Results for statistical analysis). (Insets) Time course of cocaine (A) or BTCP (B) maintained responses at the 0.25-mg training dose during the 2-h self-administration session (TO 20 included in each 10-min interval), after the animals reached stable levels of self-administration. ($*P<.05$, $**P<.01$ vs. the loading phase; see Results for statistical analysis).

a significant interaction between the dose of cocaine and the cumulative number of infusions per 10-min interval [$F(11,44) = 42.9$; $P < .001$].

3.3. Fixed-ratio dose–effect functions for BTCP self-administration

For BTCP, the mean (±S.E.M.) number of sessions required to reach the training criterion at 0.25 mg/infusion on an FR 5, TO 20 schedule of reinforcement was 12.0±1.1. The animals developed a regular pattern of intake throughout the 2-h self-administration session, characterized by a loading phase (first 10 min) followed by regular interinfusion intervals (Fig. 1B, inset). As with cocaine, this self-administration pattern was reflected by a significant effect for time [$F(7,11) = 13.5$; $P < .001$] and confirmed by a significant difference between the number of infusions during the loading phase and the number of infusions during the rest of the session (Fig. 1B, inset; $P < .01$, Newman–Keuls). Comparison of the two profiles of intake for the 0.25-mg dose of BTCP and cocaine revealed significant differences, especially during the maintenance phase where the intake of BTCP was lower than that of cocaine (Fig. 1A inset and Fig. 1B inset for comparison). These differences were confirmed by a significant effect of drug (BTCP vs. cocaine) [$F(1,11) = 18.8$; $P < .01$] and a significant interaction between drugs and the 10-min self-administration intervals [$F(11,121) = 2.5$; $P < .01$]. While there were no differences during the loading phase (first 10-min), simple effects analysis confirmed that intake of BTCP was lower than cocaine intake during the maintenance phase (Fig. 1A inset and Fig. 1B inset for comparison; $P < .05$).

BTCP self-administration also produced an inverted U-shaped dose–effect curve (Fig. 1B, left panel) confirmed by a main effect for BTCP dose [$F(3,21) = 7.2$; $P < .01$]. Inspection of the BTCP and cocaine dose–response curves demonstrated that at the two lowest doses (0.03 and 0.06 mg/infusion), the animals' intake was similar for both drugs, while at the two highest doses (0.125 and 0.25 mg/infusion), BTCP seemed to maintain responding at a lower rate than cocaine. However, the shapes of the dose–response curves for cocaine and BTCP were similar, with no statistical differences found between the two curves. Unlike with cocaine, the time to reach the baseline criterion at each BTCP dose was dose-dependent [$F(3,21) = 5.6$; $P < .01$]. The mean (±S.E.M.) number of sessions to reach the baseline criterion at each dose of BTCP was the following: 0.03 mg/infusion, 6.0±0.6 sessions; 0.06 mg/infusion, 7.1±1.7 sessions; 0.125 mg/infusion, 3.0±0.0 sessions; 0.25 mg/infusion, 3.0±0.0 sessions. At the two highest doses on the BTCP dose–response curve, the rats reached the baseline criterion more rapidly than for cocaine. However, the overall comparison of the number of sessions needed to meet the baseline criterion at each of the four doses tested between the BTCP and cocaine groups was not statistically different.

Self-administration of two lower doses of BTCP in the dose–response tests was associated with considerable variability in responding across rats throughout the self-administration session. The 0.03-mg BTCP dose did not maintain reliable self-administration. Inspection of the pattern of intake of each individual rat revealed that throughout the 2-h session, responding was consistently low for all animals (Fig. 1B, left panel). Further scrutiny of the raw data indicated that seven out of eight rats responded randomly throughout the 2-h session, while one rat exhibited an extinction-like pattern with early termination of responding (i.e., response bursts during the first 10-min followed by complete termination of responding). The mean (±S.E.M.) total number of infusions at this dose was 6.0±1.5 in 2 h (Fig. 1B, left panel). Similar results were obtained at the 0.06-mg dose of BTCP. Response patterns observed at this dose included an extinction-like profile with early termination of responding in one rat, a low level of responding in three rats, and intermittent response bursts in four rats. The mean (±S.E.M.) total number of infusions at this dose was 32.1±9.7 in 2 h (Fig. 1B, left panel).

