Psychopharmacology (1997) 131:271–277

ORIGINAL INVESTIGATION

David C. S. Roberts · Monique M. Andrews

Baclofen suppression of cocaine self-administration: demonstration using a discrete trials procedure

Received: 30 July 1996 / Final version: 8 February 1997

Abstract We have previously reported that rats display a circadian pattern of cocaine self-administration if access to drug is limited to 10-min discrete trials that are separated by at least 20 min. In the present study, the pattern of cocaine intake (1.5 mg/kg per injection) was studied in two large groups of animals that were maintained on different 12-h light/dark cycles (3 a.m. to 3 p.m. versus 10 a.m. to 10 p.m.). Regardless of the time of light onset, a circadian pattern of cocaine self-administration was observed. Maximum cocaine intake occurred during the final 6 h of the dark period and was followed by a relative abstinence period during the light phase**.** This highly predictable pattern of drug taking behavior provided an opportunity to explore the effect of baclofen, a $GABA_B$ agonist, on the initiation of self-administration behavior. In two separate studies, acute treatment with baclofen (1.25–5.0 mg/kg) was shown to suppress cocaine intake for at least 4 h. Baclofen had no significant effect on responding for food reinforcement. Previous results have indicated that baclofen appears to reduce specifically the motivation to respond for cocaine. Together, these data suggest that baclofen should be considered as a possible pharmacotherapeutic agent in cocaine addiction.

Key words Cocaine · Self-administration · Baclofen · Discrete trials procedure · GABA

Introduction

Considerable effort has been devoted to identifying drug treatments that might be effective for cocaine addiction. Clinical research has focused largely on dopaminergic, serotonergic and noradrenergic compounds (Kosten et al. 1987; Handelsman et al. 1987; Berger et al. 1989; Giannini et al. 1989; Balon 1994; Eiler et al. 1995; Margolin et al. 1995), although to a lesser extent, lithium, opiate agonists and antagonists, and carbamazepine have also been explored (Kosten et al. 1989; Lemere, 1991; Cornish et al. 1995; Kranzler et al. 1995; Montoya et al. 1995). Results from open clinical trials have sometimes been promising; however, double blind studies have generally been disappointing. No substantially effective pharmacotherapy for cocaine addiction has yet been described (Meyer, 1992; Kleber, 1995).

GABA drugs have received little clinical attention, although there are indications from basic research that GABA agonists may hold some therapeutic promise for the treatment of psychostimulant abuse (see Discussion). We have recently reported that baclofen, a $GABA_B$ agonist, dramatically affected cocaine self-administration by rats reinforced on a progressive ratio (PR) schedule (Roberts et al. 1996). Following baclofen pretreatment, rats responded to lower breaking points across a range of unit injection doses of cocaine. Baclofen had little effect on food reinforced responding on an identical PR schedule within the dose range tested. These data demonstrate that baclofen appears to selectively decrease the motivation to respond for cocaine.

The PR schedule is a powerful screening tool for evaluating changes in the reinforcing efficacy of psychostimulant drugs; however, there are a number of features of human drug taking that are not addressed by this schedule. For example, a potential therapeutic agent should decrease the motivation of an addict to initiate drug taking behavior, yet the initiation of cocaine self-administration behavior cannot be investigated with the PR procedure. Animals responding on a PR schedule may receive a priming injection at the start of the session and the response ratios for the initial few injections are typically very low. Consequently, the breaking point is established only at the end of a sequence of injections when substantial levels of cocaine have accumulated in the system. The PR schedule can be used to examine whether a drug pretreatment might interrupt cocaine self-administration in progress and it has been shown to be sensitive to a variety of pharmacological treatments, neuro-

D.C.S. Roberts (✉) · M.M. Andrews
Institute of Neuroscience, Life Sciences Research Center,
Carleton University, 1125 Colonel By Drive,
Ottawa, Canada K1S 5B6

toxic lesions as well as hormonal fluctuations (Roberts et al. 1989a, b, 1994, 1996; Depoortere et al. 1993; McGregor et al. 1996); however, the schedule does not address whether a drug pretreatment might be effective at reducing the motivation to respond for the first injection and thereby prevent relapse to drug use.

