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The $GABA_B$ Receptor-Positive Modulator GS39783 and the $GABA_B$ Receptor Agonist Baclofen Attenuate the Reward-Facilitating Effects of Cocaine: Intracranial Self-Stimulation Studies in the Rat

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There is an increasing interest in the development of nondopaminergic pharmacotherapies for cocaine abuse. Emerging preclinical and clinical data with the metabotropic $GABA_B$ receptor agonist baclofen support a role for the modulation of $GABA_B$ receptors in the treatment of drug addiction. Nevertheless, the muscle relaxant, hypothermic, and sedative properties of baclofen somewhat limit its widespread potential therapeutic utility. Recently, positive modulators of the $GABA_B$ receptor such as GS39783 (*N*,*N*′-dicyclopentyl-2-methylsulfanyl-5-nitro-pyrimidine-4,6-diamine) have been identified. These positive modulators enhance the effects of GABA (γ-aminobutyric acid) through actions at an allosteric site and are devoid of intrinsic agonistic efficacy. The aim of the present study was to assess the ability of the novel $GABA_B$-positive modulator GS39873 or baclofen to modulate the behavioral effects of cocaine. Drugs of abuse such as cocaine lower brain reward thresholds obtained using intracranial self-stimulation (ICSS). We demonstrate here that GS39783 had no intrinsic effects on ICSS reward thresholds (10–100 mg/kg p.o.) in rats, whereas the full $GABA_B$ receptor agonist baclofen (2.5–5 mg/kg p.o.) dose dependently elevated thresholds. Moreover, both GS39783 and baclofen attenuated the threshold lowering effect of cocaine administration (10 mg/kg intraperitoneally) in a dose-related manner. These data strongly suggest that activation of $GABA_B$ receptors attenuates the rewarding effects of acute cocaine. Therefore, $GABA_B$-positive modulation may represent a novel therapeutic strategy for the treatment of cocaine dependence and possibly other drugs of abuse without the side effects of full $GABA_B$ receptor agonists.

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INTRODUCTION

γ-Aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the brain, where it acts on two receptor classes: ionotropic $GABA_A$ and $GABA_C$ receptors and metabotropic $GABA_B$ receptors. Despite the identification of $GABA_B$ receptors over 20 years ago (Bowery *et al*, 1980), the molecular identity of this receptor has only recently been elucidated (Kaupmann *et al*, 1997). $GABA_B$ receptors form heterodimers comprised of $GABA_{B(1)}$, of which there are at least two known functional splice variants, $GABA_{B(1a)}$ and $GABA_{B(1b)}$, and $GABA_{B(2)}$ subunits, both of which are necessary for formation of functionally active receptors (Calver *et al*, 2002; but see, Gassmann *et al*, 2004). $GABA_B$ receptors are located both pre- and postsynaptically where they modulate, both neurotransmitter release and inhibitory postsynaptic potentials, respectively. Additionally, they function as heteroreceptors on dopamine and glutamate terminals (for a review, see Bettler *et al*, 2004).

Since Roberts and colleagues (1996) first demonstrated that the prototypical $GABA_B$ receptor agonist baclofen attenuated cocaine self-administration in rats, there has been accumulating evidence from both preclinical and clinical studies that $GABA_B$ receptors may play a key role in drug dependence (Brebner *et al*, 2002a; Cryan *et al*, 2003b). Specifically, $GABA_B$ receptor activation via baclofen or other agonists attenuates many of the neurochemical and behavioral effects elicited by drugs of abuse. Baclofen administration reduces self-administration of *d*-amphetmaine (Brebner *et al*, 2005), nicotine (Fattore

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et al, 2002; Paterson *et al*, 2004a, b), heroin (Xi and Stein, 1999; Di Ciano and Everitt, 2003) alcohol (Colombo *et al*, 2002), and cocaine (Roberts *et al*, 1996; Brebner *et al*, 2000, 2002b).

Preliminary clinical studies have demonstrated that administration of baclofen reduces craving for both cocaine and alcohol in addicted patients (Ling *et al*, 1998; Addolorato *et al*, 2002; Shoptaw *et al*, 2003). Additionally, baclofen has been reported to attenuate the activation of limbic brain regions induced by cocaine-associated cues in human neuroimaging studies (Brebner *et al*, 2002a). However, the muscle relaxant, hypothermic, and sedative properties of baclofen may limit its widespread utility in both preclinical and clinical testing (Wang *et al*, 2002; Cryan *et al*, 2004; Lobina *et al*, 2005; Jacobson and Cryan, 2005).

