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The $GABA_B$ Receptor Agonist Baclofen Attenuates Cocaine- and Heroin-Seeking Behavior by Rats

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Conditioned stimuli paired with drugs of abuse can acquire motivational properties, and are capable of inducing drug-seeking behavior and relapse to cocaine use. Converging evidence implicates the mesolimbic dopamine (DA) system, through interactions with limbic afferents to the nucleus accumbens, in behavior controlled by conditioned stimuli. The $GABA_B$ receptor agonist baclofen has been shown to decrease break points in rats responding for cocaine under progressive ratio schedules and also to attenuate activation of limbic cortical areas in human cocaine addicts. The purpose of the present study was therefore to investigate the effects of baclofen on drug-associated cue-controlled cocaine- or heroin-seeking behavior by rats. Under the second-order schedule of reinforcement used in the present study, cocaine or heroin were available after a fixed time interval, while high rates of responding during the interdrug intervals were maintained by the response-contingent presentations of drug-associated conditioned reinforcers. Baclofen decreased stimulus-maintained responding for either heroin or cocaine, but decreased only cocaine intake under an FR1 schedule. These results therefore support preliminary clinical findings and suggest that drugs with $GABA_B$ receptor agonist properties may aid abstinence in human drug addicts by decreasing the propensity to cue-induced drug-seeking and relapse.
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INTRODUCTION

Cocaine abuse has been described as a chronic relapsing disorder characterized by repeated 'binge'–abstinence–relapse cycles (Gawin and Kleber, 1986). In particular, stimuli paired with self-administered drugs of abuse can acquire motivational properties and thereby maintain drug-seeking behavior even after prolonged abstinence (O'Brien *et al*, 1998; Robinson and Berridge, 1993; Stewart *et al*, 1984). Strong evidence in support of this suggestion is the finding that these stimuli can induce conditioned physiological arousal and drug craving in humans (Childress *et al*, 1999; Ehrman *et al*, 1992), which are associated with increased activation of limbic cortical areas, including the orbital prefrontal cortex, anterior cingulate cortex, and amygdala (Breiter *et al*, 1997; Childress *et al*, 1999; Grant *et al*, 1996; Weinstein *et al*, 1997).

In an animal model of relapse, lesions or inactivations of the basolateral amygdala impaired cue-controlled cocaine-seeking and reinstatement (Grimm and See, 2000; Kantak *et al*, 2002; Kruzich and See, 2001; Whitelaw *et al*, 1996), as did infusion of dopamine (DA) receptor antagonists directly into the amygdala (See *et al*, 2001). In addition, antagonism of AMPA receptors in the nucleus accumbens core also disrupted cue-controlled drug-seeking (Di Ciano *et al*, 2001), suggesting that glutamatergic afferents from limbic cortical areas may interact with DA in the nucleus accumbens (Di Ciano *et al*, 1998a, b; Ito *et al*, 2000; Weiss *et al*, 2000) to mediate this important component of drug addictive behavior. These results suggest that pharmacological treatments to prevent conditioned stimulus-induced drug-seeking and relapse might be targeted at the mesolimbic DA system and its limbic cortical afferents (Everitt *et al*, 2001).

Baclofen is a $GABA_B$ receptor agonist that has been shown to attenuate behavior induced by conditioned stimuli when infused directly into the mesolimbic DA terminal area, the nucleus accumbens (Franklin and Druhan, 2000). Preclinical evidence that baclofen may be effective as a treatment for cocaine addiction was provided by the finding that the $GABA_B$ receptor agonist baclofen decreased the self-administration of both cocaine (Brebner *et al*, 2000a, b; Roberts and Andrews, 1997) and heroin (Xi and Stein, 1999). This effect was shown to be selective, as it did not impact on instrumental responding itself (Brebner *et al*, 2000a, b) or on the properties of a natural reinforcer (Roberts *et al*, 1996; Shoaib *et al*, 1998). Further, baclofen reduced reinstatement to cocaine self-administration in an

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animal model of relapse (Campbell *et al*, 1999), while clinical trials have revealed that baclofen can decrease cocaine craving and cocaine use, without impact on drug-induced euphoria (Ling *et al*, 1998). Moreover, in preliminary studies baclofen not only attenuated cue-induced drug craving, but also associated increases in limbic cortical activation in cocaine addicts exposed to conditioned stimuli previously paired with cocaine use (Childress, 2001).

The purpose of the present study was therefore to investigate the effects of baclofen on responding for either cocaine or heroin using a model of drug-seeking that is especially under the control of drug-associated stimuli. Under the second-order schedule of reinforcement used in the present study, the drug was available after a fixed time interval. We have previously demonstrated that high rates of responding under this schedule are maintained by contingent presentation of a drug-paired conditioned reinforcer, as omission of the drug cue decreased responding both before and after drug self-administration (Alderson *et al*, 2000; Arroyo *et al*, 1998). Furthermore, drug-seeking after psychostimulant self-administration was increased (Arroyo *et al*, 1998; Di Ciano *et al*, 2001; Pilla *et al*, 1999), reflecting the ability of these drugs to increase the control over behavior by conditioned reinforcers (Arroyo *et al*, 1998; Cador *et al*, 1991; Everitt *et al*, 2001; Killcross *et al*, 1997; Taylor and Robbins, 1984).

METHODS

Animals

A total of 21 male Lister-Hooded rats weighing 280–300 g at the time of surgery (Charles River; Kent, UK) were individually housed under a reversed 12 h light–dark cycle (lights on at 2000 h). Rats were maintained on a diet of 20 g of Purina lab chow/day, sufficient to maintain body weight and growth throughout the experiment. Water was freely available and food was given within 2 h of completion of daily testing. Experiments were carried out between 0900 and 2000 h, 6 or 7 days a week. Experiments were conducted in accordance with the United Kingdom 1986 Animals (Scientific Procedures) Act (Project License PPL 80/1324).