The discrete trials procedure offers a different method to study the motivation to initiate drug taking behavior. With this technique, rats are given the opportunity to self-administer only a single injection of cocaine during individual trials. The inter-trial interval (ITI) can be adjusted so that the influence of one injection on subsequent trials can be manipulated. Rats will self-administer during consecutive trials for many hours or even days when the ITIs are relatively short (Fitch and Roberts, 1993). A very different pattern is observed when the ITI is lengthened. Longer ITIs engender a regular circadian pattern of intake. Periods of drug abstinence during the light phase of the cycle alternate with periods of self-administration during the dark phase (Fitch and Roberts, 1993). This predictable pattern of drug taking behavior provides an opportunity to explore the initiation of self-administration behavior. The discrete trials procedure was used in the present studies to explore the pattern of cocaine intake across the light/dark cycle. After appropriate baseline parameters were evaluated, the paradigm was used to assess the effect of baclofen on the cyclic pattern of cocaine self-administration behavior.

Materials and methods

Subjects were male Wistar rats (Charles River Farms, Quebec, Canada) weighing 275-300 g at the start of the experiment. Upon arrival from the supplier, all animals were quarantined for 1 week during which time a 12-h light/dark cycle was maintained (lights off from 8 p.m. to 8 a.m.). Following quarantine, animals were housed and tested for the duration of the experiment under one of two different light/dark cycles. One group of rats (n=17) was switched to a light/dark cycle with the dark phase extending between 3 a.m. and 3 p.m. The dark phase for the other group (n=25) extended between 10 a.m. and 10 p.m.

All rats were food deprived for 24 h and trained to press a lever for food reinforcement on an FR1 schedule. Thereafter Purina Rat Chow was available ad libitum, except as noted below. 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 singly housed in 25×25×25 cm operant testing apparatus. The cannula was mounted on a counter-balanced swivel apparatus which allowed free movement within the operant chamber.

During initial training, rats were given access to a response lever for a 5-h period each day. Each lever response activated an injection pump, delivering 0.12 ml saline solution containing 0.6 mg/ml cocaine HCl over a 5-s period. Concurrent with the start of the injection, a stimulus light was activated that signaled a 20-s post-infusion time-out period during which time responses produced no programmed consequence.

Discrete trials procedure

A discrete trials procedure was initiated after animals had established a stable daily intake of cocaine (>20 injections/5 h) for at least 5 days on the FR1 schedule and showed consistent post-infusion pauses. Parameters were chosen that produced a circadian pattern of responding (see Fitch and Roberts 1993). Discrete trials were initiated at 30-min intervals for the duration of the experiment. Each trial began with the introduction of a retractable lever into the cage. Completion of a fixed ratio (FR) response requirement resulted in a cocaine injection (1.5 mg/kg per injection), illumination of a stimulus light for 20 s, retraction of the response lever and termination of the trial. Failure to complete the ratio requirement within 10 min also terminated the trial. The FR was set at 1 for the first few days of testing and was gradually increased to an FR5 by day 10 of testing. Syringes were refilled, water bottles changed and waste pans cleaned daily for both groups during one of the 20-min inter-trial intervals (ITI) between 9 a.m. and 10 a.m.

After at least 14 days on the discrete trials schedule, the effect of baclofen was assessed. In the first replication, five animals that were maintained on the 10 a.m. to 10 p.m. cycle were injected with baclofen (2.5 mg/kg) during the 20-min ITI before the lights were switched off (10.00 a.m.).

In the second replication (n=9), animals from the 3 a.m. to 3 p.m. group received an injection of baclofen (1.25, 2.5 or 5.0 mg/kg) or saline immediately prior to the 10 a.m. trial. The order of testing was counterbalanced and at least 4 baseline days separated test days. Five animals had continuous access to a second response lever. Every response on this lever resulted in the delivery of a 45-mg nutritionally balanced food pellet (Noyes Inc.). These pellets were the only source of food for this group. The remaining four animals had ad libitum access to Purina Rat Chow.

Statistics

The effect of the two different light/dark cycles was examined across the 48 daily trials. The percent of trials during which cocaine was self-administered was calculated for each animal across 3 days of baseline testing. These scores were submitted to a repeated measures ANOVA. The effect of baclofen was examined in two separate experiments. In the first replication, a paired t-test was used to compare the number of cocaine injections self-administered during eight trials following baclofen administration with the mean number of injections self-administered during the same period across the previous 3 baseline days. Data from the second replication were subjected to an ANOVA. Newman-Keuls analysis was used to compare the data from each dose of baclofen to the saline scores.