Allosteric-positive modulation of metabotropic receptors is a newly identified phenomenon, providing novel means for the pharmacological manipulation of G-protein-coupled receptors acting at a site apart from the orthosteric binding region of the receptor protein (Soudijn *et al*, 2002; Jensen and Spalding, 2004). The $GABA_B$ receptor-positive modulator GS39783 (*N*,*N*′-dicyclopentyl-2-methylsulfanyl-5-nitro-pyrimidine-4,6-diamine) has recently been identified and characterized *in vitro* (Urwyler *et al*, 2003). GS39783 potentiates both the potency and maximal efficacy of GABA-stimulated guanosine 5′-*O*-(3-[^{35}S]thio)triphosphate ([^{35}S]GTPγS) binding to membranes from a $GABA_{B(1b/2)}$-expressing Chinese hamster ovary cell line, but does not stimulate [^{35}S]GTPγS binding itself. Potentiation of $GABA_B$ receptor responses by GS39783 is also observed using native $GABA_B$ receptor preparations from rat brain. Such properties suggest that allosteric modulators may offer a number of potential pharmacological improvements over the use of conventional agonists as has been demonstrated for modulators acting at ligand-gated ion channel. In the case of $GABA_A$ receptors, such modulation has been therapeutically utilized with the benzodiazepines, which amplify the action of the endogenous neurotransmitter GABA. Indeed, we have recently shown that GS39783 does not elicit the side effects associated with baclofen when administered *in vivo* (Cryan *et al*, 2004). Thus, they represent a novel tool with which to study the role of $GABA_B$ receptors in behaviors relevant to drug dependence. In this vein, it has recently been shown that GS39783 administration attenuated cocaine self-administration in the rat (Smith *et al*, 2004).

Electrical intracranial self-stimulation (ICSS) of some brain sites is very rewarding for laboratory animals (Olds and Milner, 1954; Markou and Koob, 1993). The high reward value of ICSS has led to the hypothesis that ICSS directly activates the same neuronal circuits that are activated by natural reinforcers, and thus, provides a direct measure of brain reward function (eg Phillips *et al*, 1989; Wise *et al*, 1992). Therefore, the use of the ICSS procedure provides a unique opportunity to study the neurobiology of reward and motivation. As ICSS directly activates the brain reward pathways, there is no satiation, tolerance, or sensitization to its rewarding effects (Phillips and Fibiger, 1989; Markou and Koob, 1991; Markou and Koob, 1993). Thus, a major advantage of this procedure is that it provides a quantitative measure of reward (brain reward thresholds measured in μA) that is extremely stable over periods of months under baseline conditions (see Phillips and Fibiger, 1989; Wise *et al*, 1992; Markou and Koob, 1993; Kornetsky, 2004). All drugs of abuse, including cocaine, lower intracranial self-stimulation reward thresholds, which is hypothesized to reflect the euphorigenic effects of these drugs (Markou and Koob, 1991). Thus, the ICSS paradigm represents a highly robust and sensitive technique to assess quantitatively the magnitude of experimental manipulations on brain reward function. Therefore, the aim of the present study was to assess the effects of the novel $GABA_B$ receptor-positive modulator GS39873 or the $GABA_B$ receptor agonist baclofen to modulate the threshold lowering effect of acute cocaine on ICSS behavior.

MATERIALS AND METHODS

Animals

Male Sprague–Dawley rats (Charles River, France) weighing between 300–350 g at the time of surgery were used in these studies. The animals were housed in pairs and maintained on a 12-h light:dark cycle (lights on 06:00) in a temperature-controlled colony (22–24°C). The animals had free access to food and water. Animals were allowed to habituate for at least 4 days before surgery. All experimental procedures were subject to institutional review and conducted in accordance with the Veterinary Authority of Basel-Stadt, Switzerland.

