A POTENTIAL ROLE FOR GABA_B AGONISTS IN THE TREATMENT OF PSYCHOSTIMULANT ADDICTION

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INTRODUCTION

Recent studies have sparked interest in the possibility that γ-aminobutyric acid (GABA) drugs may be useful in the treatment of addictive disorders. A growing number of experiments support the idea that GABA-related compounds may attenuate the acute reinforcing effects of cocaine, heroin, nicotine and alcohol in rats; a small number of clinical reports also point to beneficial effects with cocaine addicts and alcoholics. This brief review will outline these findings and identify the obstacles and issues that bear on the use of GABA drugs in addiction therapy.

Thus far, the majority of the work has focused on GABA_B compounds. Considerable progress has been made recently in the development of highly specific GABA_B agonists and antagonists, and these drugs are presently being explored in a number of animal models; however, baclofen (Lioresal®), the prototypical GABA_B agonist, is the only specific GABA_B compound available for testing in humans. This severely limits the ability to cross-validate findings between preclinical and clinical studies. Baclofen has muscle relaxant and sedative properties and the only indication for which it is licensed is the treatment of multiple sclerosis. These sedative properties complicate the interpretation of animal studies, wherein baclofen is seen to reduce drug intake, and raise questions as to whether such side-effects will be a major obstacle in using baclofen to treat human drug addicts. Nonetheless, the findings reviewed below suggest that GABA_B agonists may offer a powerful method of controlling drug abuse. Here we examine whether baclofen and other GABA_B compounds have a specific effect on drug reinforcement, and how non-specific side-effects impact the conclusions of animal and human studies.

PRECLINICAL STUDIES

A number of GABA-related compounds have been shown to modulate the neurochemical and behavioural effects of cocaine. Indirect GABA agonists (such as the γ-transaminase inhibitor, γ-vinyl-GABA), benzodiazepines (alprazolam and chlordiazepoxide), and GABA_B agonists (baclofen and CGP 44532) have all been shown to influence the physiological and behavioural effects of cocaine (Goeders et al., 1989, 1993; Roberts et al., 1996; Dewey et al., 1997; Roberts and Andrews, 1997; Dewey et al., 1998; Morgan and Dewey, 1998; Shoaib et al., 1998; Campbell et al., 1999; Kushner et al., 1999; Gerassimov et al., 2000). While it is not yet entirely clear whether GABA_A or GABA_B receptors are more critically involved in mediating the effect of GABAergic drugs on cocaine reinforcement, several very recent investigations have reported that GABA_B agonists (such as baclofen, CGP 44532 and CGP35024) are particularly effective at attenuating cocaine self-administration in rodents (Roberts et al., 1996; Roberts and Andrews, 1997; Shoaib et al., 1998; Brebner et al., 1999; Campbell et al., 1999; Brebner et al., 2000a,b, 2002).

A wide variety of schedules of reinforcement have been used to examine how baclofen affects different aspects of cocaine self-administration behaviour in rats. The simplest of these is a fixed ratio (FR1) in which each response on a lever produces an injection of cocaine. Under this schedule, animals typically self-administer lower unit dosages of cocaine more frequently than higher dosages, producing a descending curve at supra-threshold doses. A number of reports have provided
consistent evidence that baclofen reduces cocaine intake on simple FR schedules (Roberts et al., 1996; Shoaib et al., 1998; Campbell et al., 1999; Brebner et al., 2000a,b). Curiously, baclofen produces a very different effect on this dose–response curve than other drugs which block the primary site of cocaine’s reinforcing action. Cocaine is thought to act as an indirect agonist at dopaminergic (DA) synapses. Pretreatment with dopaminergic antagonists, such as haloperidol, produces increases in cocaine intake, which presumably reflects a compensatory response to the decreased reinforcing efficacy (Yokel and Wise, 1975; DeWit and Wise, 1977). By contrast, baclofen pretreatment causes a suppression of cocaine intake, particularly at lower unit injection doses. Brebner et al. (2000a) demonstrated that baclofen shifted the cocaine dose–response curve downward on the FR1 schedule, and at no point was there any indication of an increase in cocaine intake. Baclofen-induced reductions in cocaine self-administration resulted from pauses in responding, rather than a change in inter-injection intervals; when self-administration did occur, the timing of injections was not affected. These results suggest that the effect of baclofen on cocaine self-administration is qualitatively different from that produced by dopamine agonists or antagonists.

