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European Journal of Pharmacology 408 (2000) 169–174

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Failure of baclofen to modulate discriminative–stimulus effects of cocaine or methamphetamine in rats

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Received 29 May 2000; received in revised form 3 October 2000; accepted 10 October 2000

Abstract

The effects of baclofen, an agonist at $GABA_B$ receptors, were evaluated in rats trained to discriminate 10.0 mg/kg of cocaine or 1.0 mg/kg of methamphetamine from saline under a fixed-ratio 10 schedule of food delivery. Baclofen (0.56–5.6 mg/kg) did not attenuate the discriminative–stimulus effects of the training dose of cocaine or methamphetamine and did not produce any shift in the cocaine and methamphetamine dose–response curves. Higher baclofen doses (3.0–5.6 mg/kg), however, markedly depressed or completely eliminated food-maintained responding. This suggests that previous reports of baclofen-induced decreases in cocaine self-administration behavior are connected, in some way, with either a general suppression of appetitive behaviors or with sedation and locomotor depression, rather than with any pharmacologically specific effect, and not accompanied by changes in subjective response to cocaine, as assessed by discriminative–stimulus measures.

Keywords: Baclofen; Cocaine; Methamphetamine; Drug-discrimination; (Rat)

1. Introduction

Baclofen is an agonist at $GABA_B$ receptors, used since the early 1970s as a centrally acting, muscle relaxant for treatment of spasticity (Bowery and Enna, 2000). Recent preclinical reports indicate that baclofen can attenuate cocaine self-administration by rats under several different conditions (Roberts et al., 1996; Roberts and Andrews, 1997; Shoaib et al., 1998; Campbell et al., 1999; Brebner et al., 2000), suggesting its potential utility as a medication for treatment of psychostimulant addiction. An initial open-label, clinical trial ($n = 10$) indicated that baclofen (20 mg, three times a day) is well tolerated by cocaine addicts and may reduce the frequency of cocaine use (Ling et al., 1998). However, a larger double-blind trial ($n = 35$, 20 mg baclofen three times a day; $n = 35$, placebo) found no statistically significant effect for baclofen over placebo on measures such as treatment effectiveness and percent negative urines, although baclofen was well tolerated and treated subjects were more likely to abstain from cocaine use between weeks 3 and 8 of the trial (Shoptaw, 2000). Baclofen also has been reported to decrease self-administration of heroin (Xi and Stein, 1999) and nicotine by rats (Corrigall et al., 2000), suggesting that its potential therapeutic utility might extend across different classes of abused drugs. It should be noted, that baclofen itself is self-administered by experimental animals, although it maintains only intermediate rates of self-administration relative to other drugs such as barbiturates (Griffiths et al., 1991). Thus, its abuse potential appears to be low based on preclinical estimates and the failure to see documented instances of abuse.

$GABA_B$ receptors are localized on dopaminergic neurons and their stimulation by baclofen can attenuate dopaminergic functioning (e.g., Klitenick et al., 1992; Westerink et al., 1996; Xi and Stein, 1999). This has been proposed as a likely explanation for baclofen's ability to attenuate cocaine self-administration. If this explanation were true, other psychostimulant-induced behaviors mediated by stimulation of dopaminergic neurons should also be altered by baclofen treatment. The psychostimulant-induced behavior most relevant to drug abuse and craving, other than reward/reinforcement, is the subjective response to drug administration, which is most frequently

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0014-2999/00/$ - see front matter
PII: S0014-2999(00)00772-X

assessed in humans through the use of subjective-rating scales and in experimental animals through the use of two-lever, choice, drug-discrimination procedures. The present study in rats investigated whether baclofen alters the discriminative–stimulus effects of the psychostimulants cocaine and methamphetamine at doses previously shown to reduce cocaine self-administration.

2. Material and methods

2.1. Subjects

Male Sprague–Dawley rats (Charles River, Wilmington, MA), initially weighing 280–350 g, were housed individually and maintained on a 12-h light/dark cycle. Experiments were conducted during the light phase. Body weights were gradually reduced to approximately 80% of free feeding by limiting daily access to food. The subjects were maintained in facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care, and all experimentation was conducted in accordance with the guidelines of the Institutional Care and Use Committee of the National Institute on Drug Abuse, NIH, and the Guide for Care and Use of Laboratory Animals (National Research Council, 1996).

