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ORIGINAL INVESTIGATION

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The $GABA_B$ antagonist CGP56433A attenuates the effect of baclofen on cocaine but not heroin self-administration in the rat

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Abstract *Rationale:* Several reports have demonstrated that the γ-aminobutyric acid $(GABA)_B$ agonist baclofen attenuates the reinforcing effects of cocaine in rats, and recent evidence indicates that it might have a similar effect on heroin self-administration. *Objectives*: The specific $GABA_B$ receptor antagonist CGP56433A was used to further evaluate the involvement of $GABA_B$ receptors in the baclofen-induced suppression of cocaine and heroin self-administration. *Methods:* In the first series of experiments, dose–response curves were generated to examine the effect of CGP56433A (0.6, 1.0, or 1.8 mg/kg, i.p.) on cocaine (1.5 mg/kg per injection) and heroin (25 µg/kg per injection) self-administration reinforced under a fixed-ratio (FR1) or progressive ratio (PR) schedule. Separate sets of experiments then examined the effect of the co-administration of CGP56433A and baclofen on responding for cocaine or heroin under both schedules. *Results:* Pretreatment with CGP56433A had no effect on cocaine or heroin self-administration, while baclofen dose dependently reduced responding for both cocaine and heroin under both the FR1 and PR schedule. CGP56433A (1.8 mg/kg) blocked the effect of baclofen on cocaine but not on heroin self-administration. *Conclusion:* The specific $GABA_B$ antagonist CGP56433A attenuated the effect of baclofen on cocaine self-administration, suggesting that $GABA_B$ receptors are critical in mediating the anti-cocaine effect of baclofen. In combination with other studies, the data demonstrate that the susceptibility of baclofen and other $GABA_B$ agonists to receptor blockade depends on the behavioral response being studied. Whether this indicates different receptor mechanisms are involved (e.g., pre- versus post-synaptic effects or differential receptor reserve) remains to be determined.

Keywords CGP56433A · Baclofen · Cocaine · Heroin · GABA · Agonist · Self-administration

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Introduction

A growing body of evidence indicates that cocaine reinforcement can be modulated by stimulation of γ-aminobutyric $acid_B$ ($GABA_B$) receptors. Several recent studies have reported that $GABA_B$ agonists such as baclofen and CGP44532 produce a robust modulation of cocaine self-administration under several different schedules of reinforcement (Roberts et al. 1996; Roberts and Andrews 1997; Shoaib et al. 1998; Brebner et al. 1999, 2000a, 2000b; Campbell et al. 1999; see Roberts and Brebner 2000 for review). While $GABA_B$ receptors are widely distributed throughout the brain (Bischoff et al. 1999; Billinton et al. 2000), several lines of evidence support the hypothesis that $GABA_B$ receptors on dopamine (DA) neurons within the ventral tegmental area (VTA) are critical in mediating baclofen's anti-cocaine effect. Microinjections of baclofen into the VTA have been shown to have direct effects on DA pathways, causing a decrease in the release of extracellular DA in the nucleus accumbens (NAC) (Kalivas et al. 1990; Kalivas 1993; Yoshida et al. 1994; Westerink et al. 1997). Evidence for a specific role for the VTA in the behavioral effects of cocaine has been suggested by the finding that intra-VTA baclofen prevents the motor-stimulant responses to peripheral cocaine (Kalivas et al. 1990) and selectively reduces cocaine self-administration under fixed ratio (FR; Shoaib et al. 1998) and progressive ratio (PR) schedules of reinforcement (Brebner et al. 2000b).

Antagonists for specific receptor subtypes are often used to help define and confirm the mechanisms associ-

Table 1 Inhibition of binding of radioligands to 17 receptors present in the central nervous system by the γ-aminobutyric acid $(GABA)_B$ receptor antagonist CGP56433A. *NMDA N*-methyl-D-aspartate, *AMPA* α-amino-3-hydroxy-5-methyl-4-isoxazoleprionic acid