Apparatus

Rats were tested in operant chambers (Med Associates; 29.5 cm × 32.5 cm × 23.5 cm). Three sides were constructed from Perspex and the fourth was made of stainless steel, on which two 4 cm wide retractable levers were secured. The two levers were 12 cm apart, and 8 cm from the grid floor. Above each lever was a cue light (2.5 W, 24 V), and a red house light (2.5 W, 24 V) was located on the opposite wall. The floor of the chamber was lined with absorbent paper and covered with a metal grid. The testing chamber was placed within a sound- and light-attenuating box, equipped with a ventilation fan that also screened external noise. Silastic tubing shielded with a metal spring extended from each animal's i.v. catheter to a liquid swivel (Stoelting, Wood Dale, IL, USA) mounted on an arm fixed outside the operant chamber. Tygon tubing extended from the swivel to a Razel infusion pump (Semat Technical Ltd, Herts, UK) located adjacent to the external chamber. The operant chamber was interfaced with a Whisker operant control system with software written in Visual C++ (Cardinal, 2000).

Surgery

Rats were anaesthetized with ketamine hydrochloride (100 mg/kg i.p.; Ketaset) and xylazine (9 mg/kg i.p.; Rompun) and supplemented with ketamine as needed (~20 mg). All rats were implanted with a single catheter in the right jugular aimed at the left vena cava. Catheters consisted of a 22 g cannula attached to Silastic tubing (0.012 ID) and fixed to nylon mesh. The mesh end of the catheter was sutured subcutaneously (s.c.) on the dorsum. All surgical instruments were thoroughly sterilized prior to surgery. To prevent infection, rats were treated postsurgically with 10 mg/kg Baytril (Bayer) s.c. for 8 days; see Caine (1992).

Procedure

Acquisition of cocaine or heroin self-administration under a fixed interval (FI) 15 min schedule of reinforcement. Daily experimental testing began 7–10 days after surgical procedures. On each testing day, rats were connected to the i.v. line prior to the start of the training session. During initial training, rats acquired a lever press response for cocaine (0.75 mg/kg/inf/0.1 ml/5 s) or heroin (0.12 mg/kg/inf/0.1 ml/10 s) under a fixed-ratio (FR1, time out 20 s) schedule of reinforcement. Under this schedule each bar press resulted in illumination of the stimulus light above the lever, retraction of both levers, and extinction of the house light for 20 s. During the 20 s 'time out', bar presses had no consequence. Following this 20 s interval, the house light was again illuminated, the stimulus light was extinguished, and the two levers were again inserted into the testing box. 'Priming' injections of drug were never given. Active and inactive levers were counterbalanced between left and right sides for individual animals. Presses on the inactive lever had no programmed consequences, but were recorded to assess general levels of activity. To prevent accidental overdose, rats were limited to 30 infusions of drug per day, or a 2 h session. Following approximately 3 days of responding for cocaine, or 6 days of responding for heroin under an FR1 schedule, rats were progressively trained to respond under an interval schedule. The interval requirement was increased each day from FI1 min to 2, 4, 8, 10, 15 min. During responding under an FI15 min schedule, rats were permitted a maximum of five infusions a day or a maximum of a 2 h session.

Contingent presentation of the CS during responding for cocaine. Following responding for cocaine or heroin under the FI15 min schedule of reinforcement for 3 days, a second-order schedule of reinforcement was introduced. A CS was presented contingently following every 10th response while responding for cocaine, or following every fifth response for heroin. The contingent CS consisted of a 1 s illumination of the stimulus light above the lever and simultaneous extinguishing of the houselight for 1 s. Therefore, under this schedule, cocaine was available following completion of the first fixed ratio (FR) of 10 responses after an overall

FI15 min had timed out; during the (FI) 15 min, each FR10 response was reinforced by presentation of the drug-paired CS. For heroin, the schedule was the same, but the CS was presented on an FR5 schedule. Animals were permitted five infusions of drug per day under this schedule.

Administration of baclofen. Following approximately 7 days of responding for cocaine or heroin under a second-order schedule of reinforcement, rats were administered four counterbalanced doses of baclofen according to a latin-square design (vehicle, 1.25, 1.9, 2.5 mg/kg). Baclofen (Sigma, UK) was dissolved in saline and all injections were administered intraperitoneally (i.p.) in a volume of 2 ml/kg 30 min prior to testing. All baclofen treatment days were separated by at least 2 days of stable responding, defined as less than 30% variability in the number of responses made in the first interval. All rats were given one habituation injection of vehicle prior to baclofen treatments.

Upon completion of the second-order experiment, the effects of baclofen on cocaine or heroin intake were assessed using an FR1 schedule of reinforcement. For these experiments, rats were retrained on an FR1 schedule of reinforcement during daily 2 h sessions and stabilized on this schedule prior to administration of the same counterbalanced doses of baclofen (for cocaine: $n=7$, consisting of six naive rats and one from the second-order study; for heroin: $n=7$ from the second-order study). Stable responding was defined as less than 10% variability in the number of drug infusions self-administered in the 2 h session. An additional subset of baclofen naive rats ($n=6$) was administered baclofen prior to responding for cocaine. All injection procedures were identical to those under a second-order schedule of reinforcement with the exception that only one day of stable responding separated each treatment day.