ICSS Electrode Implantation

Rats were anesthetized with an isoflurane–oxygen vapor mixture (1–3% isoflurane, oxygen flow rate 450–500 CCM) and secured in a stereotaxic frame (TSE Systems). The rats were prepared with a stainless-steel bipolar electrode with a diameter of 0.25 mm (MS303/2, Plastics One) cut to 11 mm in length, into the medial forebrain bundle at the level of the posterior lateral hypothalamus (AP -0.5 mm from bregma; ML ± 1.7 mm; DV -8.3 mm from dura with the incisor bar at $+5$ mm above the interaural line). The electrode was anchored to four stainless-steel skull screws (Plastics One) using dental acrylic. Animals were allowed to recover for at least 7 days before undergoing ICSS training.

ICSS Apparatus

The experimental apparatus consisted of eight Plexiglas chambers ($30.5 \times 30 \times 17$ cm^3; Med Associates Inc.) encased in Coulomb sound-attenuated boxes. The chamber consisted of a stainless-steel grid floor and a metal wheel manipulandum located on one of the shorter walls, which required a 0.2 N force to rotate it a quarter turn. Optical sensors determined when the wheel rotated 90°. Gold-contact swivel commutators (SL2C two-channel commutator; Plastics One) and bipolar leads (305–305 TT(CS), Plastics One) connected the animals to a constant current stimulator (Stimtek 1200, San Diego Instruments, San Diego, CA), which in turn was controlled via a DOS-based custom-made program ran from a PC. The stimulation parameters, data collection, and all programming functions were controlled by the computer program.

ICSS Procedure

The ICSS procedure was carried out in the light phase as described previously (Cryan *et al*, 2003a, c), which is a version of that originally developed by Kornetsky and Esposito (1981) and modified by Markou and Koob (1992). Briefly, rats were trained to rotate the wheel manipulandum on a fixed ratio 1 schedule of reinforcement to obtain 500 ms trains of electrical stimulation. Rectangular cathodal pulses (0.1 ms) at 50, 100, or 200 Hz frequencies were utilized throughout experimentation. All rats first were tested at the 100 Hz frequency, and if the current level at which they responded was below 80 μA or above 240 μA and unstable, then testing on the 50 or 200 Hz frequency, respectively, was initiated. After training to respond on the fixed ratio 1 schedule of reinforcement, rats were trained gradually on the discrete-trial procedure. In this procedure, rats received a noncontingent electrical stimulus and had 7.5 s to turn the wheel one-quarter of a rotation to receive another stimulus identical to the first. The response latency was defined as the time interval between the onset of the noncontingent stimulus and a positive response. The response latency for each test session was the average response latency on all trials, which resulted in a positive response. After a response or the 7.5 s period, the intertrial interval followed, which had an average duration of 10 s and varied randomly from 7.5 to 12.5 s. During a 2 s period immediately after a positive response, any further responses were recorded as extra responses and had no scheduled consequences. Quarter turns during the time-out period were counted as time-out responses and resulted in a delay of 12.5 s before the onset of the next trial. To determine the threshold, current intensities were varied according to the psychophysical method of limits and presented in alternating descending and ascending series (two of each) in 5 μA current intensity steps, with three consecutive trials at each step. The series was terminated by the occurrence of either 15 stimulus steps in one ascending or descending series, two consecutive sets of trials in which two of three responses were negative in a descending series, or two consecutive sets of trials in which two of three responses were positive in an ascending series. The current threshold for an ascending series was defined as the stimulus intensity half-way between the level at which the subject failed to respond on two or more of the three trials at a current intensity step and the level at which the subject responded positively on two or more of the three trials at two consecutive current intensity sets. The current threshold for a descending series was the reverse of that for an ascending series. The mean of the four current thresholds was defined as the current threshold for the subject. The ICSS session duration was approximately 30 min. After 2–4 weeks, this threshold is generally stable (less than 10% standard deviation during 5 consecutive testing days), at which time the experimental manipulations could begin.

