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ORIGINAL INVESTIGATION

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Effect of baclofen on cocaine self-administration in rats reinforced under fixed-ratio 1 and progressive-ratio schedules

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Abstract *Rationale:* Recent reports have indicated that the γ-aminobutyric acid $(GABA)_B$ agonist baclofen attenuates the reinforcing effects of cocaine. *Objectives:* To further evaluate the effect of baclofen on cocaine self-administration under a fixed ratio (FR) and progressive ratio (PR) schedule of reinforcement. *Methods:* In the first series of experiments, three dose–response curves were generated that examined the effect of three doses of baclofen (1.8, 3.2, or 5.6 mg/kg, i.p.) against four unit-injection doses of cocaine (0.19, 0.38, 0.75, and 1.5 mg/kg per injection) reinforced under a FR1 schedule. For comparison, an additional group of rats was pretreated with haloperidol (32, 56, or 100 µg/kg, i.p.). A separate experiment examined the effect of baclofen (1.8, 3.2, or 5.6 mg/kg, i.p.) on responding for concurrently available cocaine or food reinforcement. *Results:* Under the FR1 schedule, baclofen suppressed intake of low but not high unit injection doses of cocaine. In contrast to haloperidol, baclofen had no effect on the distribution of inter-injection intervals and, instead, produced long pauses in cocaine self-administration. Baclofen dose dependently reduced cocaine-reinforced responding on a PR schedule; concurrent access to a food-reinforced lever demonstrated that the animals retained the capacity to respond at high rates. *Conclusion:* The effect of baclofen pretreatment on cocaine self-administration is dependent on the unit injection dose of cocaine and on the response requirements of the schedule.

Key words Baclofen · Cocaine · GABA · Self-administration · Reward

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Introduction

Although cocaine acts as an indirect agonist at serotonin, noradrenaline, and dopamine (DA) synapses, a substantial literature now indicates that it is the mesolimbic/mesocortical DA system that plays a critical role in the reinforcing effects (Koob 1992; Roberts 1992; Woolverton and Johnson 1992). Given the primary importance of the DA system, clinical efforts have focused to a large extent on dopaminergic drugs (Dackis et al. 1987; Gawin et al. 1989; Meyer 1992; Kleber 1995 for review); however, to date, no substantially effective pharmacotherapy exists for the treatment of cocaine addiction.

Recent behavioral and physiological data have indicated that drugs specific for γ-aminobutyric acid (GABA) synapses might specifically modulate cocaine reinforcement. GABA systems are known to interact with and modulate DA neurotransmission (Klitenick et al. 1992; Santiago et al. 1993a, 1993b; Morgan and Dewey 1998), and recent studies have shown that GABA-related compounds such as chlordiazepoxide and gamma-vinyl-GABA, can influence the neurochemical and behavioral effects of cocaine (Goeders et al. 1989, 1993; Dewey et al. 1997, 1998; Kushner et al. 1997).

One particularly promising therapeutic candidate is the $GABA_B$ agonist baclofen. A number of self-administration studies have shown that baclofen attenuates cocaine reinforcement, although the magnitude and specificity of this effect appears to depend on the schedule of reinforcement used. Baclofen reduced cocaine-reinforced break points established on a progressive-ratio (PR) schedule (Roberts et al. 1996), and decreased cocaine intake in a discrete-trials procedure (Roberts and Andrews 1997). However, investigations using fixed-ratio (FR) schedules have raised some interesting questions. We have reported that relatively high doses of baclofen (2.5 or 5.0 mg/kg) do not disrupt cocaine self-administration (1.5 mg/kg per injection, i.v.) on a FR1 schedule, whereas Shoaib et al. (1998) have shown that a similar dose of baclofen did attenuate responding for 0.66 mg/kg of cocaine on a FR5 schedule. Very recently,

Campbell et al. (1999) have also reported that 2.5 mg/kg and 5.0 mg/kg of baclofen disrupts responding for low doses of cocaine (0.2 mg/kg or 0.4 mg/kg) on a FR1 schedule. While these reports would appear to be contradictory, differences in both the response requirement and the unit dose of cocaine in these studies may account for the disparate results. In order to address this possibility, one of the goals of the present investigation was to obtain complete dose–response curves for both baclofen and cocaine on a FR1 schedule.