Results

Figure 1 shows the pattern of cocaine self-administration for a representative animal. The pattern of cocaine self-administration was restricted largely to the dark phase of the light/dark cycle. Also shown in Fig. 1 is the pattern of responding for food. Food intake was found to occur in a number of “meals” that were distributed across the cycle.

Figure 2 shows the pattern of cocaine self-administration over a 24-h period for the two groups tested on different light/dark cycles. No statistically significant differences were found between groups (F<1). The probability of cocaine self-administration was found to fluctuate during the dark cycle. The highest probability of self-administration was observed through the latter half of the dark cycle, reaching a peak immediately prior to the transition from the dark to light phase. Thereafter the

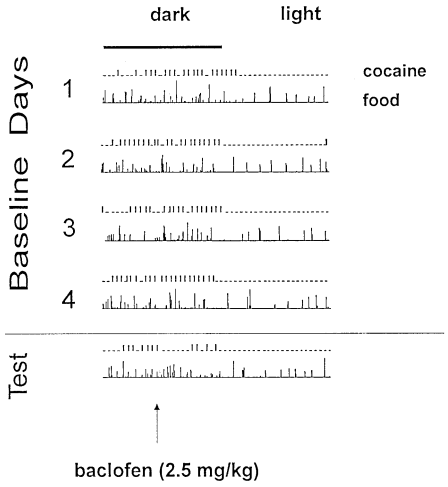


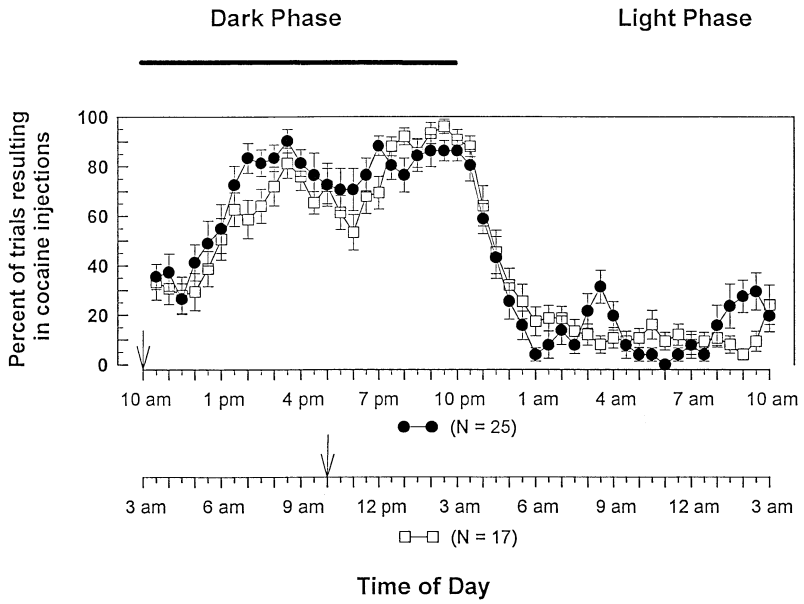
Fig. 1 Pattern of cocaine self-administration using a discrete trials procedure. Each line represents an event record for consecutive 24-h periods. The *top line of each pair* shows the pattern of cocaine self-administration. Cocaine (1.5 mg/kg per injection) was made available during 48 trials/day. Upward pen deflections indicate the trials during which a cocaine infusion was self-administered. The *lower line* indicates responses on a second lever that controlled the delivery of 45-mg food pellets. The *height of each line* represents the number of pellets delivered during 1 min. The *tallest bar* on line 2 corresponds to 12 pellets. Animals were entrained to a reverse light/dark cycle. In this example, the daily sessions began at 3 a.m., at which time the syringes were refilled, water bottles changed, waste pans cleaned and the computer program reset. Note that cocaine self-administration was restricted mainly to the dark phase of the cycle, while food intake was distributed into a number of meals across the cycle. The *top four pairs of lines* represent the baseline condition. The *bottom pair* shows the effect of baclofen (2.5 mg/kg) administered at the time shown by the *arrow*. Cocaine self-administration is suppressed for several hours after baclofen treatment

probability of cocaine self-administration declined and remained low during the light phase. A circadian pattern of cocaine self-administration was evident in both groups. The peak in cocaine self-administration always occurred at the end of the dark cycle, and was independent of the time when cage cleaning and other daily maintenance was scheduled.