Experimental Protocol

The drug combinations were administered using a within-subject counterbalanced design, whereby each animal received the drug combinations in a different order to ensure that the response was not due to the sequence of administration, while ensuring that each drug dose occurred in all possible positions in the order. Each subject required 3-day stable baselines (less than 10% standard deviation from the previous 3 days) between and before each drug injection. In this manner, each subject was administered vehicle (0.5% methylcellulose), GS39783 (10, 30, or 100 mg/kg) or baclofen (2.5 or 5 mg/kg) p.o. (2 ml/kg) 1 h prior to the ICSS trial session. Then, 10 min before the start of the ICSS trial, the subjects received either vehicle (0.9% NaCl) or cocaine hydrochloride (10 mg/kg) intraperitoneally (i.p.) (1 ml/kg). Doses of baclofen were selected based on previous studies showing baclofen reduced self-administration of cocaine in this dose range. GS39783 has been extensively characterized behaviorally in our laboratories (Cryan *et al*, 2004; Mombereau *et al*, 2004; Slattery *et al*, 2005) and the dose range selected was equal and above that which was behaviorally active in anxiety (0.1–30 mg/kg) and self-administration (3–30 mg/kg) models (Smith *et al*, 2004). Both GS39783 and baclofen were synthesized by Novartis Pharma AG (Basel).

Data Analyses

Data represent mean ± SEM percentage change in current–intensity threshold or latency time compared with the previous 3-day mean current–intensity or latency time. Two rats did not respond after pretreatment with the highest dose of baclofen (5 mg/kg): one in the saline group and one in the cocaine group. These data points were not included in the statistical analyses for the respective groups. Data were analyzed using a two-way repeated measures (RM) ANOVA. Any overall statistical differences, which were set at $P<0.05$, were further analyzed using Fisher's *post hoc* interaction tests. All data were analyzed using SigmaStat v2.03.

RESULTS

Effect of GS39783 or Baclofen Treatment on ICSS Reward Thresholds

Two-way RM ANOVA on percent change from the previous 3-day baseline revealed effects of pretreatment ($F(5, 105)=11.17$; $p<0.001$) and treatment ($F(1, 22)=101.00$; $p<0.001$), but no significant pretreatment × treatment interaction ($F(5, 105)=0.39$; $p=0.851$).

Post hoc analyses showed that neither GS39783 at any dose tested (10, 30, or 100 mg/kg) nor the lower dose of baclofen (2.5 mg/kg) affected baseline ICSS thresholds ($p>0.05$; Figure 1). However, the highest dose of baclofen tested (5 mg/kg) significantly elevated ICSS thresholds ($p<0.001$; Figure 1). Cocaine treatment resulted in a significant lowering of brain reward thresholds similar to previous findings (Markou and Koob, 1992). *Post hoc* analyses revealed that GS39783 (30–100 mg/kg) dose dependently attenuated the threshold lowering effect of cocaine (Figure 1). Both doses of baclofen employed in the present study also attenuated the threshold lowering effect of cocaine (2.5 mg/kg, $p<0.05$; 5 mg/kg, $p<0.001$: Figure 1), whereas only the highest baclofen dose tested significantly increased baseline ICSS threshold responses.