We have shown previously that cocaine-reinforced break points established on a PR schedule are particularly sensitive to baclofen pretreatment (Roberts et al. 1996). However, as the requirements of the schedule become more effortful, the possibility that baclofen may have non-specific effects on responding becomes an issue. This has been addressed to some extent by an examination of the effect of baclofen on food-reinforced responding. Shoaib et al. (1998) showed that baclofen had a relatively greater effect on cocaine- than food-reinforced responding under a multiple schedule. Using a PR schedule, we demonstrated that baclofen produces a larger effect on cocaine- than food-reinforced break points (Roberts et al. 1996). In the present study, we used concurrent access to food and cocaine reinforcement in order to demonstrate that animals that decline to self-administer cocaine following baclofen retain the capacity to respond at high rates.

Materials and methods

Subjects

Subjects in all experiments were male Wistar rats (Charles River Farms, Quebec) weighing 275–300 g at the start of the experiments. All animals were placed under quarantine for 1 week following arrival at the facility, were housed according to Canadian Council on Animal Care standards, and were maintained on a 12-h/12-h reversed light/dark cycle (lights off at 0300 hours). Following quarantine, animals were food deprived for 18-h, then trained to press a lever for food reinforcement on a FR1 schedule. Thereafter, Purina rat chow was available ad libitum, except as noted below. Water was available ad libitum throughout all phases of the experiment. Each rat was implanted with a chronically indwelling Silastic jugular cannula that exited through the skin on the dorsal surface in the region of the scapulae (Roberts and Goeders 1989). Following cannulation, rats were individually housed in 25×25×25-cm testing chambers. The cannula was connected through a stainless-steel protective spring to a counterbalanced swivel apparatus that allowed free movement within the chamber.

Procedure

Beginning the day after surgery, animals were given access to a response lever that controlled the delivery of cocaine injections on a FR1 schedule. Concurrent with the start of each cocaine injection (1.5 mg/kg per injection in 0.12 ml saline), a stimulus light located above the lever was activated to signal a 20-s post-infusion timeout period, during which responses produced no programmed consequence. Rats received daily 6-h test sessions (0900 hours until 1500 hours) which began with one priming injection. After the animals had established a stable daily pattern of cocaine intake (>30 injections/6 h and regular post-infusion pauses) on a FR1 schedule, animals were randomly assigned to experimental groups.

Cocaine dose–response curve

Rats (n=8–12) were given access during daily 3-h sessions to a response lever that delivered cocaine under a FR1 schedule. The effect of baclofen pretreatment (3.2 mg/kg, i.p., – 30 min) on self-administration of four unit injection doses of cocaine (0.19, 0.38, 0.75, or 1.5 mg/kg per injection) was assessed using a repeated-measures design. At least four baseline sessions preceded the baclofen test day, after which the unit injection dose of cocaine was adjusted according to a Latin square design.

Baclofen dose–response curves

Rats were trained to self-administer 0.75 mg/kg (n=5) or 1.5 mg/kg (n=5) per injection of cocaine under a FR1 schedule of reinforcement. Following at least 3 days of stable responding, rats received baclofen (1.8, 3.2, or 5.6 mg/kg, i.p.) 30 min prior to the test session. The order of baclofen injections was counterbalanced according to a Latin square design and test sessions were separated by at least 3 days. The time between each cocaine infusion (inter-injection interval) was also measured in order to determine the precise impact of baclofen on the pattern, or rate, of responding. For comparison, a separate group of rats trained to self-administer 0.75 mg/kg or 1.5 mg/kg per injection of cocaine (n=6) was pretreated with haloperidol (32, 56, or 100 µg/kg, i.p.) 60 min prior to the test session. The order of haloperidol doses was counterbalanced across subjects and test sessions were separated by at least 3 days.