At the 0.125- and 0.25-mg/infusion doses (Fig. 1B, left panel), all rats responded reliably with regular interinjection intervals and earned a mean (±S.E.M.) total number of infusions of 39.6±3.4 at the 0.125-mg dose and 20.1±1.0 at the 0.25-mg dose (Fig. 1B, right panel). Thus, the reduction in the BTCP dose from 0.25 to 0.125 mg/infusion produced a dose-dependent increase in the total number of infusions obtained in a 2-h session (Fig. 1B, left panel; $P < .05$), with a decrease in the length of interinfusion intervals (Fig. 1B, right panel). This was reflected by a significant interaction between the dose of BTCP and the cumulative number of infusions per 10-min interval [$F(11,77) = 33.5$; $P < .001$]. The observation of the interresponse interval (reflected by the slope of the cumulative reinforcers per unit of time) demonstrates that BTCP was self-administered at approximately 70% of the rate of cocaine at the same unit dose.

3.4. Progressive-ratio for cocaine

Increasing the unit dose of cocaine from 0.125 to 0.25 mg/infusion produced a dose-dependent increase of the total number of cocaine infusions during the progressive-ratio test, and the rats earned a mean (±S.E.M.) total number of infusions of 24.6±1.2 and 47.6±5.1, respectively (Fig. 2A, right panel). This was reflected by a significant difference between cocaine doses ($P < .05$; Fig. 2A, right panel). The BPs (i.e., the highest ratio achieved) per session were 67.2±8.5 and 248.8±40.8 for the 0.125 and 0.25 mg/infusion doses, respectively (Fig. 2A, left panel). The time required to reach the BP also increased as the unit dose of cocaine increased, and the BPs were reached in 1.5 and 4.7 h for the 0.125- and 0.25-mg/infusion doses, respectively ($P < .05$).