The fact that baclofen causes a suppression of cocaine intake, rather than producing a compensatory increase like that associated with DA antagonists, would appear to have some clinical appeal. It should be noted, however, that baclofen-induced suppression of responding on an FR1 schedule is surmountable at higher unit injection doses of cocaine (Brebner et al., 2000a). That is, baclofen failed to affect the rate of drug intake at the highest unit injection dose (1.5 mg/kg per injection). While these findings may at first appear discouraging, more recent studies using a progressive ratio (PR) schedule of reinforcement have indicated that baclofen is not without effect on high doses of cocaine.

On a PR schedule, the response requirements for each successive injection of cocaine increase exponentially, until the animal stops responding. The final ratio achieved is referred to as the ‘break-point’, and this is taken as an indicator of the animal’s motivation to respond for the drug. Higher unit injection doses of cocaine support higher break-points (for review, see Arnold and Roberts, 1997; Stafford et al., 1998). Baclofen has been reported to decrease cocaine-reinforced break-points across the entire dose–response curve, including high unit injection doses of cocaine. Because the response requirements on a PR schedule of reinforcement increase with each drug infusion, the question as to whether attenuation of cocaine self-administration is a real effect, or merely a result of a non-specific suppression in operant responding, must be addressed (Zarrindast et al., 1989; Grech and Balster, 1993). Indeed, Caine et al. (2000) have reported that baclofen reduced consumption of liquid food in rats; however, several other studies also examined the effect of baclofen and other GABA₉ agonists on food-reinforced responding under different schedules of reinforcement. Roberts et al. (1996) and Brebner et al. (1999) demonstrated that baclofen, CGP 44532 and CGP 35024 had less of an effect on food-reinforced responding, compared to cocaine-reinforced responding, on an identical PR schedule (Fig. 1). Shoaib et al. (1998) used a multiple schedule to show that baclofen decreased cocaine-reinforced responding, whereas responding during the food-reinforced component was only marginally affected. Brebner et al. (2000a,b) used concurrent access to food and cocaine reinforcement to show that animals that decline to self-administer cocaine following baclofen retain the capacity to respond for food at high rates. These studies suggest that the effect of baclofen on cocaine self-administration is not the result of a generalized disruption in responding caused by sedation or locomotor depression, and is not due to a general suppression of other appetitive behaviours, such as food-reinforced responding.

Both human and animal studies have indicated that the motivation to self-administer cocaine is not constant, and the ability of cocaine to support responding depends on a number of factors including the amount of drug on board, time of day, and the length of time since the last injection. A discrete trials schedule of reinforcement can be used to study motivation

![Fig. 1. The effect of various doses of γ-aminobutyric acid (GABA₉) agonists on responding on a progressive-ratio (PR) schedule reinforced by either cocaine (0.75 mg/kg/injection) or food (45 mg pellets). Points represent the mean (± SEM) break-points for separate groups of animals (n = 6–8). Cocaine and food supported similar baseline break-points on the PR schedule (13.8 vs 14.6). Low doses of baclofen (left), CGP 44532 (middle) and CGP 35024 (right) produced significant decreases in break-points for cocaine reinforcement, while food-reinforced break-points were only affected at the highest doses administered. (Redrawn from Roberts et al., 1996 and Brebner et al., 1999 with permissions.)](image-url)
to administer cocaine. Using this type of schedule, Fitch and Roberts (1993) demonstrated that restricting access to cocaine by manipulating the number and duration of inter-trial intervals (ITIs) within the schedule engenders very different patterns of cocaine self-administration. With relatively short ITIs, rats will self-administer during consecutive trials for many hours or even days, whereas longer ITIs engender a regular circadian pattern of intake. The predictable pattern of drug-taking behaviour associated with longer ITIs provides an opportunity to explore the initiation of self-administration behaviour. Both baclofen and CGP 44532 dose-dependently inhibit cocaine self-administration on the discrete trials procedure at doses that have no effect on responding for food (Roberts et al., 1996; Brebner et al., 1999). The length of the suppressive effect increases with the dose of the drug, with the higher doses causing an almost complete cessation of cocaine-seeking behaviour for 4 h.