No.	Receptor	Radioligand (source)	Percentage inhibition (10^{-5}M)	IC_{50} (nM)
1	$GABA_B$	^{3}H-CGP27492 (rat cortex)	100	80
2	$GABA_B$	^{3}H-CGP64213 (recombinant rat $GABA_B$ R1a)	100	17
3	$GABA_A$	^{3}H-muscimol (calf cortex)	–[a]	–[a]
4	Benzodiazepine	^{3}H-flunitrazepam (rat cortex)	–[a]	–[a]
5	NMDA	^{3}H-CGP39653 (rat brain)	–[a]	–[a]
6	AMPA	^{3}H-AMPA (rat brain)	–[a]	–[a]
7	Kainate	^{3}H-kainic acid (rat brain)	–[a]	–[a]
8	NMDA glycine site	^{3}H-DCKA (rat brain)	–[a]	–[a]
9	$Alpha_1$-adrenergic	^{3}H-prazosin (rat cortex)	–[a]	–[a]
10	$Alpha_2$-adrenergic	^{3}H-clonidine (rat cortex)	–[a]	–[a]
11	$Adenosine_1$	^{3}H-N6-cyclohexyl-adenosine (rat cortex)	–[a]	–[a]
12	$5\text{-}HT_1$	^{3}H-5-HT (rat cortex)	–[a]	–[a]
13	$5\text{-}HT_2$	^{3}H-ketanserine (rat cortex)	–[a]	–[a]
14	$5\text{-}HT_3$	^{3}H-GR65630 (rat brain)	–[a]	–[a]
15	Histamine 1	^{3}H-doxepine (rat brain)	23	–[a]
16	Muscarinic acetylcholine	^{3}H-*cis*-methyl-dioxolane (rat cortex)	–[a]	–[a]
17	Opiate (μ-site)	^{3}H-naloxone (rat cortex)	–[a]	–[a]
18	Neurokinin-1	^{3}H-substance P (bovine retina)	–[a]	–[a]

[a] No notable effect (i.e., <10%) was observed

ated with agonist-induced changes in behavior. CGP56433A is a high-affinity antagonist at the $GABA_B$ receptor [IC_{50}=80 nM for the inhibition of binding of an agonist radioligand at native $GABA_B$ receptors of rat cerebral cortex (Froestl et al. 1996) and IC_{50}=17 nM for the inhibition of binding of an antagonist radioligand at the recombinant rat $GABA_B$ receptor splice variant R1a, Table 1]. CGP56433A showed marginal or no affinities to 16 other receptors present in the central nervous system (Table 1). As CGP56433A crosses the blood–brain barrier rapidly, it has proved useful in blocking the behavioral effects of $GABA_B$ agonists. For example, CGP56433A has been shown to reverse the hypothermia and antihyperalgesia effect of baclofen and another $GABA_B$ agonist, CGP44532 (Froestl et al. 1995, 1996; Patel et al. 2001). CGP56433A has also been used to study the development of ethanol tolerance in mice (Barreto Zaleski et al. 2001) as well as the role of $GABA_B$ receptors in gene expression and seizure activity (Heese et al. 2000).

Macey et al. (2001) recently reported the unexpected phenomenon that CGP56433A failed to block the effects of the $GABA_B$ agonist CGP44532 on intra-cranial self-stimulation (ICSS). In fact, the agonist and the antagonist both produced a similar effect, i.e., an increase in ICSS thresholds. Since it has been suggested that the mesolimbic DA system may be a common pathway for mediating the reinforcing properties of ICSS and psychostimulants such as cocaine (Koob and Bloom 1988; Wise 1996), and baclofen is thought to interact with the mesolimbic system, the question arises whether a $GABA_B$ antagonist would have similar effects on ICSS and cocaine reinforcement mechanisms. In the present investigation we examined the effect of the specific $GABA_B$ antagonist CGP56433A on cocaine self-administration. Of interest was whether the $GABA_B$ antagonist would block the effect of baclofen, as might be predicted from standard receptor pharmacology, or whether the agonist and antagonist would have similar effects as reported by Macey et al. (2001) in their experiments with ICSS.