Concurrent access conditions

The effect of baclofen on concurrent cocaine- and food-reinforced responding was examined in a separate group of rats (n=6). Rats were initially trained on a FR1 schedule of cocaine reinforcement. Once stable daily patterns of intake were established (see above), a PR schedule was introduced. Cocaine infusions (1.5 mg/kg per injection) were contingent upon an increasing number of responses incremented through the following progression: 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, 402, 492, and 603 (procedure described in detail in Richardson and Roberts 1996). Once stable responding on the PR schedule had been established, testing included a concurrently available food-reinforced lever. Stable performance was defined as three consecutive days of cocaine self-administration with break points within a range of four increments. Rats were 16-h food-deprived at the beginning of the session and received access to Purina rat chow for 2 h immediately following the session. The session began with the introduction of a food-reinforced lever; the cocaine-reinforced lever was introduced 5 min later. Initially, a single response on the food lever resulted in the delivery of a 45-mg nutritionally balanced food pellet (Noyes Inc.). The schedule was incremented from FR1 to FR5 during the first four sessions. Daily baseline testing continued for at least 4 days before the effect of baclofen (1.0, 1.8, 3.2, or 5.6 mg/kg, i.p., 30 min prior to the session) was investigated. All injections were administered according to a Latin square design, and at least 3 days separated test days.

Drugs

Cocaine HCl was supplied by the National Institute on Drug Abuse (Research Triangle, N.C.). (±)-Baclofen was purchased from Research Biochemicals International. Baclofen was dissolved in pyrogen-free sterile saline. Haloperidol (ICN Biochemicals Inc, Ohio) was dissolved in glacial acetic acid and then diluted in sterile saline. The pH of the haloperidol solution was adjust-

ed to between 5.6 and 6.0 using NaOH. Dosages are expressed as the salt.

Data analysis

In the FR1 experiments, the dependent measure was the number of cocaine injections per 3-h session. Baseline rates were calculated by averaging the number of cocaine injections self-administered on the day before each test session. In the PR experiment, the dependent measure was break point (defined as the number of completed increments prior to a 1-h period during which no cocaine infusions were obtained). Baseline rates were calculated as described in the FR1 experiments. The total number of food-reinforced responses was collected for the entire 6 h, although statistical analysis was restricted to the first 2 h of the session when the effect of baclofen on cocaine-reinforced responding was observed. Data were analyzed using repeated-measures analysis of variance (ANOVA) with post-hoc Newman Keuls multiple comparisons.

Results

Cocaine dose–response curve

Animals that failed to complete testing on at least three of the four unit injection doses of cocaine were excluded from the analysis. Baclofen pretreatment (3.2 mg/kg, i.p.) was found to significantly attenuate cocaine self-administration under a FR1 schedule. The ANOVA revealed a significant treatment × dose interaction ($F_{3,12}$=6.038, P<0.01), and multiple comparisons indicated that baclofen reduced cocaine self-administration at all but the highest unit dose (1.5 mg/kg per injection) of cocaine. Baclofen had a proportionally greater effect at the lower unit doses of cocaine and little if any effect at the highest doses (1.5 mg/kg per injection; Fig. 1A). The typical response patterns following baclofen pretreatment are included for the 0.75 mg/kg and 1.5 mg/kg doses per injection). Decreases in self-administration of cocaine, when they were observed, were accounted for by a period of non-responding at the start of the test-session, rather than a reduction in the rate of responding over the course of the session (Fig. 1B).

Baclofen dose–response curves

The effect of baclofen (1.8, 3.2, or 5.6 mg/kg, i.p.) on cocaine-reinforced responding (0.75 mg/kg or 1.5 mg/kg per injection) under a FR1 schedule is illustrated in Fig. 2. In assessing the baclofen dose–response curves, only data from animals that received all three doses of baclofen were included in the analysis. ANOVA revealed a significant effect of baclofen at both unit doses of cocaine (0.75 mg/kg per injection $F_{3,16}$=7.13, P<0.01; 1.5 mg/kg per injection: $F_{3,16}$=4.55, P<0.01). Baclofen produced a greater attenuation of cocaine self-administration at the lower unit injection doses. Multiple comparisons revealed that while 3.2 mg/kg baclofen significantly attenuated responding for the low unit-dose of cocaine, a dose of 5.6-mg/kg was required to affect responding for 1.5 mg/kg cocaine.