Antagonists for specific receptor subtypes are often used to help define the mechanisms associated with agonist-induced changes in pharmacology or behaviour. Recently, several high affinity GABA_B receptor antagonists with the ability to rapidly cross the blood–brain barrier have been developed (Froestl et al., 1993), making it possible to block GABA_B receptors in animals that are self-administering cocaine. Brebner et al. (2002) reported that the specific GABA_B antagonist CGP 56433A attenuates baclofen’s effect on cocaine self-administration under FR1 and PR schedules of reinforcement. These results provide compelling evidence that baclofen’s effect on cocaine reinforcement is mediated by GABA_B receptor activation.

The neural substrates that underlie baclofen’s impact on cocaine self-administration are unknown; however, one possibility is GABAergic modulation of dopamine (DA) neurotransmission within the ventral tegmental area (VTA)/nucleus accumbens (NAC) DA system (Morgan and Dewey, 1998; McBride et al., 1998; Kushner et al., 1999). Microdialysis studies have confirmed that intra-VTA baclofen decreases extracellular DA in the NAC, and the medial prefrontal cortex (Yoshida et al., 1994; Westerink et al., 1997, 1998; Enrico et al., 1998), suggesting that GABA_B receptors within the VTA may be critical in modulating the rewarding properties of cocaine. Shaoib et al. (1998) reported that micro-injections of 200 and 300 ng of baclofen into the NAC or VTA (respectively) were required to produce decreases in cocaine self-administration on an FR5 schedule. Brebner et al. (2000b) subsequently demonstrated that as little as 56 ng of baclofen administered into the VTA was effective in reducing cocaine-reinforced break-points on a PR schedule. This dose of baclofen in the VTA was three times lower than that required to produce similar reductions in break-points when the drug was administered into the NAC or the striatum (STR) (see Fig. 2). Several other reports indicate that intra-VTA baclofen also inhibits heroin (Xi and Stein, 1999) and nicotine (Corrigall et al., 2000) self-administration, intracranial self-stimulation (Willick and Kokkinidis, 1995; Panagis and Kastellakis, 2002) and morphine place preference (Tsuji et al., 1996). Taken together, these data indicate that GABA mechanisms have the potential to modulate the efficacy of a wide range of reinforcing stimuli.

Based on the data reviewed thus far, GABA_B receptor agonists appear to attenuate the acute reinforcing effects of cocaine and other drug reinforcers in rats. It is likely that the mechanism of inhibition of drug reinforcement, at least in part, is through modulation of forebrain DA. The demonstration that baclofen’s anti-cocaine effect is not an artefact of its muscle relaxant or sedative properties, and that baclofen does not interfere with all appetitive behaviours (i.e. food-reinforced responding) is encouraging and must be cross-validated in humans. Preclinical research will continue to play an important role in the development and screening of future novel GABAergic agents for clinical use.

**CLINICAL STUDIES**

The impact of baclofen and other GABAergic drugs on drug-use motivation in animal models has encouraged studies in human addictions, though most of the human research is still in the early stages. Currently, baclofen is the only clinically available GABA_B agonist. Its short duration of action (3–4 h) poses a potential clinical challenge in the addictions, where the motivation to take a medication (and thus to avoid drug use) may wax and wane several times in the course of a day. Despite this potential limitation, some studies in cocaine populations now suggest the future promise of GABA_B agonists. Though the total number of patients studied is still modest (<50), an open-label trial (Gudeman et al., 1997; Ling et al., 1998), a controlled trial (Shoptaw, 2000), recent brain imaging studies (Childress et al., 1999, 2000, 2002 and unpublished work), and basic dose-finding (Childress et al., 2000) have each offered some encouragement, and several useful clinical observations.