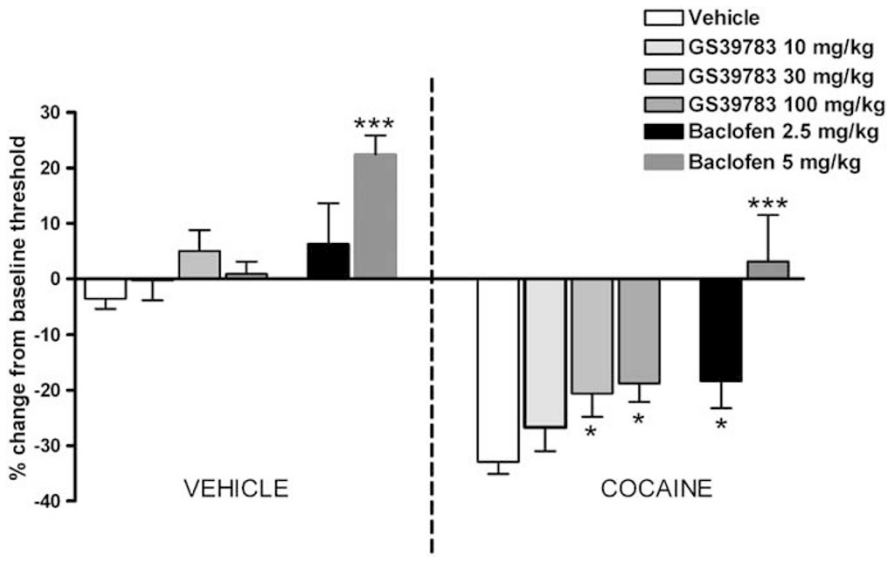

Figure 1 Effects of GS39783 or baclofen administration on ICSS reward thresholds alone and on the threshold lowering effect of cocaine. Pretreatment with GS39783 (10–100 mg/kg p.o. −1 h) had no intrinsic effect on ICSS thresholds in the saline treatment group ($p > 0.05$). Contrastingly, pretreatment with baclofen (2.5 or 5 mg/kg p.o. −1 h) dose dependently elevated reward thresholds. Cocaine administration (10 mg/kg i.p. −10 min) alone significantly lowered ICSS thresholds, an effect which was dose dependently attenuated by pretreatment with either GS39783 or baclofen. There was no significant pretreatment × treatment interaction ($p > 0.05$) Data represent mean % change from previous 3-day threshold baseline ± SEM ($n = 8$–9). Two-way RM ANOVA followed by Fisher's *post hoc* test was performed. *$p < 0.05$ and ***$p < 0.001$ compared with relevant treatment group.

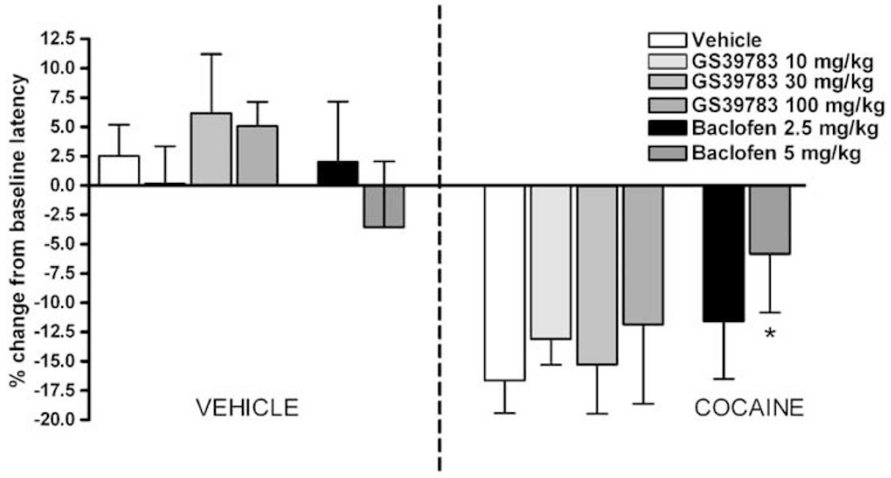

Figure 2 Effects of GS39783 or baclofen administration on ICSS response latencies alone and in the presence of cocaine. There was no significant effect of pretreatment (vehicle, GS39783, or baclofen) ($p > 0.05$) or pretreatment × treatment (cocaine or vehicle) interaction ($p > 0.05$). There was a significant effect of treatment on response latencies ($p < 0.0001$). *Post hoc* analyses revealed significant differences between all pretreatment groups followed by vehicle or cocaine treatment, with the exception of the dose of 5 mg/kg baclofen ($p < 0.05$) Data represent mean % change from previous 3-day response latency baseline ± SEM ($n = 8$–9). Two-way RM ANOVA followed by Fisher's *post hoc* test was performed. *$p < 0.05$ and compared with relevant treatment group.

Effect of GS39783 or Baclofen Treatment on ICSS Latencies

Two-way RM ANOVA revealed effects of treatment (cocaine *vs* vehicle: $F(1, 22) = 24.8$, $p < 0.001$) on response latency, but no effect of pretreatment ($F(5, 105) = 0.274$, $p = 0.925$) or pretreatment × treatment interaction ($F(5, 105) = 1.66$, $p = 0.167$). *Post hoc* analyses showed significant decreases in response latency for all GS39783 doses examined and the 2.5 mg/kg dose of baclofen, but not after the highest 5 mg/kg dose of baclofen in the cocaine treatment groups compared with saline administration (Figure 2).