Statistical Analyses

For all self-administration sessions, the number of active and inactive lever presses were recorded. In addition, the total number and temporal pattern of cocaine or heroin infusions were also recorded. Bar presses on the active lever are presented as the mean $\pm$ SEM number of responses. The number of responses on either the active or inactive lever during responding under an FR1 schedule of reinforcement was analyzed with one-way ANOVAs on the effect of dose. Responding under a second-order schedule of reinforcement is variable, both within and between subjects, especially for heroin (Alderson *et al*, 2000). Therefore, responding under a second-order schedule of reinforcement was expressed as percent change from baseline. Baseline was taken as the average of the last 2 days of responding prior to any baclofen treatments, calculated separately for each animal during each interval. Data were analyzed using one-way repeated-measures ANOVAs for each interval of responding under a second-order schedule for drug, with planned comparisons of vehicle to each dose. Separate analyses were conducted for responding on the active and inactive levers. For clarity, only the first cocaine- or heroin-free interval and the second interval (after the first self-administered drug infusion) were analyed.

Latency to the first CS and the first drug infusion were analyzed with one-way repeated-measures ANOVAs for the first cocaine- or heroin-free interval only. Latency provides a measure of the motivation to respond for the reinforcer (either the CS or cocaine). For all analyses, criteria for significance were set at $p \leqslant 0.05$.

RESULTS

Effects of Baclofen on Cocaine Self-administration

FR1 schedule. Administration of baclofen prior to cocaine self-administration under an FR1 schedule of reinforcement dose-dependently decreased cocaine intake (Figure 1). A one-way ANOVA on the effect of dose revealed a significant effect ($n=7$; $F(3,18)=5.089$, $p=0.010$). Planned comparisons revealed that the number of infusions self-administered after the 1.9 and 2.5 mg/kg doses of baclofen were significantly different from vehicle ($p<0.05$). No significant effects were revealed for responding on the inactive lever (number of responses following vehicle: 0.8 $\pm$ 0.6, 1.25 mg/kg: 0.8 $\pm$ 0.4, 1.9 mg/kg: 0.8 $\pm$ 0.6; 2.5 mg/kg: 1.4 $\pm$ 0.9).

Second-order schedule. Administration of baclofen to rats prior to responding under the FI15(FR10:S) schedule of reinforcement for cocaine produced dose-dependent decreases in responding during the first cocaine-free interval (mean baseline = 187 $\pm$ 26.9 responses), and during the second interval following the first self-administered cocaine infusion (mean baseline = 257 $\pm$ 43.0 responses). Responding decreased to approximately 20 and 30% of baseline during the first and second intervals, respectively, following administration of the highest dose of 2.5 mg/kg (Figure 2). One-way ANOVAs revealed a significant effect of dose during both intervals ($n=12$; first interval: $F(3,33)=3.906$, $p=0.017$; second interval: $F(3,33)=9.093$, $p<0.0001$). Planned comparisons revealed that responding was significantly different from vehicle following administration of the 1.9 and 2.5 mg/kg doses of baclofen during both the first and second intervals ($p<0.05$). No significant effects were revealed for responding on the inactive lever. (*For the first interval*: number of responses following vehicle: 4.2 $\pm$ 0.8; 1.25 mg/kg: 5.6 $\pm$ 1.8; 1.9 mg/kg: 4.3 $\pm$ 1.4; 2.5 mg/kg:

Figure 1 Mean+SEM effect of baclofen on cocaine self-administration under an FR1 schedule of reinforcement during a 2 h session. *Different from vehicle ($n=7$; planned comparisons, $p<0.05$).