Both the open-label trial (Ling et al., 1998) and the controlled trial (Shoptaw, 2000) were conducted in the context
of a structured 16-week outpatient programme which included weekly therapy and regular urine monitoring; the target dose of baclofen for both trials was 20 mg three times daily. In the open-label study (n = 10), baclofen reduced self-reported craving and cocaine use in nine of 10 patients for an average of 5 weeks during the trial; reduction in cocaine use was verified by urine toxicology. The controlled trial (n = 35) showed similar results, finding a significant reduction in self-reported craving, and a non-significant reduction in self-reported cocaine use. Urine toxicologies showed a trend for reduced cocaine use in weeks 3–8 of the trial.

These modestly encouraging results may actually have underestimated baclofen’s potential as an ‘anti-relapse’ medication. Patients who managed to ‘detoxify’ from cocaine and those who continued to use cocaine regularly were combined in the analyses testing for baclofen’s clinical benefit. This analytical strategy could obscure the benefit of a medication which acts primarily to prevent relapse — benefiting, by definition, the patients who manage to stop their cocaine use, even briefly. If baclofen’s reduction of cocaine reinforcement in humans is surmountable, as it is in rats (Roberts et al., 1996; Brebner et al., 2000a,b), it may not be useful for stopping ongoing, high-dose cocaine use. To get the clearest assessment of baclofen’s ‘anti-relapse’ potential, it will be necessary either to have a clinical design featuring patients who are already detoxified, or — as a planned post hoc comparison — to analyse these patients’ outcomes separately from those who continued unremitting cocaine use.

Recent brain imaging studies (Childress et al., 1999, 2000, 2002) underscored baclofen’s promise as an ‘anti-relapse’ agent, and offered a window onto its potential mechanism of action. Using positron emission tomography (PET) and radio-labelled water as a blood flow tracer, Childress et al. (1999) initially tested unmedicated cocaine patients, finding that cocaine (vs non-drug) video cues triggered craving and differential limbic (anterior cingulate; amygdalar) activation in cocaine patients, but not in controls. Both the cue-induced craving and the increase in limbic blood flow were hypothesized to reflect increased activity of the mesolimbic DA system, activated by cues for both natural rewards (Phillips et al., 1991; Hoebel et al., 1992) and for cocaine (Hernandez and Hoebel, 1988; Weiss et al., 2000). Because of its ability to reduce cocaine motivation in preclinical models (Roberts et al., 1996; Brebner et al., 2000a,b; Roberts and Brebner, 2000), baclofen was used as a pretreatment agent in this imaging paradigm. Cocaine patients were given baclofen (10–20 mg twice daily) for 7–10 days prior to the PET session, with the last dose received prior to the imaging session. The 7–10-day pretreatment period allowed a gradual induction of baclofen, and minimized the contribution of any initial sedative effects. No patients reported sedation by the day of the PET scan. Three patients who received baclofen within 1–2 h prior to the cocaine-video session showed substantial blunting of cue-induced craving, and did not show limbic anterior cingulate and amygdalar activation to the cocaine (vs non-drug) videos (Childress et al., 2002). Figure 3A shows the lack of limbic activation in the three baclofen pretreated patients, as compared with the activation of both the amygdala/basal forebrain and anterior cingulate seen in the cohort of unmedicated cocaine patients (Fig. 3B; n = 14). Interestingly, baclofen pretreatment was also associated with an (unanticipated) increase in cerebellar blood flow during the cocaine videos (vs non-drug cues). Patients who received baclofen ≥4 h prior to the cocaine videos showed diminished effect of the medication, consistent with its relatively short duration of action.