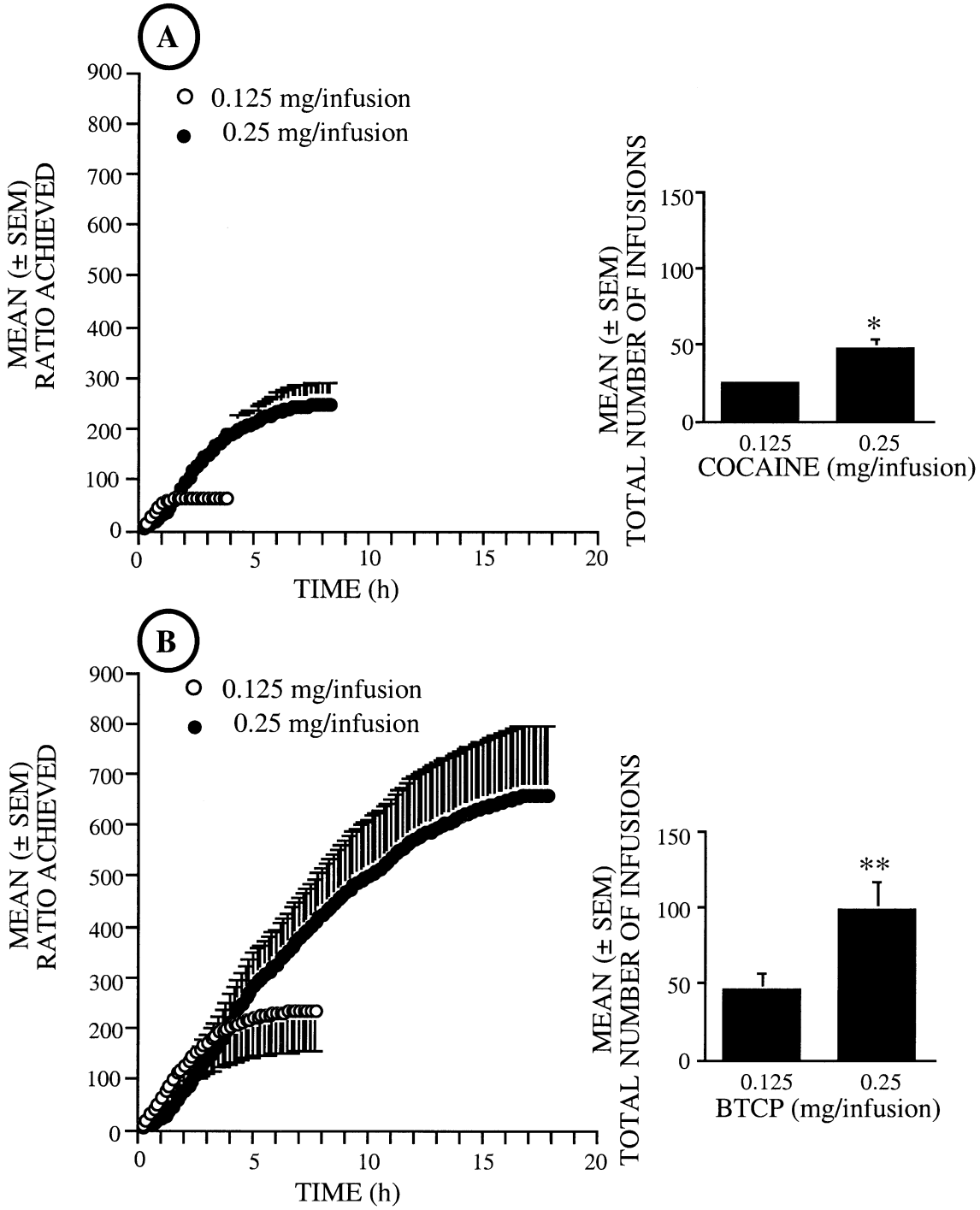

Fig. 2. Self-administration of cocaine ($n=5$) or BTCP ($n=7$) on a progressive-ratio schedule. (A) Increasing the dose of cocaine dose-dependently increased the highest ratio completed measured per 10-min interval (left panel). In the right panel, the total number of infusions earned during the progressive-ratio session is presented. (B) Effect of increasing the unit dose of BTCP on BPs measured per 10-min interval (left panel). In the right panel, the total number of BTCP infusions earned during the progressive-ratio session is presented. ($*P<.05$, $**P<.01$ see Results for statistical comparison).

3.5. Progressive-ratio for BTCP

As with cocaine, increasing the dose of BTCP from 0.125 to 0.25 mg/infusion produced a dose-dependent increase of the total number of infusions, and the rats earned a mean (±S.E.M.) total number of infusions of 45.8±10.5 and 98.9±17.3, respectively (Fig. 2B, right panel; $P<.01$). The BPs were 236.6±83.3 and 658.9±136.2 for the 0.125- and 0.25-mg/infusions doses, respectively (Fig. 2B, left panel). The time required to reach the BPs increased from 3.4 to 11.5 h when the dose of BTCP increased from 0.125 to 0.25 mg/infusion doses, respectively ($P<.01$). Compar-

ison of the progressive-ratio performances for BTCP and cocaine demonstrated that there was a difference in drug intake between the two groups [$F(1,10) = 5.9$; $P < .05$] and a significant overall effect for the two doses tested [$F(1,10) = 19.3$; $P < .01$]. Simple effects analysis confirmed that the rats emitted more BTCP-reinforced than cocaine-reinforced responses, especially at the 0.25-mg dose (Fig. 2A and B, right panel for comparison; $P < .001$).

4. Discussion

The results show that like cocaine, BTCP supports the acquisition of intravenous self-administration, reliably maintains responding for this drug following acquisition, and produces an inverted U-shaped dose–response function (Fig. 1A and B) comparable to that for cocaine under an FR 5 schedule of reinforcement. However, differential effects between cocaine and BTCP were observed in a progressive-ratio schedule of reinforcement where BTCP supported higher BPs.

On the FR 5 schedule, both cocaine and BTCP were reliably self-administered in a comparable manner. In particular, rats that had no prior psychostimulant exposure readily acquired BTCP self-administration (0.25 mg/infusion; FR 5) with an acquisition time course similar to that of cocaine (0.25 mg/infusion; FR 5) but with a slower rate of self-administration (see Fig. 1A and B, insets for comparison). BTCP and cocaine produced a similar "loading-phase" pattern (Fig. 1A and B, insets), but at the same unit dose, BTCP was self-administered at a relatively slower rate than cocaine suggesting that on a molar basis the onset of action of BTCP and cocaine was similar, but that BTCP had a longer duration of action. Since the two groups of rats were in the same weight range, this conclusion is not confounded by differences in body weight. Consistent with the hypothesis of a longer duration of action for BTCP are the recent findings by Deleuze-Masquefa et al. (2000), showing that BTCP was detectable in the mouse brain as early as 10 min after a single intraperitoneal injection, and that BTCP concentrations remained elevated for at least 4 h, whereas cocaine concentrations decreased dramatically 30 min after the injection (Benuck et al., 1987). Over the same range of doses the behavior maintained by both cocaine and BTCP was characterized by the same inverted U-shaped dose–response curve (see the Results section and Fig. 1A and B, left panels for comparison). However, inspection of the self-administration profiles generated by the two highest BTCP and cocaine doses indicates that BTCP was self-administered at a lower rate compared to cocaine (Fig. 1A and B, right panels for comparison), suggesting that BTCP may be more potent than cocaine. Moreover, while the overall number of sessions required to establish stable responding was similar for both cocaine and BTCP, responding at the two highest doses of BTCP stabilized more quickly compared to cocaine, and this observation may be indicative of a stronger reinforcing action of BTCP. However, the data obtained with the FR 5 schedule do not provide unequivocal information as to whether BTCP and cocaine differ in rewarding effect. To determine whether such differences exist, a progressive-ratio schedule of reinforcement was employed (Arnold and Roberts, 1997; Richardson and Roberts, 1996).