2.2. Apparatus

Ten operant chambers enclosed in sound-attenuating isolation enclosures were used (Coulbourn Instruments, Lehigh Valley, PA). Each chamber contained two levers, separated by a recessed tray into which a pellet dispenser could deliver 45 mg food pellets (F0021, Bioserv, Frenchtown, NJ). Each press of a lever with a force of at least 0.4 N through 1 mm was recorded as a response and accompanied by an audible click. The operant chambers were controlled by microcomputers using the MED Associates MED-PC software package (MED Associates, East Fairfield, VT).

2.3. Drug-discrimination procedure

Rats were trained as described previously (Munzar et al., 1999a,b; Munzar and Goldberg, 1999, 2000) under a discrete-trial schedule of food pellet delivery to respond on one lever after an injection of a training dose of either 1.0 mg/kg of methamphetamine (eight subjects) or 10.0 mg/kg cocaine (ten subjects) and on the other lever after an injection of 1.0 ml/kg of saline vehicle. At the start of the session, a white house light was turned on and, in its presence, the rats were required to make 10 consecutive responses on the lever appropriate to the pre-session treatment. The completion of 10 consecutive responses on the correct lever produced delivery of a 45 mg food pellet and initiated a 45-s timeout during which lever-pressing responses had no consequences and the chamber was dark. Responses on the incorrect lever had no specified consequences other than to reset the response requirement to 10 on the correct lever. After each timeout, the white house light was again turned on and the next trial began. Each session ended after completion of 20 trials or after 30 min elapsed, whichever occurred first.

Discrimination-training sessions were conducted 5 days/week under a double alternation schedule (i.e., DDSSDDSS, etc., D = drug, S = saline). Training continued until there were eight consecutive sessions during which rats completed at least 90% of their responses on the correct lever and no more than four responses occurred on the incorrect lever during the first trial.

Test sessions were then initiated which were identical to training sessions with the exception that 10 consecutive responses on either of the two levers ended a trial; however, switching responding from one lever to the other lever continued to reset the response requirement. Test sessions were usually conducted on Tuesdays and Fridays. During test sessions, different doses of baclofen were either substituted for the training dose of methamphetamine or cocaine or were administered together with the training dose of methamphetamine or cocaine. Subsequently, the effects of selected doses of baclofen on the cocaine and methamphetamine dose–response curves were established.

2.4. Drugs

S(+)-Methamphetamine HCL, (−)-cocaine HCL and (±)-baclofen were purchased from Sigma (St. Louis, MO) and dissolved in 0.9% NaCl. Doses refer to the weight of the salt. Drugs were injected IP in a volume of 1.0 ml/kg 15 min before the session (cocaine and methamphetamine) or 30 min before the session (baclofen).

2.5. Data analysis

Results are expressed as percentage of total responses on the methamphetamine- or cocaine-appropriate lever. Response rates are expressed as responses per second averaged over the session, with responding during time-outs not included in calculations. All results are presented as group means (±S.E.M.).

The statistical analysis of substitution and pre-treatment tests involved one-way analysis of variance (ANOVA) for repeated measures. Significant main effects were analyzed further by subsequent paired comparisons using Dunnett's test. Changes were considered to be significant when $P < 0.05$. ED_{50} values for the cocaine and methamphetamine dose–response curves after different pre-treatments were defined as the dose connected with 50% cocaine- or methamphetamine-appropriate lever selection and were calculated using linear regression as described before (Munzar and Goldberg, 1999). Shifts in the dose–

response curves were considered to be significant when 95% confidence intervals of ED_{50} values did not overlap.

3. Results

3.1. Maintenance of discrimination baseline

Once the training criterion was reached, performance during maintenance sessions was almost always maintained at 100% responding on the appropriate lever in both methamphetamine- and cocaine-trained rats.