Verification of Electrode Placement

Histological staining of cryostat-cut rat brain sections demonstrated that the electrode tips were located in the lateral hypothalamus of the animals used in the present study (see Figure 3 for a schematic representation of the

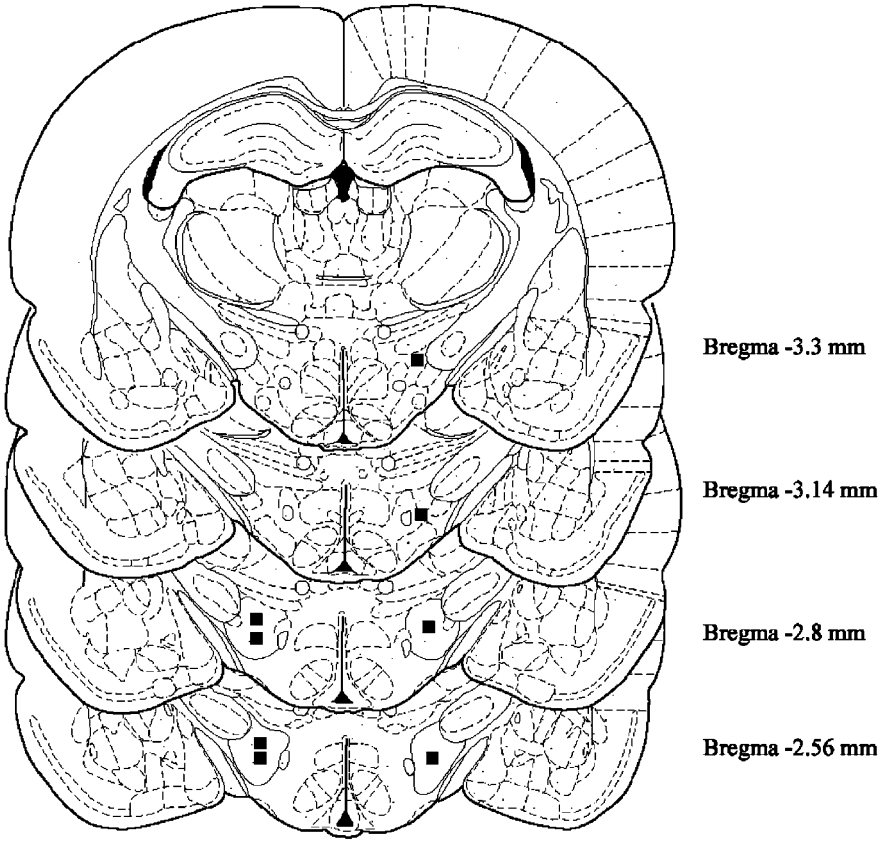

Figure 3 Schematic representation of the location of electrode tips. (■ represents the location of the electrode tips). Diagrams were drawn using Paxinos and Watson (1986) stereotaxic brain atlas maps. The electrode placement of one animal could not be determined due to a histological error.

placement sites). The placement of one electrode tip could not be conclusively verified due to a histological error.

DISCUSSION

The results of the present study demonstrate that $GABA_B$ receptor activation attenuates the acute rewarding effects of cocaine as assessed using the ICSS paradigm. Both the full $GABA_B$ receptor agonist baclofen and the novel positive allosteric receptor modulator GS39783 attenuated the threshold lowering effect of systemic cocaine administration in a dose-related manner. Furthermore, we demonstrated that baclofen administration alone elevated reward thresholds, whereas the positive modulator did not have any intrinsic effect on ICSS reward thresholds.

Utilizing the discrete-trial ICSS procedure, we demonstrate that systemic baclofen administration elevated brain reward thresholds (Figure 1). This is in agreement with a previous study employing a rate-shift ICSS reward protocol, which demonstrated that baclofen increased the current required to obtain 25 lever presses in 1 min (Willick and Kokkinidis, 1995). Taken together, these results suggest that activation of the $GABA_B$ receptor with a full agonist diminishes the rewarding effects of ICSS. Further, CGP44532, another selective $GABA_B$ receptor agonist, also elevates ICSS thresholds (Macey *et al*, 2001; but see, Dobrovitsky *et al*, 2002). Interestingly, it has been demonstrated that intraventral tegmental area (intra-VTA) (Xi and Stein, 1999) but not systemic (Fadda *et al*, 2003) baclofen administration decreased dopamine release in the nucleus accumbens. As ICSS responding is correlated with dopamine levels in this region (Garris *et al*, 1997), it is plausible in the present study that $GABA_B$-mediated reduction in dopamine may underlie the elevation of ICSS thresholds.