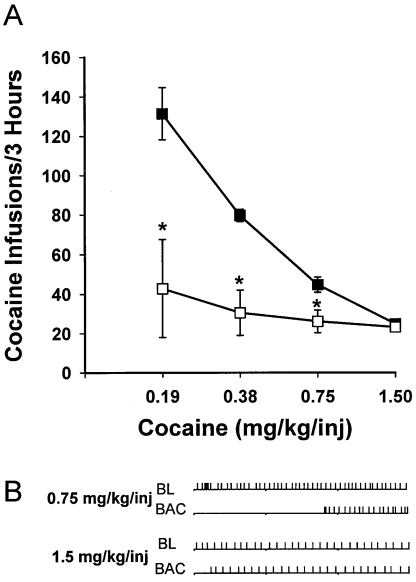

Fig. 1 **A** Effect of baclofen (3.2 mg/kg, i.p.) on self-administration of various doses of cocaine. Rats (n=8–12) were trained to respond for several doses of cocaine (0.19, 0.38, 0.75, or 1.5 mg/kg per infusion) under a fixed-ratio (FR)1 schedule of reinforcement. Points represent the mean (±SEM) number of responses during baseline (*BL*) days (*closed squares*) and over the 3-h test session (*open squares*). Animals were pretreated with baclofen 30 min prior to the test session. At all but the highest unit dose of cocaine, baclofen produced a significant reduction in responding (P<0.05). **B** Reductions in cocaine intake were accounted for by periods of non-responding at the beginning of the test session, which resulted in a decrease in the total number of injections

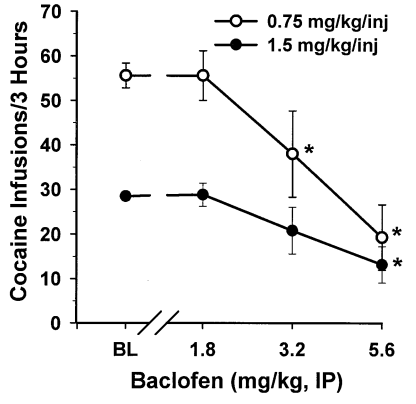

Fig. 2 Effect of baclofen (1.8, 3.2, or 5.6 mg/kg, i.p.) on cocaine self-administration on a fixed-ratio (FR)1 schedule. *Points* represent the mean (±SEM) number of injections self-administered during a 3-h baseline (BL) or test session. Separate groups (n=5 per group) of animals were trained to respond for either 0.75 mg/kg or 1.5 mg/kg per injection of cocaine and were pretreated with baclofen 30 min before the session. Baclofen produced a greater attenuation of cocaine self-administration at the lower unit injection doses. Self-administration of the lower unit dose (0.75 mg/kg per injection) was significantly affected by both 3.2 mg/kg and 5.6 mg/kg baclofen (P<0.05), whereas the high unit injection dose (1.5 mg/kg) was significantly reduced only by 5.6 mg/kg baclofen (P<0.05)

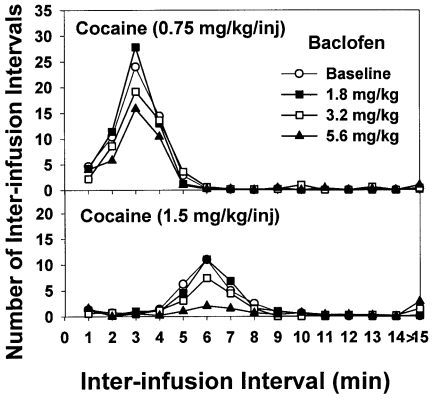

Fig. 3 Effect of baclofen (1.8, 3.2, or 5.6 mg/kg, i.p.) on the distribution of inter-infusion intervals during cocaine self-administration on a fixed-ratio (FR)1 schedule. *Points* represent the mean number of injections of cocaine that occurred during the indicated intervals for animals trained to respond for either 0.75 mg/kg per injection (*top*) or 1.5 mg/kg per injection (*bottom*). *Curves* represent the effect of pretreatment with various doses of baclofen. While baclofen produced a dose-dependent reduction in the total number of infusions, it failed to affect the distribution of inter-infusion intervals at either concentration of cocaine. Reductions in self-administration were accounted for by periods of non-responding at the beginning of the test sessions. Note that an hour-long pause in responding would result in only a single entry in the greater than 15-min interval and would account for a substantial decrease in the total number of injections