Figure 3 shows the effect of baclofen treatment on cocaine self-administration. In this case, baclofen was injected midway through the dark period at a point when cocaine self-administration was highly probable. Inspection of Fig. 3 shows that baclofen treatment substantially decreased the likelihood of cocaine self-administration for at least 4 h.

Figure 4 shows the effect of baclofen in two replications. In the first replication, baclofen was injected at the beginning of the dark cycle (time A, Fig. 4). Baclofen (2.5 mg/kg) was found significantly to decrease the number of cocaine injections self-administered during the 4-h period following the treatment. Comparison of the number of injections taken during the 4 h after baclofen compared to the same time period on the preceding 3 baseline days revealed a significant decrease in number of injections ($P<0.05$, Student's *t*-test). In the second replication, baclofen was injected at the mid-point of the dark

Fig. 2 Circadian pattern of cocaine self-administration reinforced on a discrete trials procedure. Two groups of rats were given the opportunity to self-administer a single injection of cocaine (1.5 mg/kg per injection) on an FR5 schedule during 10-min trials. In one group (n=25) the dark phase extended from 10 a.m. to 10 p.m. In the other group (n=17) the dark phase extended between 3 a.m. and 3 p.m. No significant differences were observed between groups. The time of routine cage maintenance is indicated for each group by the arrow on the respective x-axis. The proportion of injections self-administered by each animal during each of the 48 trials was calculated across a 5-day period. Points represent the average (±SEM) proportion of trials that animals self-administered cocaine



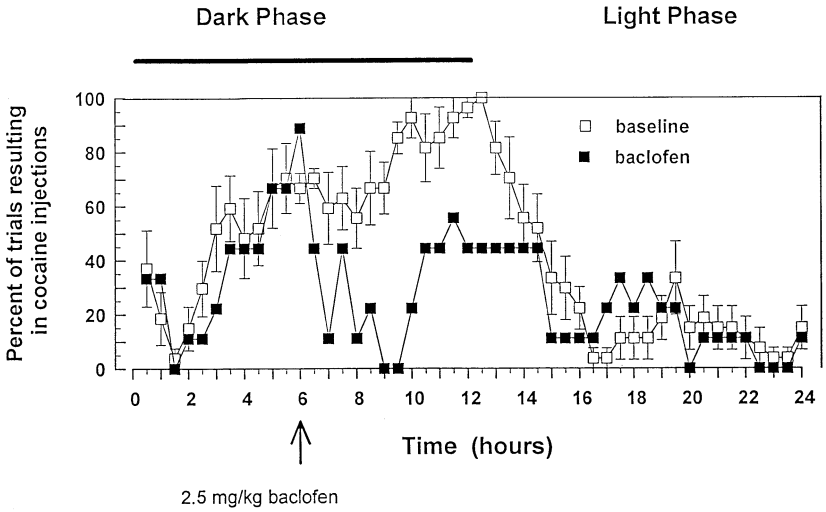


Fig. 3 The effect of baclofen on cocaine self-administration reinforced on a discrete trails procedure. Animals (*n*=9) were given the opportunity to self-administer a single injection of cocaine (1.5 mg/kg per injection) on an FR5 schedule during 10-min trials. Trials were initiated continually every 30 min. The proportion of injections self-administered by each animals during each trial was calculated across a three day baseline period. The mean (±SEM) proportion was calculated for the group and shown on the graph as *open squares*. The observed number of injections self-administered on the baclofen test day is shown as *closed squares*. The time of the baclofen injection (2.5 mg/kg) is shown by the *arrow*. Baclofen produced a marked reduction in cocaine self-administration for at least 4 h post-injection. See Fig. 4 for summary statistics