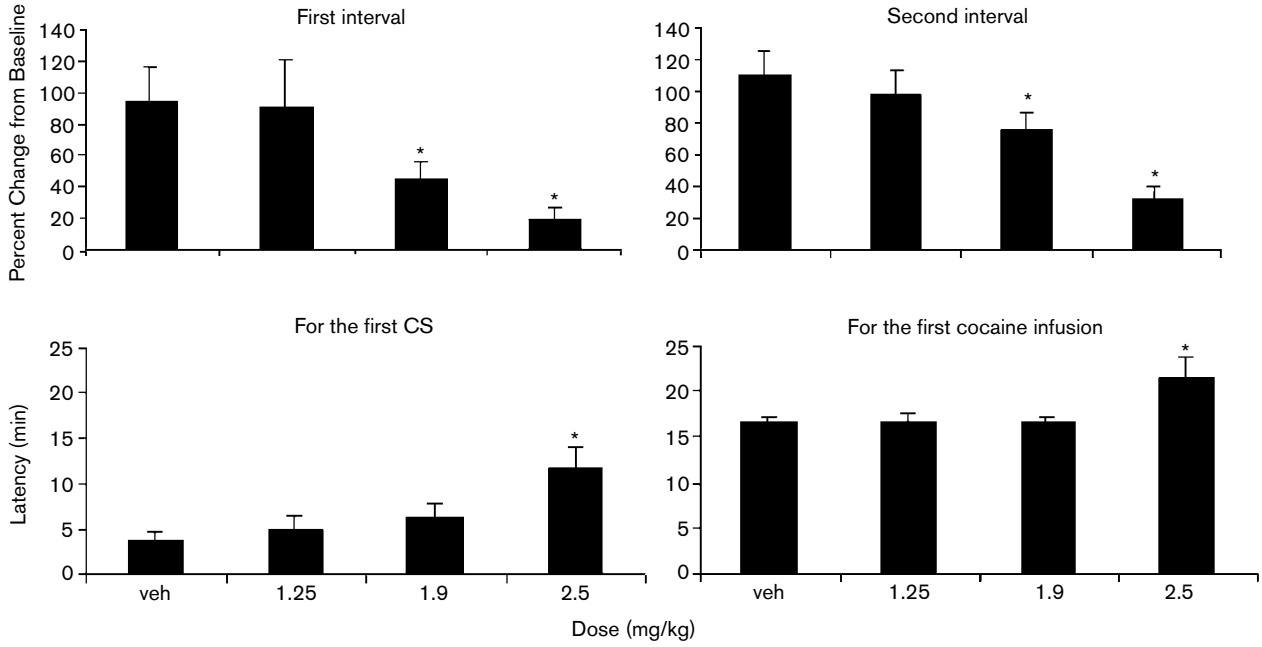

Figure 2 Effect of four counterbalanced doses of baclofen on mean+SEM responding for cocaine under a second-order schedule of cocaine reinforcement (FI15(FR10:S)). Top left: Percent change from baseline responding on the active lever during the first cocaine-free, interval. Top right: Cue-maintained responding following the first self-administered cocaine infusion. Bottom left: Latency to receive the first presentation of the CS. Bottom right: Latency to receive the first cocaine infusion. *Different from vehicle ($n = 12$; planned comparisons, $p < 0.05$).

3.7 ± 1.2. *For the second interval*: number of responses following vehicle: 8.2 ± 1.9; 1.25 mg/kg: 4 ± 0.9; 1.9 mg/kg: 6.8 ± 2; 2.5 mg/kg: 5.8 ± 1.7.)

Latencies. Administration of four counterbalanced doses of baclofen to rats 30 min prior to responding for cocaine under the second-order schedule of reinforcement (FI15(FR10:S)) produced dose-dependent increases in the latency to receive presentation of the first CS and the first cocaine infusion after the FI15 min had timed out (Figure 2). One-way ANOVAs on the effect of dose revealed significant increases in latencies for the CS ($n = 12$; ($F(3, 33) = 7.795$, $p < 0.001$) and US ($F(3, 33) = 3.769$, $p = 0.02$). Planned comparisons revealed that the latencies following the 2.5 mg/kg dose were significantly longer than following vehicle ($p < 0.05$).

Inspection of individual data from three representative rats illustrates the effects of 1.9 and 2.5 mg/kg of baclofen on responding for cocaine under the FI15(FR10:S) schedule of reinforcement, compared to responding following vehicle or under a simple interval schedule (Figure 3). Figures on the left represent responding during an FI15 min schedule of reinforcement without the contingent CS, where responding accelerated during the interval, characteristic of interval schedules of responding. By comparison, during responding under simple second-order schedule of reinforcement during which a drug-associated CS was presented following every 10th response, post-reinforcement pauses were observed following CS presentation that were superimposed on the scalloped pattern of responding for the drug. These are most evident in the top panel, and are typical of responding for the CS under a ratio schedule. Under this schedule, responding for cocaine increased greatly towards the end of the interval, and it was responding during the latter part of this interval that was especially disrupted by baclofen, as illustrated in the right panels. In addition, the highest 2.5 mg/kg dose of baclofen also increased the latency to receive the first CS presentation and infusion of cocaine.

Effects of Baclofen on Heroin Self-Administration

FRI schedule. Administration of four counterbalanced doses of baclofen prior to responding for heroin under an FR1 schedule of reinforcement did not decrease the number of self-administered heroin infusions (Figure 4). ANOVA revealed no significant effects for responding on either the active or inactive levers ($n = 7$; number of responses on the inactive lever following vehicle: 0.28 ± 0.28; 1.25 mg/kg: 3.4 ± 1.7; 1.9 mg/kg: 1.7 ± 09; 2.5 mg/kg: 1 ± 0.7).

Second-order schedule. Administration of baclofen to rats prior to responding under the FI15(FR5:S) schedule of reinforcement for heroin produced dose-dependent decreases in responding during the first heroin-free interval (mean baseline $= 121 \pm 21.8$ responses) and slight decreases during the second interval (mean baseline $= 136 \pm 25.9$ responses), following the first self-administered heroin infusion (Figure 5). Response rates decreased to approximately 60% of baseline during both the first and second intervals following administration of the highest 2.5 mg/kg of baclofen. Planned comparisons revealed that responding following the 2.5 mg/kg dose was significantly different from vehicle during the first interval only ($n = 9$; $p < 0.05$). No significant effects were revealed for responding on the inactive lever. (*For the first interval*:

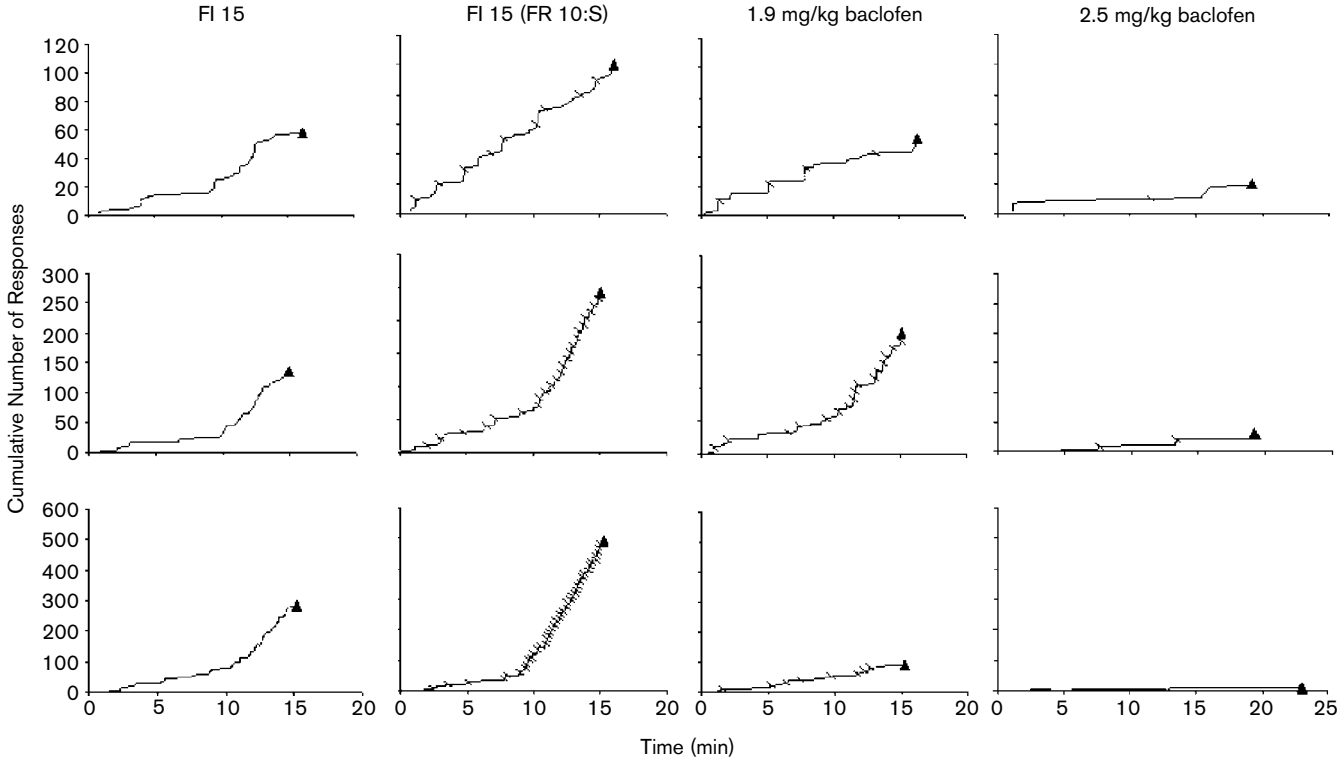

Figure 3 Individual cumulative response graphs from three representative individual rats selected to illustrate the range of responding for cocaine under an FI15(FR10:S) schedule of reinforcement. Left panels represent responding under an FI15 min schedule of reinforcement for cocaine in the absence of any CS presentations, when responding accelerated during the interval, characteristic of interval schedules of responding. The second panel on the left illustrates control levels of responding under the FI15(FR10:S) schedule of reinforcement following treatment with vehicle during which a drug-associated CS was presented following every 10th response; post-reinforcement pauses were observed following CS presentation that were superimposed on the scalloped pattern of responding for the drug. Under this schedule, responding for cocaine increased greatly towards the end of the interval, and it was responding during the latter part of this interval that was especially disrupted by baclofen, as illustrated in the right panels following administration of the 1.9 (second from right panels) or 2.5 mg/kg (right panels) doses. The 2.5 mg/kg dose also increased the latency to the first CS and cocaine infusion.

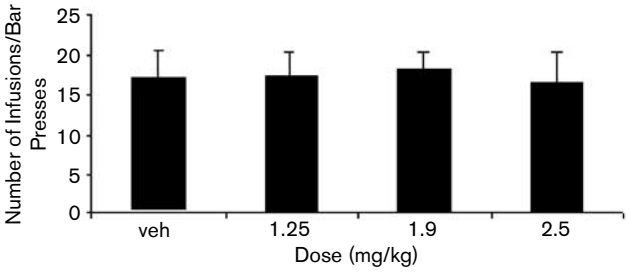

Figure 4 Mean+SEM effects of baclofen on the self-administration of heroin under an FR1 schedule of reinforcement during a 2 h session. ($n = 7$). No significant effects were revealed.

number of responses on inactive lever following vehicle: 4.8 ± 1.8; 1.25 mg/kg: 6.3 ± 1.5; 1.9 mg/kg: 3.5 ± 0.9; 2.5 mg/kg: 6.3 ± 1.7. *For the second interval*: number of responses on the inactive lever following vehicle: 2.8 ± 1.3; 1.25 mg/kg; 2.6 ± 1.6; 1.9 mg/kg: 0.8 ± 0.4; 2.5 mg/kg: 1.6 ± 1.)

Latencies. Administration of four counterbalanced doses of baclofen to rats 30 min prior to responding for heroin under the second-order schedule of reinforcement (FI15(FR5:S)) did not produce any changes in the latency to receive either the first CS presentation or the first heroin infusion (Figure 5). One-way ANOVAs on the effect of dose revealed no significant effects ($n = 9$).

Inspection of individual data from three representative rats illustrates the effects of 1.9 or 2.5 mg/kg of baclofen on responding for heroin under the FI15(FR5:S) schedule of reinforcement, compared to responding following vehicle or under a simple interval schedule in the absence of the contingent presentation of CS (Figure 6). Figures on the left represent responding during an FI15 min schedule of reinforcement with no contingent presentation of the CS, where accelerated responding during the interval is observed, characteristic of interval schedules of reinforcement. By comparison, during responding under a second-order schedule of reinforcement under which a heroin-associated CS was presented following every fifth response, post-reinforcement pauses following CS presentation were observed, superimposed on the scalloped pattern for drug. These were most evident for the rat in the second row, and are typical of responding for the CS under a ratio schedule. Under this schedule, responding for heroin increased greatly towards the end of the interval, and it was responding during the latter part of this interval that was disrupted by baclofen, as illustrated in the right panels. Thus, responding during the early part of the interval was not decreased by baclofen, nor did latencies to receive the first CS or to receive the first heroin infusion.