3.2. Generalization and pre-treatment tests

Baclofen failed to generalize to methamphetamine at doses ranging from 0.56 to 5.6 mg/kg (Fig. 1). The higher doses of 3.0 and 5.6 mg/kg of baclofen significantly decreased response rates ($F_{5,35} = 8.238$, $P < 0.001$). Baclofen also failed to generalize to cocaine over the same range of doses (Fig. 1), with the exception of a small (around 25%) but statistically significant level of generalization ($F_{5,34} = 3.201$, $P = 0.018$) at the highest dose of 5.6 mg/kg. Most investigators, however, use a higher criterion than 25% as evidence of even partial substitution. Whether or not this finding is meaningful would require testing of higher baclofen doses, which was precluded by the marked and significant ($F_{5,40} = 6.918$, $P < 0.001$) rate-decreasing effects of the 5.6 mg/kg dose (responding was completely eliminated in five of nine subjects).

Baclofen (0.56–5.6 mg/kg) also did not attenuate the discriminative–stimulus effects of the training doses of 1.0 mg/kg of methamphetamine or 10.0 mg/kg cocaine (Fig. 1). As in the generalization study, coadministering baclofen with methamphetamine or cocaine significantly decreased rates of responding in both methamphetamine-trained ($F_{5,35} = 4.628$, $P = 0.002$) and cocaine-trained ($F_{5,45} = 8.596$, $P < 0.001$) rats. When the high 5.6 mg/kg