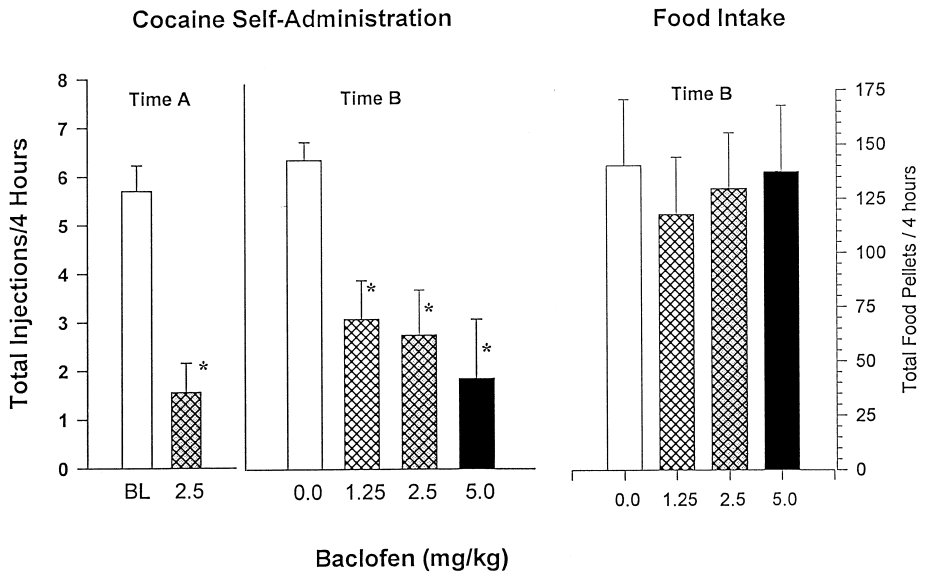


Fig. 4 The effect of baclofen on cocaine self-administration and food intake. Cocaine injections were made available during 10-min discrete trails that were initiated every 30 min. The effect of baclofen was examined in two replications. In the first replication (*n*=5), baclofen (2.5 mg/kg) was administered at the beginning of the dark cycle (*time A*). In the second replication (*n*=7–9), rats received various doses of baclofen (1.25–5.0 mg/kg) or vehicle 6 h into the dark cycle (*time B*). *Bars* represent the mean (±SEM) number of cocaine injections delivered during the 4-h period following treatment or during the comparable baseline period. Baclofen produced a significant decrease in cocaine self-administration. Vehicle injections had no significant effect. A subset (*n*=5) of the baclofen group tested at time B had continuous access to a second lever that controlled the delivery of food pellets on an FR1 schedule. *Bar*s represent the mean (±SEM) number of food pellets delivered during the 4-h period following drug treatment or during a comparable baseline period. Baclofen had no significant effect on the number of food pellets delivered

phase (time B, Fig. 4). Baclofen produced a significant suppression of cocaine intake [$F(3, 29)=4.185$, $P<0.05$]. Vehicle injections had no significant effect on responding. All three doses of baclofen (1.25, 2.5 and 5.0 mg/kg) significantly reduced the number of cocaine injections self-administered.

Baclofen had no apparent effect on responding for food. No statistically significant effect was observed (compared to baseline) on the number of food pellets delivered during the 4-h period following treatment or on the total number of pellets delivered over 24 h ($F<1$). Figure 1 (bottom) illustrates the effect of baclofen on cocaine self-administration and on food intake for a representative animal. Food intake occurred in small bouts of

several minutes duration. Baclofen had no appreciable effect on the pattern of food intake.

Discussion

Psychostimulant abuse in humans is characterized by alternating periods of "binging" and abstinence (Kleber and Gawin 1987). Presumably, the motivation to use cocaine oscillates, and depends on such variables as the time since the last dosage, fatigue and accumulated drug effects. Non-human primates and rats also display cycles of intake when given unlimited access to cocaine (Deneau et al. 1969; Johanson et al. 1976; Bozarth and Wise 1985). During abstinent periods, a non-contingent drug injection can serve to "prime" an animal to reinstate self-administration behavior. This may be equivalent to the "cocaine-induced cocaine craving" observed in human addicts (Jaffe et al. 1989). It appears therefore that in both humans and in rats, the effects of cocaine carry over from one administration to another and serve to maintain drug taking behavior. The conditions in effect during most FR or PR self-administration experiments in rats are analogous to drug taking behavior during a binge in humans. Animals have usually been "primed" and the effects of one injection carry over to influence subsequent injections. The results are necessarily influenced by the drug levels that accumulate during the test session.