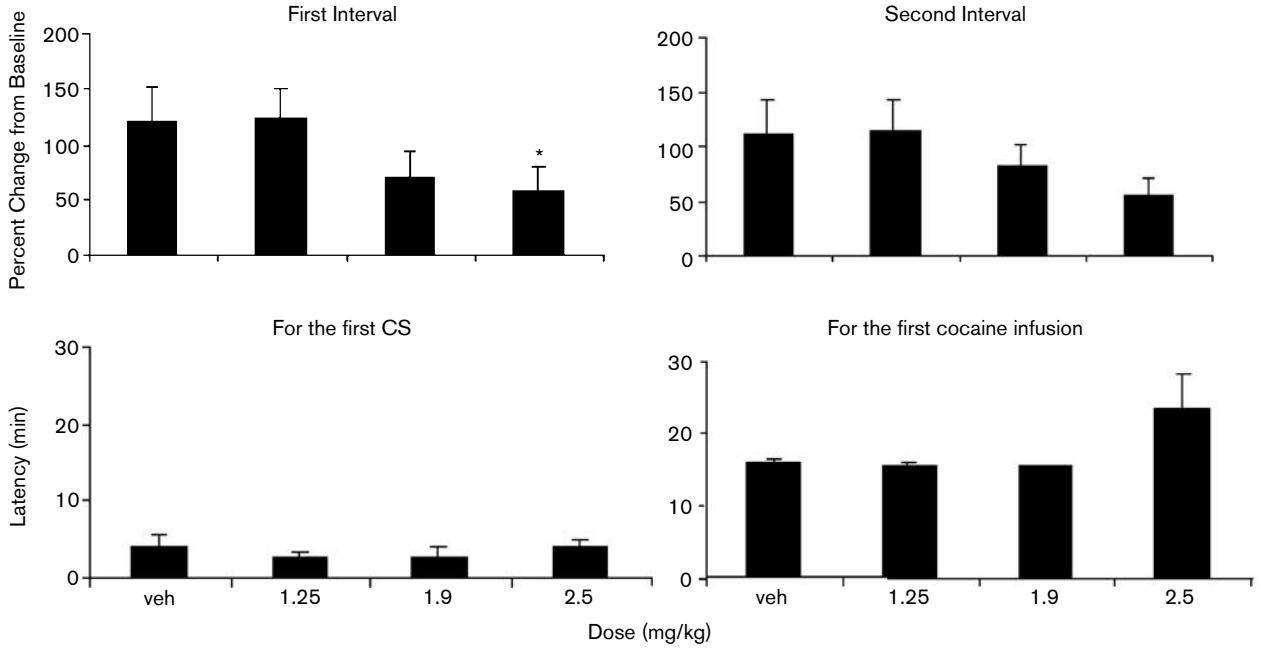

Figure 5 Effect of four counterbalanced doses of baclofen on mean+SEM responding for heroin under a second-order schedule of heroin reinforcement (FI15(FR5:S)). Top left: Percent change from baseline responding on the active lever during the first heroin-free, interval. Top right: Cue-maintained responding following the first, self-administered heroin infusion. Bottom left: Latency to receive the first presentation of the CS. Bottom right: Latency to receive the first heroin infusion. *Different from vehicle ($n = 12$; planned comparisons, $p < 0.05$).