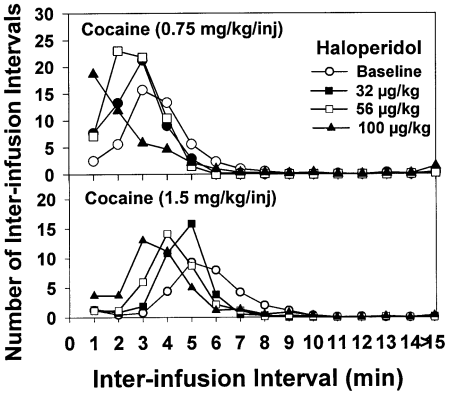

Fig. 4 Effect of haloperidol (32, 56, or 100 µg/kg, i.p.) on the distribution of inter-infusion intervals during cocaine self-administration on a fixed-ratio (FR)1 schedule. *Points* represent the mean number of injections of cocaine that occurred during the indicated intervals for animals (n=6) trained to respond for 0.75 mg/kg or 1.5 mg/kg per injection. *Curves* represent the effect of pretreatment with various doses of haloperidol. Haloperidol produced a dose-dependent shift to the left of the modal inter-injection interval; this effect is qualitatively different from the effect of baclofen

The distribution of inter-injection intervals was found to be dose-dependent, with the time between infusions, increasing as the unit dose of cocaine increases (Fig. 3). Although reductions in the total number of responses were evident following some doses of baclofen, they were accounted for by periods of non-responding, usually at the beginning of the test sessions. Baclofen pretreatment failed to shift the peak inter-injection intervals at any of the doses administered, indicating that the rate of cocaine self-administration was identical to baseline patterns once the rats began responding.

Haloperidol pretreatment (32, 56, or 100 µg/kg, i.p.) increased responding for both 0.75 mg/kg and 1.5 mg/kg per injection of cocaine over the 3-h session. Examination of the inter-injection intervals revealed that haloperidol caused a dose-dependent shift to the left (Fig. 4).

Concurrent access conditions

The typical baseline pattern of responding for concurrently available cocaine and food reinforcement is illustrated in Fig. 5 (top). With concurrent access, cocaine-reinforced responding on the PR schedule predominates until a break point is reached. The pattern of cocaine-self-administration under these conditions was indistinguishable from that previously observed on a PR schedule (Roberts et al. 1989b, 1996). That is, the addition of a food-reinforced lever did not appear to change the response characteristics or the break points from previous observations. During the first 5 min of the session, when only the food lever was available, all animals responded at high rates. However, when the cocaine lever was introduced, four of the six animals responded almost exclusively on the cocaine lever until the break point was reached, at which time responding was redirected toward the food lever. The remaining two animals alternated between the cocaine and the food-reinforced levers after the introduction of the cocaine lever, and did not begin to respond exclusively on the food-lever until after the break point for cocaine was reached. Regardless of individual response patterns, the number of food pellets delivered over the entire 6-h session was relatively consistent across animals (approximately 400).

Baclofen pretreatment (3.2 mg/kg, i.p.) dramatically reduced cocaine-reinforced break points and altered the pattern of responding for concurrently available cocaine or food reinforcement (Fig. 5, bottom). Responding was not suppressed, but instead redirected towards the food-reinforced lever.

Baclofen was found to have a differential effect on food- and cocaine-reinforced responding (Fig. 6, left) under concurrent access conditions. One-way, repeated-measures ANOVA revealed a significant effect of dose ($F_{4,20}$=5.9, P<0.01) and post-hoc tests indicated that the two highest doses of baclofen produced a significant decrease in cocaine-reinforced break-points. Figure 6 (right) shows the effect of baclofen pretreatment on food-reinforced responding on a FR5 schedule. Statistical analysis of the total responses during the first 2 h (when the effects of baclofen on cocaine self-administration were observed) failed to reveal a statistically significant effect.