In contrast to the FR 5 schedule, BTCP maintained higher BPs compared to cocaine on the progressive-ratio schedule at each of the two doses that maintained reliable self-administration (Fig. 2). The rats, therefore, self-administered more BTCP than cocaine on this schedule. Moreover, there were no differences in body weight between the two groups of rats as was the case during the cocaine and BTCP dose–response study. These observations are surprising in light of earlier findings that cocaine and BTCP at equimolar concentrations produce equivalent BPs on a progressive-ratio schedule and that BTCP substitutes for cocaine (French et al., 1995). In addition, BTCP maintained higher BPs, and the time required to reach the BP at each dose was twice as long for BTCP than cocaine.

Several procedural issues may have contributed to the different BPs for BTCP reported here and in previous work (French et al., 1995). In the present study, animals were experienced with only one drug reinforcer, whereas in the study by French et al. (1995), BTCP was substituted for cocaine following prior operant training with cocaine. Therefore, the higher BPs maintained by BTCP compared to cocaine in the present study may be explained by the fact that the rats were directly trained to self-administer the drug with which they were subsequently tested on the progressive-ratio schedule. Thus, it is possible that the initial self-administration training with BTCP was a critical factor in establishing its full reinforcing potential. The progressive-ratio schedule employed here also differs from that used by French et al., in that a slower progression in the ratio requirement was used. The change in this parameter possibly may have contributed to the higher BP in the present study. However, there is evidence that the rate of progression in the ratio requirement does not influence the value of the measured BP for food in different species (e.g., Stafford and Branch, 1998). Moreover, other studies have shown that the escalation procedure to reach the BP for cocaine has been designed, in particular, to reduce the length of the progressive-ratio sessions (for review, see Richardson and Roberts, 1996). Therefore, this particular schedule difference in the present study and in the study by French et al. is unlikely to be responsible of the higher BPs maintained by BTCP.

A possible explanation for the higher BPs maintained by BTCP over cocaine at the two doses tested may be differences in elimination profiles and the generation of active metabolites between the two compounds. Benzoylecgonine, cocaine's main metabolite, has little pharmacological activity (for review, see Benowitz, 1992). In contrast, BTCP has two active metabolites, which potently bind to the DA

transporter, 1-[1-(2-benzo[*b*]thiophenyl)cyclohexyl]piperidin-4-ol (4-OH-pip-BTCP) and 1-[1-(2-benzo[*b*]thiophenyl)cyclohexyl]piperidin-3-ol (3-OH-pip-BTCP) (Deleuze-Masquefa et al., 1997, 2000). These two compounds, as well as BTCP, were detected in the mouse brain after a peripheral injection of BTCP (Deleuze-Masquefa et al., 2000), suggesting that these two active metabolites could strengthen the pharmacological effect of BTCP. Particularly, 3-OH-pip-BTCP was found to have high affinity for the DAT (approximately five times that of BTCP), and consequently may have contributed to the BTCP-maintained behavior (Deleuze-Masquefa et al., 2000). An alternative interpretation of the different reinforcing actions of BTCP and cocaine may be that BTCP and cocaine bind to the DAT at different sites (Maurice et al., 1991a, 1993). While it has been well described that inhibition of DA reuptake is the crucial factor responsible for the rewarding effects of cocaine (Ritz et al., 1987; Spanagel and Weiss, 1999), it is possible that the action of these two drugs on different binding sites on the DAT can produce differential effects. For example, it has been demonstrated that cocaine euphoria and reward are associated closely with the ratio of DAT sites occupied (Volkow et al., 1997). Thus, the fact that BTCP has a higher affinity for the DAT than cocaine but at a different site (Maurice et al., 1991a, 1993), may be responsible for a higher ratio of DAT occupancy at the same concentration, and thus to produce greater rewarding effects as reflected by the elevated BPs.