The mechanisms that maintain drug taking behavior may be very different from the mechanisms that trigger relapse to drug use after periods of drug abstinence. Experimental procedures that model the initiation of drug taking would be more important for the evaluation of pharmacotherapies for cocaine than procedures that address binge behavior. In order to characterize the initiation phase of drug seeking behavior, we have used a discrete trials procedure in an effort to minimize the carry-over effects of one injection onto the next trial. By lengthening the inter-trial interval (ITI), different patterns of drug intake can be elicited (Fitch and Roberts 1993). If trials are presented as frequently as four per hour then a binge/abstinent pattern of intake is observed, with animals self-administering cocaine during consecutive trials for 24–36 h. By contrast, if access is restricted to two discrete trials per hour then a clear diurnal pattern of drug intake is evident.

Consistent with our previous report, two discrete trials per hour engendered a remarkably consistent circadian pattern of drug intake. The effect was replicated in two separate groups, each with a different 12-h light/dark cycle. The fact that both groups showed virtually identical patterns across the light/dark cycle rules out the possibility that other factors, such as regular cage maintenance and miscellaneous laboratory activities, controlled the timing of the behavior. The probability of cocaine self-administration remained low during the light phase, and increased at the start of the dark phase. The probability of responding for cocaine was near certainty for each and every animal at the end of the dark cycle. In order to assess other aspects of circadian activity, some animals were given continuous access to a second lever that, when pressed, resulted in the delivery of a 45-mg food pellet. Food intake, and to some extent the activity cycle, could be monitored by tracking the pattern of food deliveries. Figure 1 illustrates the typical pattern of food and drug intake. Rats tended to eat in a series of bouts spaced across the day/night cycle. Interestingly, there were many instances, usually during the light cycle, when animals responded for food reinforcement but declined the opportunity to self-administer cocaine. These data show that there were periods when the animals were awake and active yet were apparently not motivated to respond for cocaine.

Negus et al. (1995) have shown that rhesus monkeys also display a diurnal variation in cocaine and heroin self-administration. Discrete daily self-administration sessions were used to show that responding during afternoon sessions is less sensitive to changes in reinforcer magnitude and saline substitution than responding during morning and evening sessions. That is, lower doses of drug were more effective at maintaining responding when tested during the middle of light phase of the monkey's diurnal cycle. Rats and rhesus monkeys therefore appear to show similar diurnal rhythms, and both show increased likelihood of responding for drug reinforcement during their respective active periods – during the light period for rhesus monkeys and during the dark period for rats.

The fact that rats initiate drug taking at predictable times was used to advantage in the present experiments. In two separate replications, we examined the effect of baclofen treatment. In one group, baclofen was administered at the beginning of the dark cycle when the probability of cocaine self-administration was increasing. In the second group, baclofen was administered in the middle of the dark phase when the probability of responding was higher. In both cases, baclofen significantly decreased cocaine self-administration. Across the two replications there was 71% reduction in cocaine self-administration during the 4-h period following baclofen treatment. This represents a 40% reduction in total drug intake for the day. Vehicle injections had no effect.

Since baclofen was administered systemically, the locus of its effect remains unclear. It is possible that the effects of GABA compounds are achieved through a modulate of the mesolimbic dopamine system which is known to be important for the expression of cocaine reinforcement (Koob 1992; Roberts 1992; Woolverton and Johnson 1992) The DA cells of the ventral tegmental area project principally to the nucleus accumbens, which Mogenson and colleagues (1993) have emphasized is "strategically" situated to integrate signals from limbic structures and to translate this motivational information into motor output. The majority of neurons in the nucleus accumbens are GABAergic medium spiny neurons.

These cells, which presumably receive the cocaine-potentiated signal, make reciprocal connections with the DA cells in the VTA. Thus, the GABA projection and GABA inter-neurons within the VTA have the capacity powerfully to influence DA release and DA cell firing (Klitenick et al. 1992; Cameron and Williams 1993; Engberg and Nissbrandt 1993; Engberg et al. 1993; Rick and Lacey 1994; Seutin et al. 1994). Willick and Kokkinidis (1995) have reported that intra-VTA injections of baclofen produce an apparent decrease in the reinforcing efficacy of MFB stimulation. Baclofen infusions produced a rightward shift in rate/intensity functions produced by rats responding for intracranial stimulation without affecting other measures of performance such as maximal rates of responding. Taken together, the self-stimulation and self-administration data strongly suggest that $GABA_B$ agonists should be considered as candidates for pharmacotherapeutic agents in cocaine addiction.