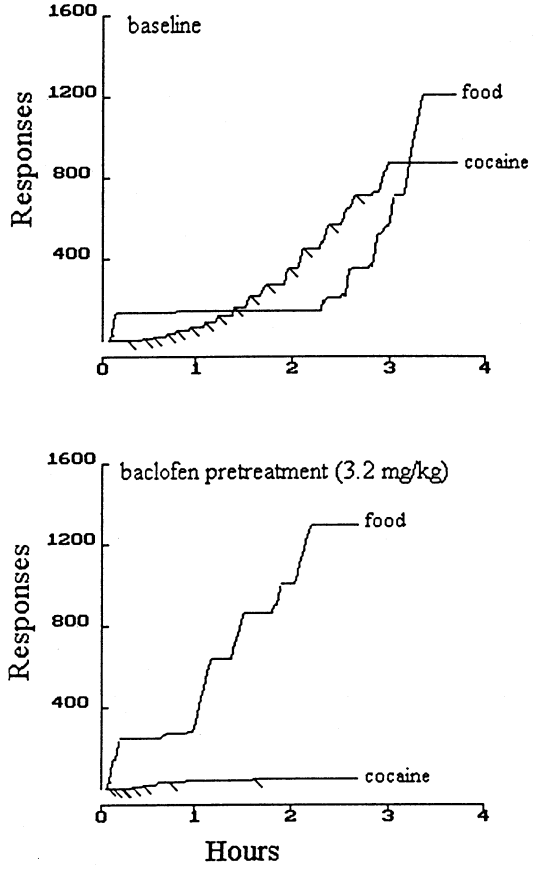

Fig. 5 Representative records illustrating the effect of baclofen (3.2 mg/kg, i.p.) on cocaine self-administration reinforced on a progressive-ratio (PR) schedule. Food reinforcement was concurrently available on a fixed-ratio (FR)5 schedule. During the first 5 min of the session, only the food-reinforced lever was available; thereafter, both food- and cocaine levers were concurrently available for the duration of the session. *Short downward marks* represent cocaine infusions while *upward increments* in the record represent lever responses. Under baseline testing conditions (*top*), this animal demonstrated high rates of responding on the food-reinforced lever until the cocaine lever was introduced; thereafter, it responded almost exclusively on the cocaine-reinforced lever while the response requirements were relatively low. Food-reinforced responding re-emerged as the cocaine break point was approached. Following baclofen (*bottom*), responding on the cocaine-reinforced lever was observed only at low ratios and responding switched exclusively to the food-reinforced lever very early in the session. This pattern of results does not suggest a generalized disruption of operant responding

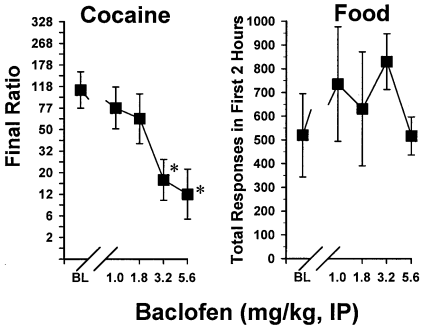

Fig. 6 Effect of baclofen on responding for concurrently available cocaine and food reinforcement. *Left*: *points* represent the mean (±SEM) break points on a progressive-ratio (PR) schedule of cocaine reinforcement (1.5 mg/kg per injection) under baseline (BL) conditions or following various doses of baclofen. *Right*: *points* represent mean (±SEM) food-reinforced responses [on a fixed-ratio (FR)5 schedule] during the first 2 h of the sessions represented in the left panel. See Fig. 5 for details. Baclofen pretreatment caused a dose-dependent decrease in break points for cocaine (*P<0.05). The *right panel* illustrates that during the first 2 h, when cocaine self-administration was suppressed, animals emitted more than 500 responses (on average) on the food-reinforced lever. These results do not support the hypothesis that baclofen produces a non-specific disruption of operant responding

Discussion

The effect of baclofen pretreatment on cocaine self-administration was shown to be dependent on the unit injection dose of cocaine and on the response requirements of the schedule. Previous results have demonstrated that, on a FR schedule, baclofen suppresses intake of low (0.2 mg/kg and 0.4 mg/kg per injection: Campbell et al. 1999) and medium (0.66 mg/kg per injection: Shoaib et al. 1998) but not high (1.5 mg/kg per injection: Roberts et al. 1996) unit injection doses of cocaine. The present data confirm these reports and demonstrate this dose-response relationship in a single experiment. The effect of baclofen was also shown to be dependent on the schedule of reinforcement. At the same unit dose of cocaine (1.5 mg/kg per injection), responding on a FR1 was not affected by baclofen pretreatment, whereas responding on a PR schedule was significantly decreased. These data are consistent with our previous demonstration (Roberts et al. 1996) that baclofen (2.5 mg/kg, i.p.) decreased break points across a broad range of unit injection doses of cocaine (0.18–1.5 mg/kg per injection). The entire data set is compatible with the behavioral economic interpretation offered by Campbell et al. (1999). They argue that dose and response requirements are both constituents of unit price (Bickel et al. 1990), and that baclofen appears to have greater efficacy as the unit price increases. Other drugs, such as fluoxetine, L-tryptophan, and carbamazepine, show a similar profile (Carroll et al. 1990a, 1990b, 1990c).