Recent characterization of a novel $GABA_B$ receptor-positive allosteric modulator, which is devoid of the side effects of full receptor agonists, even at high doses (Cryan *et al*, 2004) has provided a new tool for assessing the $GABA_B$ system *in vivo*. In the present study, we demonstrate that GS39783 had no intrinsic effect on ICSS thresholds at any dose examined (Figure 1). The observations that GS39783, in contrast to baclofen, does not alter baseline ICSS responding is in agreement with the lack of effects in other behavioral tests in both rats and mice, which are sensitive to baclofen administration, these include locomotor activity tests, the rotarod motor coordination task, cognitive tasks, and hypothermia measurements (Cryan *et al*, 2004; Jacobson and Cryan, 2005).

There are a number of preclinical and clinical observations demonstrating the potential use of $GABA_B$ receptor agonists to attenuate the behavioral effects elicited by drugs of abuse (see Brebner *et al*, 2002a; Cryan *et al*, 2003b). $GABA_B$ receptor agonists, such as baclofen, have been

shown to decrease self-administration of cocaine under both a fixed ratio schedule (Roberts *et al*, 1996; Brebner *et al*, 1999; Xi and Stein, 1999) or a second-order schedule of reinforcement (Di Ciano and Everitt, 2003). Additionally, baclofen attenuates cocaine-conditioned locomotion in rats (Hotsenpiller and Wolf, 2003). The antiaddictive properties of $GABA_B$ receptor agonists is not specific to cocaine as baclofen attenuates heroin self-administration under a second-order schedule of reinforcement (Di Ciano and Everitt, 2003). Further, the $GABA_B$ receptor agonists baclofen or CGP44532 attenuated self-administration of *d*-amphetamine (Brebner *et al*, 2005), alcohol (Colombo *et al*, 2002), and nicotine (Paterson *et al*, 2004a, b), in addition to decreasing amphetamine-induced rearing (Zhou *et al*, 2004).

Cocaine administration has been shown in numerous ICSS studies to produce a robust lowering of ICSS thresholds or the current required to maintain responding in the rate-shift paradigm in both rats (Kornetsky and Esposito, 1981; Markou and Koob, 1992) and mice (Gilliss *et al*, 2002; Gill *et al*, 2004). In the present study, cocaine (10 mg/kg) lowered ICSS threshold by $\sim$30% when administered 10 min prior to the start of the session (Figure 1). Despite the fact that only the highest dose of baclofen used significantly elevated baseline thresholds, both doses employed in the study (2.5 and 5 mg/kg) attenuated the threshold lowering effect of cocaine (Figure 1). Importantly, however, GS39783, which had no intrinsic affect on ICSS thresholds, also attenuated the effect of cocaine on ICSS thresholds (Figure 1). This pattern of results demonstrates that activation of the $GABA_B$ receptor system blocks the rewarding effect of cocaine in this procedure. The attenuation of the ability of cocaine to facilitate ICSS demonstrated here with baclofen and GS39783 corroborate the findings previously demonstrated with the $GABA_B$ receptor agonist CGP44532 (Dobrovitsky *et al*, 2002) These data are also consistent with the findings showing that baclofen decreases other behavioral effects of cocaine (Brebner *et al*, 2002a). Moreover, our current data with GS39783 are also in agreement with recent studies, which demonstrated that GS39783 administration attenuated cocaine self-administration (Smith *et al*, 2004). Although it appears that baclofen is more effective than GS39783 at blocking the facilitatory effects of cocaine on ICSS, with complete blockade at highest dose tested, this effect is propelled by the intrinsic effect of baclofen on ICSS thresholds. Interestingly, when compared with thresholds under vehicle treatment, the quantitative difference of cocaine treatment induced by both drugs was identical (baclofen 5 mg/kg, $\Delta = 19.29\%$; GS39783 100 mg/kg, $\Delta = 19.61\%$). Together, these data suggest that positive modulation of the $GABA_B$ system may represent an attractive therapeutic strategy for cocaine dependence.