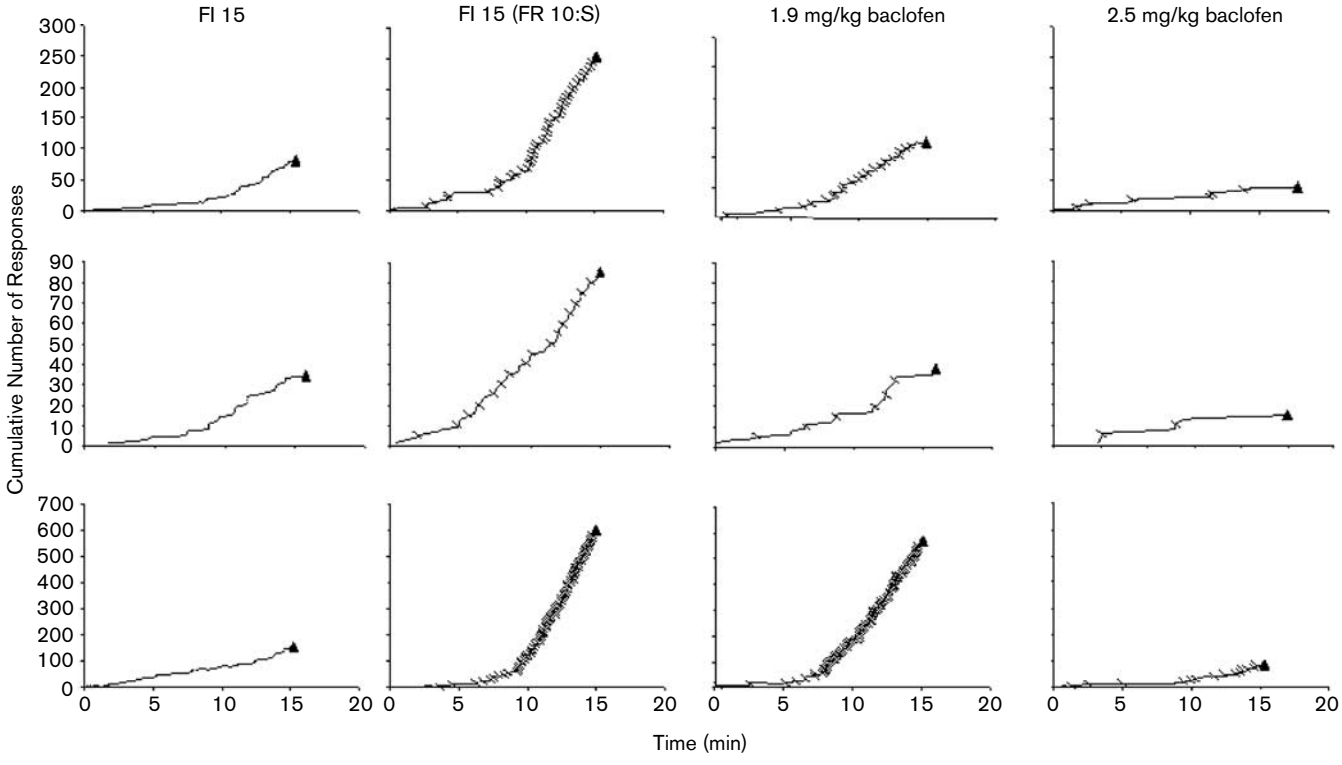

Figure 6 Individual cumulative response pattern from 3 representative rats selected to illustrate the range of responding for heroin under an FI15(FR5:S) schedule of reinforcement. Left panels represent responding under an FI15 min schedule of reinforcement for heroin, in the absence of any contingent CS presentations, when responding accelerated during the interval. The second panel on the left illustrates responding under an FI15(FR5:S) schedule of reinforcement following vehicle treatment when every 5th response was followed by a CS presentation; post-reinforcement pauses were evident following CS presentation that were superimposed on the scalloped pattern of responding for the drug. Under this schedule, responding for heroin increased greatly towards the end of the interval, and it was responding during the latter part of this interval that was especially disrupted by baclofen, as illustrated in the right panels following administration of the 1.9 mg/kg (second from right panels) or 2.5 mg/kg (right panels) doses.

DISCUSSION

The purpose of the present study was to investigate the effects of the GABA$_B$ receptor agonist baclofen on the taking and seeking of cocaine or heroin under an FR1 and a second-order schedule of reinforcement, respectively. Administration of baclofen produced dose-dependent decreases in cue-controlled responding for both drugs under a second-order schedule of reinforcement, although the effects were more pronounced for cocaine. By contrast, only responding for cocaine, but not heroin, under an FR1 schedule was decreased by pretreatment with baclofen. These results therefore suggest that baclofen decreased cue-maintained responding for either cocaine or heroin, and additionally decreased the reinforcing properties only of cocaine.

Differential Effects of Baclofen on Cocaine and Heroin Reinforcement

Pretreatment with baclofen produced dose-dependent decreases in cocaine self-administration, but had no effect on heroin self-administration under continuous reinforcement, suggesting that baclofen reduced the reinforcing effects of cocaine but not heroin. The present finding that baclofen decreased the reinforcing properties of cocaine confirms previous reports that baclofen decreased cocaine self-administration and responding for cocaine under a progressive ratio schedule of reinforcement (Brebner *et al*, 1999; Roberts and Andrews, 1997; Roberts *et al*, 1996; Shoaib *et al*, 1998). But by contrast to previous findings (Brebner *et al*, 2002; Xi and Stein, 1999, 2000), the reinforcing properties of heroin were not changed by baclofen. The lack of effect of baclofen in the present study may be related to the dose of heroin used, since it has been demonstrated that baclofen is effective in decreasing the self-administration of low doses of cocaine, but was ineffective in reducing responding for doses of cocaine higher than that used in the present study (Brebner *et al*, 2000a, b; Roberts *et al*, 1996). In this regard, the dose of heroin used in the present study (0.12 mg/kg/infusion) was high relative to the dose used in other studies (0.06 mg/kg/infusion (Xi and Stein, 1999, 2000); 0.025 mg/kg/infusion (Brebner *et al*, 2002)). However, it is interesting to note that baclofen may have differential effects on cocaine and heroin self-administration, as the GABA$_B$ receptor antagonist CGP56433A reversed baclofen-induced decreases in cocaine, but not heroin, self-administration, suggesting a direct role for GABA$_B$ receptors in cocaine reinforcement only (Brebner *et al*, 2002).

Effects of Baclofen on Drug-Seeking Maintained by a Cocaine- or Heroin-Paired Conditioned Reinforcer

Second-order schedules of reinforcement provide an animal model of cue-controlled drug-seeking. Response rates before and after drug self-administration have been shown to be maintained by the contingent presentation of drug-associated stimuli acting, therefore, as conditioned reinforcers (Alderson *et al*, 2000; Arroyo *et al*, 1998; Everitt and Robbins, 2000). Therefore, the first cocaine- or heroin-free interval can be viewed as a period of cue-maintained drug-seeking, while subsequent intervals provide a measure of the influence of self-administered drug on subsequent cue-maintained drug-seeking.

Although response rates under second-order schedules of drug reinforcement are maintained by contingent presentations of the conditioned reinforcer (Arroyo *et al*, 1998; Di Ciano *et al*, 2001; Goldberg 1973, 1976; Goldberg *et al*, 1975; Pilla *et al*, 1999), the primary reinforcer also supports responding and in particular influences response patterning. Observation of cumulative records of responding in the present study revealed an acceleration of responding towards the end of each interval. This scalloping is typical of interval schedules, and has been observed for both primary and secondary reinforcers (Kelleher, 1966). Superimposed on this scalloped responding were post-reinforcement pauses typical of ratio schedules, in this instance each FR resulting in the presentation of the drug-associated conditioned reinforcer. Indeed, the effect of the CS to increase responding was greatest towards the end of the interval, when responding for drug accelerated.