Baclofen and haloperidol are similar in that they both reduce cocaine-reinforced break points on a PR schedule (Richardson et al. 1994; Roberts and Ranaldi 1995; Roberts et al. 1996); however, the FR data indicate that each drug affects cocaine self-administration in a fundamentally different way. On FR schedules, DA antagonists shift the cocaine dose–response curve to the right (Hubner and Moreton 1991; Caine and Koob 1994), increasing the intake of cocaine at all supra-threshold doses. This has been interpreted as a compensatory response to a diminished drug effect (Yokel and Wise 1975; DeWit and Wise 1977) and shows that the haloperidol blockade, at least at low doses, can be surmounted by increased cocaine intake. Analysis of the inter-injection intervals showed, as expected, that haloperidol shifted the peak inter-injection intervals to the left, indicating

a uniform and dose-dependent increase in rate of drug intake. By contrast, baclofen shifted the cocaine intake curve downward on the FR1 schedule; at no point in the dose-response curve was there any indication of an increase in cocaine intake. Analysis of the pattern of cocaine self-administration confirmed that baclofen did not alter the modal inter-injection time (Fig. 3) and, while the total number of injections decreased, the peak interval remained the same. Baclofen-induced reductions in cocaine self-administration were found to be due to periods of non-responding at the beginning of the test session, or long pauses between responses, rather than a decrease in the rate of responding over the course of the test sessions. If both baclofen and haloperidol decrease the reinforcing effects of cocaine, it is unclear why they have fundamentally different effects on FR1 responding.

We have previously speculated that rate of drug intake is regulated not only by the reinforcing effects but also limited by toxic or aversive reactions (Roberts and Zito 1987). Manipulations that influence both of these effects equally, such as dilution of the unit dose or blockade at the primary site of action, could produce a compensatory increase in intake without affecting this putative balance. However, a variety of treatments have now been shown to produce dramatic changes in the motivation to self-administer cocaine, as demonstrated by the PR schedule, without causing corresponding changes in the rate of drug intake on a FR1 schedule (Roberts et al. 1989a; Loh and Roberts 1990; McGregor and Roberts 1993). These data suggest that there are some mechanisms that regulate drug intake that are distinct from those that mediate the reinforcing effects. Since animals do not show a compensatory increase in cocaine intake following baclofen pretreatment, we infer that the limiting factors that control drug intake are unchanged while the primary reinforcing properties of cocaine have been altered.

Consistent with previous reports (Roberts et al. 1996), the present results demonstrate that baclofen produced a dose-dependent reduction in break points for responding for cocaine on a PR schedule. The observation that baclofen's effect on cocaine self-administration is proportional to the demand characteristics of the schedule raises the issue whether sedation or other non-specific effects might account for the results. Baclofen has been reported to have sedative effects (Paredes and Agmo 1989; McManus and Greenshaw 1991) and can potentially suppress responding, particularly at higher doses (Zarrindast et al. 1989; Grech and Balster 1993). In order to rule out the possibility that baclofen produced a decrease in cocaine self-administration by interfering with the capacity of the rats to complete the operant response, the present experiment re-examined the effect of baclofen in animals given concurrent access to cocaine and food reinforcement. Analysis of food-reinforced responding (restricted to the first 2 h following baclofen administration when the drug effect would be strongest) showed that responding on the food-reinforced lever was not significantly reduced from baseline, regardless of the dose of baclofen administered. Indeed, at all but the highest dose of baclofen, the number of food-reinforced responses was somewhat increased, suggesting that baclofen produced a redirection from cocaine-directed, toward food-seeking behavior. Our results clearly demonstrate that animals were capable of completing several hundred responses on the food-reinforced lever during the time when cocaine-reinforced responding was suppressed. These data indicate that baclofen's effect on cocaine self-administration is not attributable to a generalized disruption of operant responding, and rule out the potential that a cocaine-baclofen combination produced a non-specific or toxic reaction.