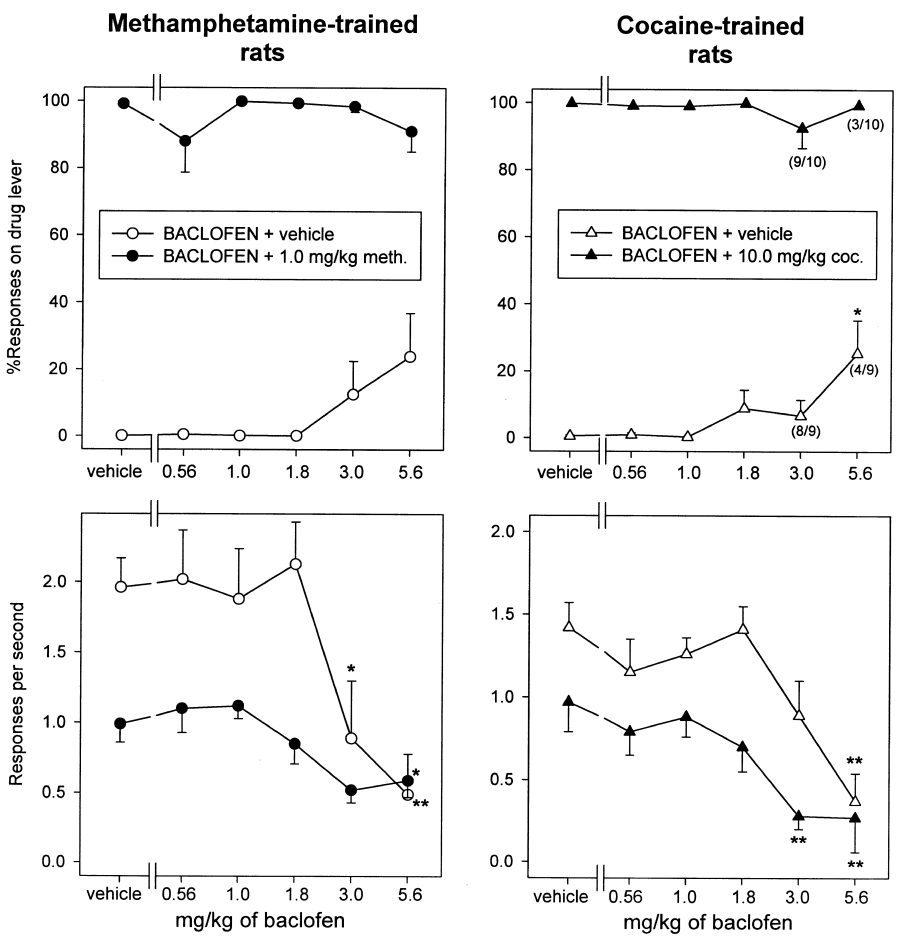

Fig. 1. Effects of baclofen in rats trained to discriminate either 1.0 mg/kg of methamphetamine or 10.0 mg/kg of cocaine from saline. Data are means (±S.E.M.) from eight methamphetamine-trained rats and 9–10 cocaine-trained rats. The percentage of responses on the methamphetamine- or cocaine-appropriate lever is shown as a function of baclofen dose during test sessions when baclofen was substituted for the training dose of cocaine or methamphetamine (open symbols) and during test sessions when baclofen was given together with the training dose of methamphetamine or cocaine (filled symbols). Response rates are expressed as responses per second. $^{*}P < 0.05$, $^{**}P < 0.01$, post-hoc comparison with the vehicle pretreatment after significant one-way ANOVA for repeated measures main effect, Dunnett's test. The numbers within parentheses indicate the number of rats that continued responding after the high doses of baclofen vs. the total number of rats in which the dose was tested.

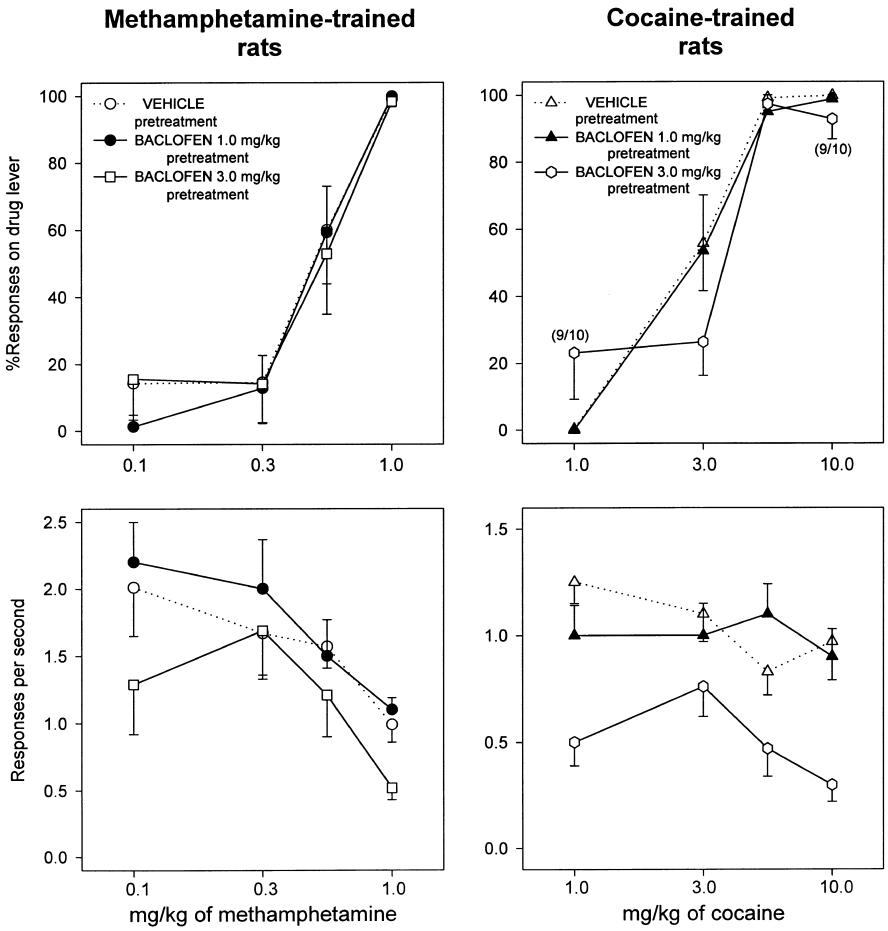

Fig. 2. Methamphetamine and cocaine dose–response curves after pretreatment with vehicle, 1.0 and 3.0 mg/kg baclofen. Data are means (±S.E.M.) from eight methamphetamine-trained rats and 8–10 cocaine-trained rats. Other details are as in Fig. 1.

dose of baclofen was administered together with the training dose of cocaine, responding was completely eliminated in seven of 10 subjects.