There is evidence that opiates might also produce some of their reinforcing effects via activation of the mesolimbic DA system. Drugs such as heroin are thought to excite DA neurons in the VTA indirectly by binding to μ-opioid receptors and hyperpolarizing inhibitory, GABA-containing interneurons (Johnson and North 1992). Two recent studies that examined the effect of GABAergic drugs on heroin self-administration showed that the gamma-transaminase inhibitor gamma-vinyl-gaba (GVG) and baclofen reduced heroin self-administration and heroin-induced increases in NAC DA release (Gerasimov and Dewey 1999; Xi and Stein 1999). A second objective of the present report was to characterize the effect of baclofen on heroin self-administration reinforced under FR and PR schedules, and to determine whether these effects would be blocked or augmented by the co-administration of CGP56433A.

Methods

Subjects

Subjects were male Sprague Dawley rats (Harlan, Ind.) weighing 275–300 g at the start of the experiments. All the experimental procedures described in this report were carried out in accordance with the *Guide for the Care and Use of Laboratory Animals* (National Research Council, revised 1996) and were reviewed and approved by the Wake Forest University Animal Care and Use Committee. All animals were placed under quarantine for 1 week following arrival at the facility and were maintained on a 12-h/12-h reversed light/dark cycle (lights off at 0300 hours). Purina Rat Chow and water were 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, each rat was individually housed in 1 of 16 identical 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 or heroin injections on a FR1 schedule. Concurrent with the start of each cocaine (1.5 mg/kg per injection in 0.12 ml saline) or heroin (25 µg/kg per injection in 0.12 ml saline) infusion, a stimulus light located above the lever was activated to signal a 20-s post-infusion time-out period, during which time responses produced no programmed consequence. Rats received daily 6-h test sessions (0900 hours until 1500 hours) which began with one non-contingent injection. After a stable pattern of drug intake (40 injections/6 h and regular post-infusion pauses) was established, which generally required about 1 week, subjects were randomly assigned to experimental groups.

Effect of CGP56433A on cocaine self-administration

Two separate groups of rats were tested under a FR1 schedule (n=4) or a PR schedule (n=5) of cocaine reinforcement (1.5 mg/kg per injection). Under the PR schedule, cocaine infusions were contingent on 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). Training on the PR schedule continued until the break point over three consecutive days varied by less than three increments. Break point was defined as the number of completed increments on the PR schedule before a 1-h period when no injections were obtained. Once stable rates of responding were established, which generally took about 1 week, all rats were pretreated with CGP56433A (0.6, 1.0, or 1.8 mg/kg, i.p.) 30 min prior to the test sessions. The order of CGP56433A injections was counterbalanced according to a Latin square design, and test sessions were separated by at least three baseline days of cocaine self-administration.

Effect of baclofen and CGP56433A on cocaine self-administration

In order to determine whether CGP56433A blocked baclofen-induced decreases in cocaine self-administration, a group of rats (n=8) was trained to respond for cocaine (1.5 mg/kg per injection) under a FR1 schedule of reinforcement as previously described. Once stable rates of responding were established under the FR1 schedule, rats were pretreated with CGP56433A (0, 0.6, 1.0, or 1.8 mg/kg, i.p.) followed by a high dose of baclofen (5.6 mg/kg, i.p.) in two successive injections 30 min prior to the start of the daily session. CGP56433A injections were counterbalanced according to a Latin square design and were separated by at least 3 days of stable responding.

Two additional groups of rats were trained to respond under a PR schedule of reinforcement (1.5 mg/kg per injection) as previously described. One group (n=8) was pretreated with baclofen (1.8, 3.2, or 5.6 mg/kg, i.p.), while the second group (n=8) was pretreated with CGP56433A (1.8 mg/kg, i.p.) and baclofen (1.8, 3.2, or 5.6 mg/kg, i.p.) in two successive injections. All drug treatments were administered 30 min prior to the start of the daily session. The dose of baclofen injections in both groups was counterbalanced according to a Latin square design and test sessions were separated by at least 3 days of responding over which break points varied by less than three.

Effect of baclofen on heroin self-administration

A separate group of rats was trained to respond for 25 µg/kg heroin under a FR1 schedule (n=7). Following 3 days of stable responding, rats received various doses of 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.