It should be emphasized that because of the different demand characteristics of the schedules under concurrent access conditions, the present design does not allow a direct comparison of the effects of baclofen on the motivation to respond for food- or cocaine-reinforcement. The food component was introduced solely to demonstrate that rats retain the capacity to perform an operant response during the time period when cocaine-reinforced responding was suppressed and thus rule out a non-specific effect of baclofen. The food schedule (FR5) was chosen, through pilot experiments, so that at least as many responses were emitted on the food lever as on the cocaine-reinforced lever through the 6-h session. Although it has been demonstrated that a concurrently available non-drug reinforcer can affect cocaine-reinforced behavior (Glick et al. 1987; Carroll et al. 1989; De Vry et al. 1989; Comer et al. 1995), in the present investigation the initial break points for cocaine were not significantly altered by the introduction of the food lever once animals moved to the concurrent-responding phase of the experiment.

Several other papers have examined the impact of baclofen on food-reinforced responding in an attempt to address the selectivity of its effects. Shoaib et al. (1998) used a multiple schedule to show that baclofen decreased cocaine-reinforced responding, while responding during the food-reinforced component was only marginally affected. We have previously demonstrated that baclofen had little effect on food-reinforced responding on a PR schedule identical to the one used in cocaine self-administration experiments (Roberts et al. 1996). In that study, the food-reinforced group was cocaine naive. This may have been an important factor, since it has recently been shown that prolonged exposure to cocaine may alter the physiology of GABAergic systems (Zeigler et al. 1991; Pecins-Thompson and Peris 1993; Bonci and Williams 1996; Peris 1996; Shoji et al. 1997), and potentially, the behavioral response to GABA drugs. It is therefore possible that the cocaine self-administration group was more sensitive than the food-reinforced (cocaine-naive) group to the sedative, disruptive, or other non-specific effects of baclofen. Thus, the observed differential effects may have been due to the disparate drug histories, rather than a selective effect on cocaine. In this investigation the use of a concurrent access schedule of reinforcement allowed us to examine cocaine and food-reinforced responding in the same animal, thus controlling for drug

history. Our results confirm and extend previous observations (Roberts et al. 1996; Roberts and Andrews 1997; Shoaib et al. 1998) that baclofen selectively attenuates the reinforcing effects of cocaine in rats.

The demonstration that systemic baclofen reduced the break point for responding for cocaine suggests that $GABA_B$ agonists have the potential to modulate reward processes. However, these data do not address the anatomical site of action. Given the primary importance of DA terminals within the nucleus accumbens (Roberts et al. 1977, 1980) and other forebrain structures, it is logical to speculate that baclofen might produce its anticocaine effect through modulation of the mesolimbic DA system. The majority of neurons in the nucleus accumbens are GABAergic medium spiny neurons (Kita and Kitai 1988). These neurons, which make reciprocal connections with DA cells in the ventral tegmental area (VTA) presumably receive the cocaine-potentiated dopaminergic signal. Thus, the GABA projection and GABA-interneurons within the VTA have the capacity to powerfully influence DA release and DA cell firing (Klitenick et al. 1992; Cameron and Williams 1994; Churchill and Kalivas 1994; Kalivas and Duffy 1995). Manipulation of GABA systems has been shown to have direct effects on DA pathways (Klitenick et al. 1992; Santiago et al. 1993a, 1993b; Morgan and Dewey 1998), causing dose-dependent decreases in extracellular DA concentrations in the central nervous system of primates and rodents. A recent investigation using in vivo microdialysis (Dewey et al. 1997) has reported that GABA also attenuates cocaine-induced dopamine release in the nucleus accumbens and corpus striatum in rats.

The present results, along with recent preclinical (Dewey et al. 1998; Shoaib et al. 1998; Campbell et al. 1999) and clinical (Ling et al. 1998) reports support the idea that compounds that target GABA transmission represent a potentially useful strategy for the development of a pharmacological treatment for cocaine addiction.

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