Clinical observations with baclofen have been encouraging. Gudeman et al. (1996) have investigated the effects of baclofen (20–60 mg/day) in an open trial. Very preliminary data suggest that baclofen may suppress cocaine craving during the early phase of cocaine withdrawal. A. R. Childress (personal communication) has also observed that some patients taking baclofen report a decreased intensity of cocaine craving.

Acknowledgements This study was supported by NIDA contract No. NO1DA-3-7302 and the Medical Research Council of Canada.

References

Balon R (1994) Fluoxetine for cocaine dependence in methadone maintenance. J Clin Psychopharmacol 14: 360

Berger P, Gawin FH, Kosten TR (1989) Treatment of cocaine abuse with mazindol. Lancet 333: 283

Bozarth MA, Wise RA (1985) Toxicity associated with long-term intravenous heroin and cocaine self-administration in the rat. JAMA 254: 81–83

Cameron DL, Williams JT (1993) Dopamine D_1 receptors facilitate transmitter release. Nature 366: 344–347

Cornish JW, Maany I, Fudala PJ, Neal S, Poole SA, Volpicelli P, O'Brien CP (1995) Carbamazepine treatment for cocaine dependence. Drug Alcohol Depend 38: 221–227

Deneau G, Yanagita T, Seevers MH (1969) Self-administration of psychoactive substances by the monkey. Psychopharmacology 16: 30–48

Depoortere RY, Li DH, Lane JD, Emmett-Oglesby MW (1993) Parameters of self-administration of cocaine in rats under a progressive-ratio schedule. Pharmacol Biochem Behav 45: 539–548

Eiler K, Schaefer MR, Salstrom D, Lowery R (1995) Double-blind comparison of bromocriptine and placebo in cocaine withdrawal. Am J Drug Alcohol Abuse 21: 65–79

Engberg G, Nissbrandt H (1993) Gamma hydroxybutyric acid (GHBA) induces pacemaker activity and inhibition of substantia nigra dopamine neurons by activating GABA(B) receptors. Naunyn-Schmiedeberg's Arch Pharmacol 348: 491–497

Engberg G, Klingpetersen T, Nissbrandt H (1993) GABA(B) Receptor activation alters the firing pattern of dopamine neurons in the rat substantia nigra. Synapse 15: 229–238

Fitch TE, Roberts DCS (1993) The effects of dose and access restrictions on the periodicity of cocaine self-administration in the rat. Drug Alcohol Depend 33: 119–128

Giannini AJ, Folts DJ, Feather JN, Sullivan BS (1989) Bromocriptine and amantadine in cocaine detoxification. Psychiatry Res 29: 11–16

Gudeman D, Shoptaw S, Majewska D, Scherf S, Yeats D, Ling W (1996) Preliminary report of baclofen as a cocaine craving medication. College on Problems of Drug Dependence Abstracto 1: 50

Handelsman PL, Escovar IM, Marion IJ et al (1987) Amantadine for treatment of cocaine dependence in methadone-maintained patients. Am J Psychiatry 145: 533

Jaffe JH, Cascella NG, Kumor KM, Sherer MA (1989) Cocaine-induced cocaine craving. Psychopharmacology 97: 59–64

Johanson C-E, Balster RL, Bonese KF (1976) Self-administration of psychomotor stimulant drugs: the effects of unlimited access. Pharmacol Biochem Behav 4: 45–51

Kleber HD (1995) Pharmacotherapy, current and potential, for the treatment of cocaine dependence. Clin Neuropharmacol 18 [Suppl. 1]: S96–S109

Kleber HD, Gawin FH (1987) The physiology of cocaine craving and "crashing". Arch Gen Psychiatry 44: 299–300

Klitenick MA, DeWitte P, Kalivas PW (1992) Regulation of somatodendritic dopamine release in the ventral tegmental area by opioids and GABA; an in vivo microdialysis study. J Neurosci 12: 2623–2632

Koob GF (1992) Drugs of abuse: anatomy, pharmacology and function of reward pathways. Trends Pharmacol Sci 13: 177–184