Effect of CGP56433A on heroin self-administration

The effect of CGP56433A on heroin-reinforced responding was assessed in a separate groups of rats trained to respond for a unit injection dose of 25 µg/kg heroin under a FR1 schedule (n=5) as previously described. Once stable rates of responding were established, rats were pretreated with various doses of CGP56433A (0.6, 1.0, or 1.8 mg/kg, i.p.) 30 min prior to the test sessions. The order of CGP56433A injections was counterbalanced according to a Latin square design and test sessions were separated by at least 3 days.

Effect of baclofen and CGP56433A on heroin self-administration

In order to determine whether CGP56433A blocked baclofen-induced decreases in heroin self-administration, two separate experiments were conducted in which rats were trained to respond for 25 µg/kg per injection of heroin under a FR1 or PR schedule of reinforcement as previously described. Once stable rates of responding were established on the FR1 schedule, two groups of rats (n=7 per group) were pretreated with baclofen (1.8, 3.2, or 5.6 mg/kg, i.p.) alone, or in combination with the high dose of CGP56433A (1.8 mg/kg, i.p.) 30 min prior to the start of the daily session. The effect of baclofen on heroin-reinforced responding under a PR schedule was assessed in two additional groups of rats (n=6–8 per group). Rats were trained to self-administer 25 µg/kg per injection of heroin under a FR1 schedule as previously described. Once responding under FR1 conditions stabilized, rats were switched to the PR schedule. Daily sessions were 8 h in length. When responding on the PR schedule, stabilized rats received various doses of baclofen (0, 1.8, 3.2, or 5.6 mg/kg, i.p., counterbalanced according to a Latin square design) alone or in combination with the high dose of CGP56433A (1.8 mg/kg, i.p.) 30 min prior to the session. All pretreatments were counterbalanced according to a Latin square design and test sessions were separated by at least 3 days of stable responding.

Data analysis

Each dose–response curve was analyzed using repeated-measures analysis of variance (ANOVA), with dose as a repeated factor and drug condition as a between-subjects factor. Neuman-Keuls tests (one-tailed) were used to examine individual comparisons among animals that completed testing across all drug doses.

Drugs

Cocaine hydrochloride and heroin were supplied by the National Institute on Drug Abuse (Research Triangle, N.C.). CGP56433A was synthesized and provided by Novartis Pharma AG. All compounds were dissolved in sterile saline. Dosages are expressed as the salt.

Results

Effect of CGP56433A on cocaine self-administration

Systemic administration of the $GABA_B$ antagonist CGP56433A had no effect on responding for cocaine

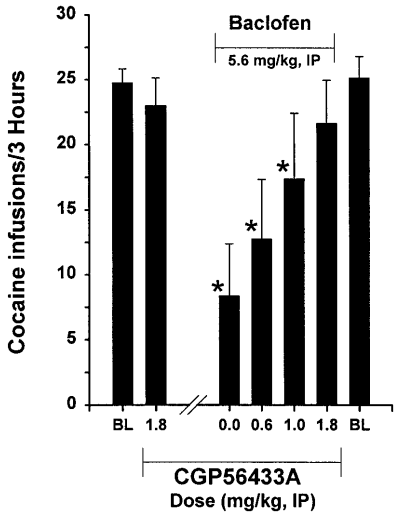

Fig. 1 The effect of the γ-aminobutyric acid $(GABA)_B$ antagonist CGP56433A and baclofen on cocaine self-administration. Two separate groups of rats were trained to respond for cocaine (1.5 mg/kg per injection) under a fixed ratio (FR)1 schedule of reinforcement. The *two bars* on the *left* represent the mean (±SEM) number of responses for one group of rats (n=4) during baseline (*BL*) conditions or following pretreatment with CGP56433A (1.8 mg/kg, i.p.). Also shown are responses from a second group of rats (n=8) pretreated with baclofen (5.6 mg/kg, i.p.) and various doses of CGP56433A (0, 0.6, 1.0, or 1.8 mg/kg, i.p.). All pretreatments were administered 30 min prior to the test session. The 1.8-mg/kg dose of CGP56433A did not affect responding under the FR1 schedule. Baclofen significantly attenuated cocaine intake during the first 3 h of the test session (*P<0.05 compared with BL), and CGP56433A dose dependently attenuated this effect. Cocaine intake in rats treated with CGP56433A (1.8 mg/kg) plus baclofen (5.6 mg/kg) did not differ from BL conditions