3.3. Effects of selected doses of baclofen on methamphetamine and cocaine dose–response curves

Baclofen (1.0 and 3.0 mg/kg) did not produce any significant shift in either the methamphetamine or the cocaine dose–response curves, when it was coadministered with different doses of methamphetamine or cocaine (Fig. 2) as revealed by overlapping 95% confidence intervals of ED_{50} values (Table 1). Coadministering 3.0 mg/kg of baclofen with different doses of both cocaine or methamphetamine did, however, markedly decrease rates of responding.

Table 1
ED_{50} values (95% confidence intervals) in mg/kg of cocaine and methamphetamine for percentage of cocaine- and methamphetamine-appropriate responding when cocaine and methamphetamine were administered with vehicle (saline) and with selected doses of baclofen

Cocaine	+saline (1.0 ml/kg)	2.65 (2.03–3.27)
	+baclofen (1.0 mg/kg)	3.22 (2.27–4.17)
	+baclofen (3.0 mg/kg)	3.29 (2.03–4.55)
Methamphetamine	+saline (1.0 ml/kg)	0.55 (0.34–0.76)
	+baclofen (1.0 mg/kg)	0.56 (0.38–0.74)
	+baclofen (3.0 mg/kg)	0.49 (0.29–0.69)

4. Discussion

In the present study, baclofen failed to alter the discriminative–stimulus effects of either lower or higher doses of cocaine or methamphetamine. For example, a 3.0 mg/kg dose of baclofen failed to shift the cocaine dose–response curve when it was coadministered with a range of cocaine doses. A higher dose of baclofen (5.6 mg/kg) was not tested against cocaine (or methamphetamine) curves, because this dose, alone or in combination with the training dose of cocaine, completely eliminated food-reinforced responding in most subjects. In contrast, various types of dopamine antagonists can either partially or fully block the discriminative–stimulus effects of both cocaine (reviewed by Callahan et al., 1997) and methamphetamine (Munzar and Goldberg, 2000). Non-dopaminergic drugs which can

indirectly modulate dopaminergic transmission, such as serotonergic or noradrenergic antagonists, also can shift the dose–response curves for methamphetamine or cocaine discrimination, although they are usually ineffective in attenuating discriminative–stimulus effects of the high training dose (Munzar and Goldberg, 1999; Munzar et al., 1999b). Since the range of doses of baclofen tested in the present study and the parenteral route of administration were similar to those in previous cocaine self-administration studies (Roberts et al., 1996; Roberts and Andrews, 1997; Shoaib et al., 1998; Campbell et al., 1999; Brebner et al., 2000), the present findings fail to support even indirect modulation of dopaminergic neurotransmission as a mechanism underlying baclofen's actions on cocaine-self-administration behavior. It is important to note, however, that despite the established receptor selectivity of drug-discrimination procedures, effects on dopaminergic neurotransmission were not directly assessed in the present experiment. Also, the neurochemical processes mediating cocaine's discriminative–stimulus effects and its ability to maintain self-administration behavior may show some dissociation. Although both of these behavioral actions of cocaine and methamphetamine may be amendable to antagonism by various compounds acting directly or indirectly on dopaminergic neurotransmission (Mello and Negus, 1996; Callahan et al., 1997; Caine et al., 1999; Munzar et al., 1999a), this does not necessarily mean that they would be equally amendable to modulation by drugs from other pharmacological classes.

Although baclofen did not modify the discriminative–stimulus effects of either cocaine or methamphetamine, it markedly and significantly decreased rates of responding for food in the present study, suggesting that previous reports of baclofen-induced decreases in cocaine self-administration behavior might be connected, in some way, with sedation and locomotor depression, rather than with any pharmacologically specific effect. It is also possible that baclofen suppresses a range of appetitive behaviors, including feeding behavior. This seems unlikely, however, since baclofen has been reported to enhance and not depress food intake when administered systemically (Ebenezer and Pringle, 1992) or directly into the nucleus accumbens (Stratford and Kelley, 1997; Ward et al., 2000).