The finding that GS39783 attenuates the threshold lowering effects of cocaine demonstrates that use-dependent activation of the $GABA_B$ receptor, via positive modulation, is sufficient to decrease the rewarding properties of cocaine. Further, the fact that GS39783, even at high doses, does not significantly alter baseline ICSS reward values suggest that positive modulation of the $GABA_B$ receptor may provide a more behaviorally selective attenuation of the rewarding effects of cocaine than baclofen. These results provide another demonstration of the disparity between the actions of full $GABA_B$ receptor agonists and those induced by positive modulators (Cryan and Kaupmann, 2005). Interestingly, despite the attenuation of the threshold lowering effect of cocaine on ICSS responding, GS39783 did not alter the increase in response latency elicited by cocaine administration, whereas baclofen (5 mg/kg) attenuated this response (Figure 2). It is known that baclofen causes sedation (Cryan *et al*, 2004), yet there was no significant difference between baseline response latencies and the highest dose of baclofen tested, despite elevating ICSS thresholds (Figures 1 and 2). This suggests that there is dissociation between the reward value of ICSS and response latencies. Similar findings have been shown with regard to other pharmacological agents, some of which induce motor impairments but do not alter baseline ICSS thresholds (Fenton and Liebman, 1982; Markou and Koob, 1992; Harrison and Markou, 2001).

Baclofen also has been shown to attenuate the neurochemical effects of drugs of abuse. Specifically, various drugs of abuse increase dopamine release in the nucleus accumbens, an area highly implicated in reward pathways (Deadwyler *et al*, 2004). This elevation in dopaminergic transmission is attenuated by systemic (Fadda *et al*, 2003) or intra-VTA (Xi and Stein, 1999) baclofen administration. It is of note that inhibitory $GABA_B$ receptors are present on dopaminergic and glutamatergic neurones in the VTA (Bowery *et al*, 1987; Wirtshafter and Sheppard, 2001), as well as on interneurones (Rahman and McBride, 2002). Therefore, activation of these $GABA_B$ receptor populations may partially explain the attenuation of the behavioral effects of cocaine in the current studies. Interestingly, Gong and colleagues (1998) demonstrated that intraventral pallidum administration of phacolfen (a $GABA_B$ receptor antagonist) elevated ventral pallidum extracellular dopamine concentrations, which provides supporting evidence for this proposition. It will be of future interest to examine the neurochemical effects on the dopaminergic system of GS39783 alone, and in combination with cocaine.

Currently, there is an increasing interest in the development of nondopaminergic pharmacotherapies for various drug addictions (Cryan *et al*, 2003b; Gorelick *et al*, 2004; Volkow and Li, 2004; Sofuoglu and Kosten, 2005). Blockade of the acute rewarding effects of abused drugs such as cocaine can occur via three principles (i) as a substitute for cocaine, thus leading to similar neurochemical effects (Gorelick *et al*, 2004; Heidbreder and Hagan, 2005; Sofuoglu and Kosten, 2005); (ii) as a cocaine antagonist by blocking the binding of cocaine to the dopamine transporter (Desai *et al*, 2005); or (iii) as a ligand acting at a site independent of cocaine effects (Gorelick *et al*, 2004) such as with $GABA_B$ receptor modulators. Further, it is clear that there are many more facets to the addiction process that need to be addressed in order to develop successful pharmacotherapeutic strategies; tackling drug-induced withdrawal; and craving being of paramount importance Therefore, interventions should not be limited to inhibiting the rewarding effects of a drug, but should also include strategies to enhance the saliency value of natural reinforcers, strengthen inhibitory control, decrease conditioned responses, and improve withdrawal-induced deficits in mood and anxiety (Volkow and Li, 2004). The fact that $GABA_B$ receptor-

positive modulators reduce anxiety in preclinical paradigms (Cryan *et al*, 2004) suggests that they may assist in the treatment of addiction beyond simply reducing the primary rewarding effects of the reinforcer. The examination of the behavioral effects of GS39783 in animal models of drug withdrawal and relapse is now warranted.

In summary, the present study demonstrates that $GABA_B$ receptor activation via baclofen or GS39783 attenuates the effects of acute cocaine administration on ICSS reward thresholds. Furthermore, although baclofen administration elevates ICSS reward thresholds in a dose-related manner, the positive modulator, GS39783, had no intrinsic effect on baseline ICSS responding. These data, combined with the emerging preclinical and clinical data, suggest that $GABA_B$ receptor activation represents a potential new therapy for drug addiction. Additionally, the data in the present study suggest that rather than using a full agonist, such as baclofen, which displayed anhedonic-like effects, positive modulation of the $GABA_B$ system represents a more selective blockade of the rewarding properties of cocaine.

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