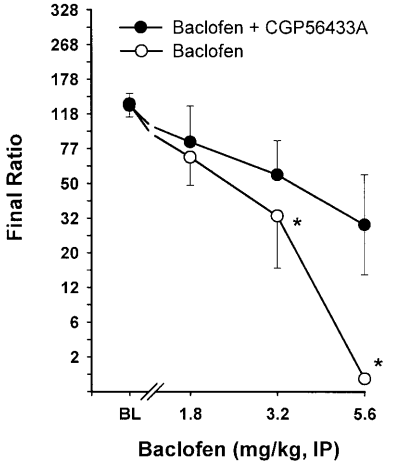

Fig. 2 Effect of baclofen and the γ-aminobutyric acid $(GABA)_B$ antagonist CGP56433A on cocaine self-administration reinforced on a progressive ratio schedule. Separate groups of rats (n=8 per group) were trained to self-administer cocaine (1.5 mg/kg per injection). *Open circles* represent the mean (±SEM) break points after various doses of baclofen (1.8, 3.2, or 5.6 mg/kg, i.p.). *Closed circles* represent mean break points after treatment with baclofen in combination with CGP56433A (1.8 mg/kg, i.p.). All drugs were administered 30 min prior to the test session. Break points were significantly reduced compared with baseline (*BL*) conditions after the intermediate and high doses of baclofen (*P<0.05). A significant drug × dose interaction was observed (see Results). No CGP56433A plus baclofen data point was significantly different from BL

(1.5 mg/kg per injection) under either a FR1 or PR schedule of reinforcement (data not shown). The number of cocaine injections during the first 3 h of the FR1 test session did not vary from baseline levels under the FR1 schedule, and break points were not significantly changed after any of the doses of CGP56433A (see Fig. 1 for the effect of 1.8 mg/kg CGP56433A).

Effect of baclofen and CGP56433A on cocaine self-administration

Figure 1 illustrates the effect of combining a high dose of baclofen with various doses of CGP56433A in rats responding for cocaine under a FR1 schedule of reinforcement. Baclofen (5.6 mg/kg, i.p.) caused a significant reduction in responding during the first 3 h of the test session. ANOVA revealed that CGP56433A dose dependently blocked the effect of baclofen on responding ($F_{4,28}$=5.09, P<0.01). Newman Keuls multiple comparisons revealed that the effect of baclofen was significantly attenuated by the 1.8-mg/kg dose of CGP56433A (P<0.05). This experiment was used as a dose finding study to establish an effective CGP56433A dose. The 1.8 mg/kg dose was used in subsequent experiments to examine the effect on the baclofen dose–response function.

The effect of baclofen on cocaine-reinforced responding under a PR schedule is illustrated in Fig. 2 (open circles). Baclofen produced a dose-dependent decrease in break points ($F_{3,21}$=21.72; P<0.01). Newman Keuls multiple comparisons revealed that the two highest doses of baclofen (3.2 mg/kg and 5.6 mg/kg, i.p.) caused significant reductions in responding when compared with baseline, with the highest dose causing an almost complete cessation of responding in the entire group of rats. Also illustrated in Fig. 2 is the effect of CGP56433A on baclofen-induced reductions in cocaine-reinforced responding under the PR schedule (closed circles). ANOVA showed a significant drug × dose interaction ($F_{3,42}$=3.2, P<0.05). Analysis of the simple main effects revealed a significant difference between the baclofen and CGP56433A + baclofen groups, indicating that the expected dose-dependent decrease in responding produced by baclofen was attenuated by the co-administration of CGP56433A.

Effect of CGP56433A on heroin self-administration

CGP56433A pretreatment (0.6, 1.0, or 1.8 mg/kg, i.p.) failed to produce a significant effect on heroin-reinforced responding under a FR1 schedule during the first 3 h of the test session when the effect of treatment would have been the strongest (data not shown).