Kosten TR, Schumann B, Wright D, Carney MK, Gawin FH (1987) A preliminary study of desipramine in the treatment of cocaine abuse in methadone maintenance patients. J Clin Psychiatry 48: 442–444

Kosten TR, Kleber HD, Morgan C (1989) Treatment of cocaine abuse with buprenorphine. Biol Psychiatry 26: 637–640

Kranzler HR, Bauer LO, Hersh D, Klinghoffer V (1995) Carbamazepine treatment of cocaine dependence: a placebo-controlled trial. Drug Alcohol Depend 38: 203–211

Lemere F (1991) Lithium treatment of cocaine addiction. Am J Psychiatry 148: 276

Margolin A, Avants SK, Kosten TR (1995) Mazindol for relapse prevention to cocaine abuse in methadone-maintained patients. Am J Drug Alcohol Abuse 21: 469–481

McGregor A, Baker GB, Roberts DCS (1996) Effect of 6-hydroxydopamine lesions of the medial prefrontal cortex on intravenous cocaine self-administration under a progressive ratio schedule of reinforcement. Pharmacol Biochem Behav 53: 5–9

Meyer RE (1992) New pharmacotherapies for cocaine dependence...revisited. Arch Gen Psychiatry 49: 900–904

Mogenson GJ, Bradzynski SW, Wu M, Yang CR, Yim CC (1993) From motivation to action: A review of dopaminergic regulation of limbic→nucleus accumbens→pedunculopontine nucleus circuitries involved in limbic-motor integration. In: Kalivas PW, Barnes CD (eds) Limbic motor circuits and neuropsychiatry. CRC Press, Boca Raton, pp 193–236

Montoya ID, Levin FR, Fudala PJ, Gorelick DA (1995) Double-blind comparison of carbamazepine and placebo for treatment of cocaine dependence. Drug Alcohol Depend 38: 213–219

Negus SS, Mello NK, Lukas SE, Mendelson JH (1995) Diurnal patterns of cocaine and heroin self-administration in rhesus monkeys responding under a schedule of multiple daily sessions. Behav Pharmacol 6: 763–775

Rick CE, Lacey MG (1994) Rat substantia nigra pars reticulata neurons are tonically inhibited via GABA(A), but not GABA(B), receptors in vitro. Brain Res 659: 133–137

Roberts DCS (1992) Neural substrates mediating cocaine reinforcement: The role of monoamine systems. In: Lakoski JM, Galloway MP, White FJ (eds) Cocaine: pharmacology, physiology and clinical strategies. CRC Press, Boca Raton, pp 73-90

Roberts DCS, Goeders NE (1989) Drug self-administration: experimental methods and determinants. In: Boulton AA, Baker GB, Greenshaw AJ (eds) Neuromethods. 13th edn. Humana Press, Clifton, N.J., pp 349–398

Roberts DCS, Bennett SAL, Vickers GJ (1989a) The estrous cycle affects cocaine self-administration on a progressive ratio schedule in rats. Psychopharmacology 98: 408–411

Roberts DCS, Loh EA, Vickers GJ (1989b) Self-administration of cocaine on a progressive ratio schedule in rats: dose-response relationship and effect of haloperidol pretreatment. Psychopharmacology 97: 535–538

Roberts DCS, Loh EA, Baker GB, Vickers GJ (1994) Lesions of central serotonin systems affect responding on a progressive ratio schedule reinforced either by intravenous cocaine or by food. Pharmacol Biochem Behav 49: 177–182

Roberts DCS, Andrew M, Vickers GJ (1996) Baclofen attenuates the reinforcing effects of cocaine in rats. Neuropsychopharmacology 15: 417–423

Seutin V, Johnson SW, North RA (1994) Effect of dopamine and baclofen on *N*-methyl D-aspartate induced burst firing in rat ventral tegmental neurons. Neuroscience 58: 201–206

Willick ML, Kokkinidis L (1995) The effect of ventral tegmental administration of GABA(A), GABA(B) and NMDA receptor agonists on medial forebrain-bundle self-stimulation. Behav Brain Res 70: 31–36

Woolverton WL, Johnson KM (1992) Neurobiology of cocaine abuse. Trends Pharmacol Sci 13: 193–200