By contrast to the effects of baclofen on cocaine and heroin intake, pretreatment with baclofen reduced cue-controlled drug-seeking for both of these drugs under a second-order schedule of reinforcement. Given the finding that baclofen also decreased cocaine reinforcement, it is tempting to speculate that decreases in responding for cocaine under a second-order schedule of reinforcement were related to an attenuation of cocaine reinforcement only. However, it has previously been shown that responding under a second-order schedule increased during the second interval on the first day of extinction when saline was substituted for cocaine (Di Ciano and Everitt, 2001). Therefore, proportional changes in responding during both the first and second intervals in the present study suggest that decreased responding for cocaine following pretreatment with baclofen was related not only to a reduction in the reinforcing effect of cocaine, but also to a decrease in the motivational impact of the CS. Indeed, the relatively lesser attenuation of responding for heroin under the second-order schedule perhaps reflects the selective effects of baclofen on the motivational impact of the CS, without any change in heroin reinforcement. These findings therefore suggest that baclofen decreased drug-seeking in these experiments through its ability to attenuate the conditioned reinforcing properties of the drug-associated CS, an effect that was enhanced by a reduction in the reinforcing effect of cocaine, but not heroin.

Analysis of responding for cocaine under a second-order schedule of reinforcement provided further support for the finding that baclofen reduced not only the additional reinforcing properties of the drug-paired CS, but also the reinforcing properties of cocaine. As discussed above, response patterning under a second-order schedule of reinforcement reflects not only the ability of the conditioned reinforcer to maintain responding, but also the reinforcing value of the drug. Therefore, changes in the latency to respond for the CS and US may have reflected a change in the reinforcing property of cocaine, the CS, or both.

GABA$_B$ receptor agonists such as baclofen can produce catalepsy and reduce motor activity, and such effects might therefore nonspecifically have reduced responding for cocaine or heroin. However, the results of the present study suggest that this is not a likely explanation for the effects of baclofen as doses similar to those used here did not

influence responding for a natural reinforcer (Roberts *et al*, 1996; Shoaib *et al*, 1998). Moreover, heroin intake was not reduced, even at the highest dose tested, further confirming the view that baclofen did not decrease heroin- or cocaine-seeking through some of its nonspecific locomotor effects.

Potential Mechanism by which Baclofen Reduced Cocaine- and Heroin-Seeking

Especially in view of the differential ability of baclofen to modulate cocaine or heroin self-administration, the finding of a similar influence of this drug on cocaine- or heroin-seeking under a second-order schedule of reinforcement is important as it suggests a common neural mechanism of drug-seeking maintained by stimuli paired with different drugs of abuse. This parsimonious view of drug-seeking is emerging from animal studies that have demonstrated that cue-maintained cocaine- and heroin-seeking are both affected by dopaminergic mechanisms. For example, systemic administration of the D2 DA receptor agonist bromocriptine reinstated both cocaine- and heroin-seeking (Wise *et al*, 1990), as did direct administration of *d*-amphetamine into the nucleus accumbens (Stewart and Vezina, 1988).

Pretreatment with the GABA receptor agonist vigabatrin blocked conditioned increases in nucleus accumbens DA efflux (Gerasimov *et al*, 2001) that were associated with exposure to environmental stimuli predictive of drug reward (Di Ciano *et al*, 1998a, b; Weiss *et al*, 2000). Thus, baclofen may attenuate conditioned increases in DA efflux via actions on ventral tegmental DA neurons, as further indicated by the observation that its infusion directly into the VTA disrupted conditioned place preference to a morphine-paired environment (Tsuji *et al*, 1996). This mechanism may be common to drug-related incentive processes, as both cocaine (Shoaib *et al*, 1998) and heroin (Xi and Stein, 2000) reinforcement were attenuated by infusion of baclofen into the VTA, while infusion into the nucleus accumbens only attenuated cocaine reinforcement (Brebner *et al*, 2000a, b; Shoaib *et al*, 1998). Thus, baclofen may attenuate both cocaine and heroin incentive motivational processes through its ability to decrease nucleus accumbens DA release via effects in the VTA. However, other sites of action of the systemically administered drug are also likely, since infusion of GABA receptor agonists into the prefrontal cortex and nucleus accumbens, but not the basolateral amygdala, abolished conditioned activity expressed following exposure to a drug-paired environment (Franklin and Druhan, 2000). Thus, baclofen may disrupt conditioned influences on behaviour also via its action in limbic-cortical sites.

Conclusions

The purpose of the present study was to evaluate the effect of baclofen on the seeking and taking of cocaine and heroin. Pretreatment with the $GABA_B$ receptor agonist decreased cocaine, but not heroin, self-administration, while drug-seeking maintained by the contingent presentation of a stimulus paired with either cocaine or heroin was decreased following pretreatment with baclofen. Similar effects of baclofen on cocaine and heroin seeking suggest a common underlying neural mechanism, especially in view of the differential effects of baclofen on cocaine and heroin reinforcement. These data support preliminary clinical findings demonstrating that baclofen reduced drug craving (Ling *et al*, 1998) and limbic cortical activation following exposure to cocaine-associated stimuli (Childress, 2001). Taken together, the present results suggest that baclofen or other drugs acting at $GABA_B$ receptors may be a potential treatment for drug addiction, especially cue-induced relapse to drug use.

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