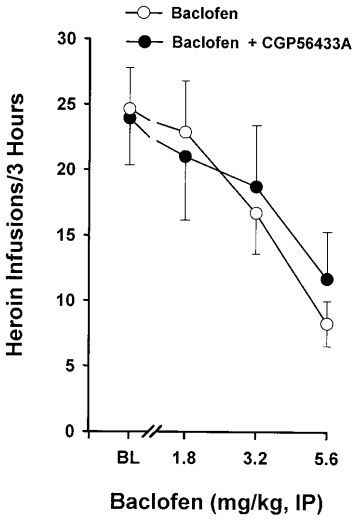

Fig. 3 Effect of baclofen and CGP56433A on responding for heroin self-administration reinforced under a fixed ratio (FR)1 schedule. Two separate groups of rats (*n*=8 per group) were trained to respond for heroin (25 µg/kg per injection) under a FR1 schedule of reinforcement. *Open circles* represent the mean (±SEM) number of infusions of heroin during the first 3 h of the session under baseline conditions (*BL*) or after various doses of baclofen (1.8, 3.2, or 5.6 mg/kg, i.p.). *Closed circles* represent the mean number of responses in the second group treated with various doses of baclofen and the high dose of CGP56433A (1.8 mg/kg, i.p.). All pretreatments were administered 30 min prior to the test session. Baclofen dose dependently reduced heroin self-administration when compared with BL; heroin intake was significantly reduced after all three doses (P<0.05). The co-administration of the antagonist CGP56433A did not block the effect of baclofen

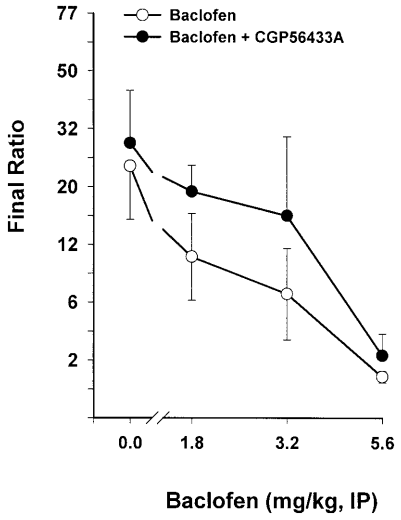

Fig. 4 Effect of baclofen and CGP56433A on heroin-reinforced break points. Two groups of rats were trained to respond for heroin (25 µg/kg per injection) under a progressive ratio schedule of reinforcement. Points represent the mean (±SEM) break points after various doses of baclofen (0, 1.8, 3.6, or 5.62 mg/kg, i.p.) alone (*open circles, n*=8) or in combination with CGP56433A (*closed circles, n*=6). All drugs were administered 30 min prior to the test session. Break points were significantly reduced compared with baseline (*BL*) conditions after all three doses of baclofen (P<0.05). CGP56433A failed to produce a statistically significant effect on the baclofen dose–response curve

Effect of baclofen and CGP56433A on heroin self-administration

Baclofen dose dependently attenuated the self-administration of 25 µg/kg per injection of heroin under a FR1 schedule of reinforcement. Figure 3 (open circles) shows that the two higher doses of baclofen (3.2 mg/kg and 5.6 mg/kg, i.p.) caused a significant decrease in the number of injections of heroin that were self-administered during the first 3 h of the session ($F_{4,24}$=12.29, P<0.05). The effect of the $GABA_B$ antagonist CGP56433A on the baclofen dose–response curve is also illustrated in Fig. 3 (closed circles). ANOVA revealed a significant effect of dose, but no effect of group or dose × group interaction was seen. CGP56433A (1.8 mg/kg, i.p.) failed to block the effect produced by the two higher doses of baclofen, and heroin-reinforced responding was significantly reduced during the first 3 h of the test session.

The effect of baclofen on heroin-reinforced responding (25 µg/kg per injection) under a PR schedule is illustrated in Fig. 4 (open circles). ANOVA revealed a significant effect of dose when baclofen (0, 1.8, 3.2, or 5.6 mg/kg) was administered 30 min prior to the beginning of the test session ($F_{3,18}$=10.49, P<0.01). Newman Keuls multiple comparisons indicated that heroin-reinforced break points were significantly reduced following all three doses of baclofen (P<0.01). Figure 4 also shows that the high dose of CGP56433A (1.8 mg/kg) did not block baclofen's effect on heroin-reinforced break points (closed circles). While two of the CGP56433A data points were somewhat above those of the baclofen-alone group, ANOVA failed to reveal a statistically significant effect.