Another possible explanation for the higher BPs maintained by BTCP over cocaine may be differential actions on the 5-HT system. An increasing number of studies suggests that there is an important 5-HT component in the behavioral effects of cocaine in animals (Carroll et al., 1990a,b; Loh and Roberts, 1990; Spealman, 1993) and humans (Aronson et al., 1995; Buydens-Branchey et al., 1997; Satel et al., 1995; Walsh et al., 1994). Specifically, it has been shown that the stimulation of 5-HT1B receptors is responsible for the enhancement of the positive reinforcement induced by the selective DA reuptake inhibitor GBR12909 (Parsons et al., 1996). Like GBR12909, BTCP is a DAT blocker and acts as well as a reuptake inhibitor for 5-HT, again, with a higher potency than cocaine ($K_i = 42$ nM for BTCP vs. $K_i = 250$ nM for cocaine; Lebel et al., 1994). Therefore, via its effect on the 5-HT transporter, BTCP may increase synaptic 5-HT concentrations and thereby activate 5-HT1B receptors that have been shown to be involved in the reinforcing actions of DA uptake inhibitors and in the facilitation of cocaine-induced DA increases in the mesolimbic DA neurotransmission (Parsons et al., 1996, 1998b, 1999).

One strategy for the treatment of drug addiction focuses on the use of compounds that substitute for the actions of the primary drug of abuse but have a longer duration of action paired with lower intrinsic abuse potential and lower toxic side effects (Rothman, 1990; Kreek, 1997). In the case of cocaine, therapeutic agents with indirect agonist properties (e.g., uptake inhibitors) are likely to be more effective than direct DA receptor agonists because of emetic and other side effects associated with drugs of the latter class. Previous findings indicated that following an intraperitoneal injection, BTCP can substitute for the reinforcing actions of cocaine and does so with greater effect than cocaine (Martin-Fardon and Weiss, 2000), thus identifying this compound as a potential substitution drug. The present experiment was performed to compare the reinforcing effects of BTCP to those of cocaine in previously drug-naïve rats. Although the dose–effect curves for BTCP and cocaine were similar on the FR schedule, the results of the progressive-ratio test on the two doses that maintained a high rate of responding indicate that BTCP at the same concentration as cocaine produces greater reinforcing actions. It must be emphasized, however, that while the results of both the FR 5 and progressive-ratio experiments suggest that BTCP has greater reinforcing efficacy than cocaine, this conclusion is limited since only two doses (0.125 and 0.25 mg/infusion) of each compound were tested. Future studies using a greater range of doses will therefore be required to conclusively confirm this hypothesis.

Whether the behavioral profile of BTCP identified by these results qualifies this drug as a possible agonist substitution drug remains unclear. In addition to the substitution for the primary effect of the drug of abuse, the criteria for suitability as an agonist therapeutic drug include slow onset of action and long-lasting effects with a slow offset of action. Methadone, for example, while supporting self-administration by rats (Werner et al., 1976) and monkeys (Stewart et al., 1996), is an effective agonist treatment drug for heroin addiction (Kreek, 1997). Methadone can substitute for the reinforcing effects of heroin and has long-lasting effects when administered orally to humans, without producing a rush-like phenomenon that contributes critically to abuse liability (Kreek, 1997). BTCP, similar to methadone, can substitute for the reinforcing effect of cocaine and is self-administered by rats. The observation that the average time to reach the BP was much longer for BTCP than for cocaine may perhaps indicate that this particular drug has a longer duration of action. Consistent with this hypothesis are the earlier findings of Deleuze-Masquefa et al. (2000) describing that after an intraperitoneal injection of BTCP in mice, this drug was detected in the plasma for 16 h and in the brain for 4 h. Therefore, in view of its greater affinity for the DAT relative to cocaine and the contribution of its biologically active metabolites, BTCP may have a substantially longer duration of action than cocaine. On the other hand, the higher BPs maintained by BTCP relative to cocaine is not consistent with the criteria for an effective substitution drug. Nonetheless, further investigation of BTCP's potential as a substitution drug would seem important. In particular, focus on different routes of administration (i.e., intravenous vs. oral) as well as the role of the active metabolites in BTCP's duration of

action may yield data consistent with the profile of a substitution drug.

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