In some previous studies (Roberts and Andrews, 1997; Shoaib et al., 1998; Brebner et al., 2000), rats were trained to respond for both self-administration of cocaine and delivery of food within the same experimental session, in order to evaluate selectivity of baclofen's effects. In these studies, the same doses of baclofen, which markedly depressed or eliminated food-maintained responding in the present study (3.0 and 5.6 mg/kg), markedly decreased cocaine self-administration responding but had either no effect (Roberts and Andrews, 1997; Brebner et al., 2000) or only small rate-decreasing effects (Shoaib et al., 1998) on food-maintained responding. However, there were marked differences in baseline rates of responding for food in the present study and in these previous studies, which might contribute to the discrepant findings. In previous cocaine self-administration studies, food-reinforced responding, when studied, was maintained at relatively low rates (below 10 responses/min) compared to the high rates of responding maintained by food in the present drug-discrimination study (response rates averaged between 1 and 2 responses/s).

In most previous studies, baclofen was studied against a range of doses of the drug reinforcer, cocaine, but only against a single relatively large reinforcer magnitude (pellet size) with food. Since baclofen's effects on cocaine self-administration were most pronounced at lower injection doses of cocaine (e.g., Campbell et al., 1999; Shoaib et al., 1998; Brebner et al., 2000), a similar effect on food-maintained responding might have been missed by not varying magnitude of food reinforcement. Similar inverted U-shaped biphasic dose/magnitude–response curves with food and cocaine can be obtained when amount of food per reinforcement and dose of cocaine per injection are varied under identical fixed-ratio schedules (Goldberg, 1973) and such a baseline might be more appropriate for assessing selectivity of baclofen's effects on drug-reinforced behavior. There is a recent report by Caine et al. (2000) that, when cocaine dose and liquid food concentration are varied under identical fixed-ratio schedules of cocaine injection or food delivery, baclofen (1.8–5.6 mg/kg) produces comparable decreases in both cocaine- and food-reinforced responding and those decreases are most pronounced at lower reinforcer magnitudes. Thus, although baclofen can reduce responding maintained by cocaine at doses with no effect on low rates of responding maintained by food (as reported in previous studies), these effects of baclofen occur at doses which can markedly depress either food-maintained responding occurring at high rates (present study) or responding maintained by lower magnitudes of food reinforcement (Caine et al., 2000).

In conclusion, the present results suggest that the previously reported effects of baclofen in attenuating cocaine self-administration are not likely correlated with any alteration in the subjective effects of cocaine indicating that the neurochemical processes mediating these two behaviors show some dissociation. This also appeared to be the case in the initial clinical study of baclofen as a pharmacotherapy in human cocaine addicts (Ling et al., 1998). When treated with 60 mg/day of baclofen, "patients generally reported decreased cocaine craving and reduction in cocaine use..." but "...none experienced any subjective differences in their cocaine highs." Also, the attenuation of cocaine self-administration described in previous reports may not be very selective, since it occurred at doses of baclofen with marked depressant effects on food-reinforced responding under the conditions noted above, which may be an indication of sedation. Clinically, drowsiness is one of the most frequently reported side effects of baclofen

use (e.g., Hattab, 1980) and Ling et al. (1998) noted that baclofen treatment for cocaine abuse had to be discontinued in a human subject who was a truck driver and reported that baclofen treatment was interfering with driving. Finally, withdrawal from chronic baclofen treatment can induce seizures and brief psychotic episodes (e.g., Lee et al., 1992) and there are both in vitro (Cottrell and Robertson, 1987) and in vivo (Schwartzwelder et al., 1987) preclinical studies indicating that baclofen may be proconvulsant (exacerbates convulsions or itself produces them). Although this suggests caution with baclofen in patients that may be self-administering cocaine, this does not mean that baclofen would not be useful in the treatment of psychostimulant dependence with appropriate clinical supervision. Its abuse liability appears to be low (Griffiths et al., 1991) and in the preliminary clinical trials to date it appears to be well tolerated in most individuals (Ling et al., 1998; Shoptaw, 2000). The present findings, however, do suggest that conclusions from previous studies about the effectiveness of baclofen and its selectivity may be too optimistic. It remains for future clinical studies to fully clarify the place of baclofen in drug abuse treatment.

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