Discussion

The results of the present investigation provide further support for the hypothesis that $GABA_B$ receptor modulation attenuates cocaine reinforcement. Baclofen has previously been shown to reduce cocaine self-administration, although the magnitude of the effect appears to depend on the unit-injection dose of cocaine and the response requirements of the schedule (Roberts et al. 1996; Roberts and Andrews 1997; Campbell et al. 1999; Shoaib et al. 1999; Brebner et al. 2000a, 2000b; see Roberts and Brebner 2000 for review). Consistent with previous reports, high doses of baclofen were shown to disrupt responding for cocaine under both FR and PR schedules of reinforcement. Here we also show that the specific $GABA_B$ antagonist CGP56433A blocks the anti-cocaine effect of baclofen. These results provide compelling evidence that baclofen's effect on cocaine reinforcement is mediated by $GABA_B$ receptor activation.

The results of the present experiments also demonstrated that baclofen reduces heroin intake. Xi and Stein (1999) have previously reported that baclofen reduced

heroin reinforcement in rats responding under a FR schedule. The present investigation supports and extends their finding by demonstrating that baclofen also decreased heroin self-administration under a PR schedule. The observation that baclofen can reduce both cocaine and heroin self-administration suggests that $GABA_B$ receptor activation may cause a generalized suppression of drug reinforcement. However, the results of the experiments involving CGP56433A suggest that there may be differences in the pharmacological specificity of this suppression.

Pretreatment with CGP56433A alone had no effect on either cocaine or heroin self-administration under a FR1 or PR schedule or reinforcement. This is consistent with previous reports that $GABA_B$ antagonists produce no overt behavioral effects when administered alone at doses that completely block the actions of $GABA_B$ agonists (Getova et al. 1997, 1998; Heese et al. 2000; Barreto Zaleski et al. 2001).

The present finding that CGP56433A failed to block the effect of baclofen on heroin self-administration was unexpected. The dose of CGP56433A (1.8 mg/kg) that completely blocked the effect of a relatively high dose of baclofen on cocaine-reinforced responding produced no statistically significant attenuation of baclofen-induced suppression of heroin self-administration. It is possible that larger doses of CGP56433A might have blocked the effect of baclofen on heroin intake; however, it should be noted that a dose of 0.3 mg/kg CGP56433A is sufficient to block completely the antihyperalgesic effect of baclofen (Patel et al. 2001). This suggests that the highest dose used in the present investigation (1.8 mg/kg) should have been sufficient. Macey et al. (2001) used doses up to 10 mg/kg and found no blockade of the effect of a $GABA_B$ agonist on ICSS thresholds. In fact, the agonist (CGP44532) and the antagonist (CGP56433A) were found to shift ICSS thresholds in the same direction. These studies demonstrate that the susceptibility of baclofen and other $GABA_B$ agonists to receptor blockade depends on the behavioral response being studied. Whether this indicates that different receptor mechanisms are involved (e.g., pre- versus post-synaptic effects or differential receptor reserve) remains to be determined.

An increasing number of studies have demonstrated that $GABA_B$ receptor activation modulates the effects of various reinforcers including cocaine, heroin, ICSS, alcohol, and nicotine (Roberts et al. 1996; Roberts and Andrews 1997; Ling et al. 1998; Brebner et al. 1999, 2000a, 2000b; Campbell et al. 1999; Shoaib et al. 1999; Xi and Stein 1999; Addolorato et al. 2000; Akhondzadeh et al. 2000; Corrigall et al. 2000; Shoptaw 2000). Although several studies have demonstrated that baclofen attenuates cocaine self-administration, the present investigation is the first to report that the highly specific $GABA_B$ antagonist CGP56433A blocks this effect. It has been suggested that opiate and psychostimulant reinforcement may share some similarities, and the demonstration that baclofen also reduces heroin self-administration under a PR schedule does support this hypothesis. However, the fact that CGP56433A does not block baclofen's effect on heroin self-administration highlights the differences between these two classes of drugs. Clearly further investigation will be necessary to determine whether the differences lie in the qualitative effects produced by these reinforcers or in the neurochemical systems that are involved in mediating the effects.

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