Though preclinical studies of baclofen in cocaine-administering rats have not yet addressed whether its benefits will be maintained with chronic administration, there are some encouraging preliminary data. A treatment-seeking cocaine patient who was also a paraplegic reported that he had been taking baclofen for >3.5 years, as prescribed for muscle spasms related to his spinal cord injury (A. R. Childress et al., unpublished work). He spontaneously reported that, when he had increased his baclofen from 10 mg four times daily to 20 mg four times daily to quell his strong spasms, the street cocaine ‘didn’t get me high anymore’, and his cocaine craving was reduced, ‘It was like I didn’t have to do anything about it — I could still remember what it (the cocaine high) was like, but I didn’t have to go after it’. A PET session conducted while he was taking 20 mg four times daily (with one of his daily doses in the hour prior to the cocaine videos) revealed images remarkably similar to those in Fig. 3A: there was a lack of differential activation of the amygdala/basal forebrain and anterior cingulate to the cocaine (vs non-drug) videos. [Interestingly, the paraplegic patient also reported that cigarettes ‘didn’t taste right’ when on baclofen, diminishing his interest in smoking. His report, with chronic baclofen administration, is consistent with the ratings of smokers in the Cousins et al. (2001) study of acute baclofen (one 20 mg dose) in cigarette smokers.]

These data, and those from clinical dose-finding with a cohort of 13 treatment-seeking cocaine patients (Childress, 2000; Childress et al., 2000), suggest that baclofen may help protect against cue-induced craving, and that its benefits can potentially be sustained for years. There is some suggestion, from the paraplegic patient’s account, that higher doses of baclofen (in the range of 20 mg four times daily) may also blunt the direct reinforcing properties of cocaine. Moreover, these benefits occurred in the absence of significant sedation or other side-effects. Though some cocaine patients taking baclofen do experience initial sedation, it tends to wane rapidly in 5–7 days. A graded induction onto the target dose is helpful. Many patients do not complain of sedation at all; it is an individual variable that does not show a strong relationship to dose. Whether initial sedation, probably reflecting a polymorphism in the individual’s GABAA receptor, has any predictive value for treatment response in drug dependence could be systematically tracked in future clinical studies.

Given that the mesolimbic DA system has been implicated in a variety of motivated behaviours and that baclofen may directly modulate this system, there could be concerns about loss of libido or appetite for food. Though animal research shows varied effects of baclofen on penile erections [e.g. inducing them in freshwater snails (Romanova et al., 1996), reversing apomorphine-induced erections in rats (Zarrindast and Farahvash, 1994)], there are virtually no complaints of baclofen’s impact on libido or performance in the human research literature, or on the Internet bulletin board which counsels paraplegics on sexual re-adjustment after spinal injury (baclofen is a common anti-spastic medication). Similarly, though there are preclinical reports that baclofen could either suppress (Zarrindast et al., 1989) or induce (Ward et al., 2000)
feeding in rats, there are no complaints of either anorexia or hyperphagia/weight gain in the human literature. Apparently, there is a dose-range of baclofen which can offer therapeutic benefits without the side-effects (impotence, weight gain) that often reduce compliance with other psychiatric medications.

In addition to these clinical benefits, there is also indirect evidence that baclofen is safe when combined with cocaine — important for any medication intended for cocaine outpatients. None of the outpatients who used cocaine during the Ling et al. (1998) open-label study, the Shoptaw et al. (2000) controlled study, or the dose-finding study (Childress et al., 2000), experienced significant adverse events. A systematic safety study of cocaine in patients treated with baclofen or placebo is ongoing (Franklin et al., 2001).

Given that baclofen is a familiar, FDA-approved medication, is well-tolerated, has minimum side-effects, is safe in combination with cocaine, and seems to have benefits even with chronic administration, what are its limitations? Is there a need for development of novel GABA$_B$ agonists? Absolutely. The short-lived action of baclofen, which dictates four times a day dosing, makes it difficult to use with outpatients, particularly with substance users whose daily lives are often in a state of tumult at the outset of treatment. A very-long-acting (or depot) GABAB agonist would not only be easier to use, but would also circumvent the ‘daily decision’ of taking vs not-taking a medication, which may prevent the drug high. Another goal might be to determine whether the muscle relaxant and anti-addictive effects of GABAB agonists can be dissociated. It is likely that the sites in the brain that mediate the effect of baclofen on drug reinforcement and craving are distinct from those that mediate the muscle relaxant effects. However, it is not clear whether this anatomical distinction could result in novel GABAB agonists which could have preferential limbic vs spinal effects. If even a small dissociation could be achieved, a new generation of psychiatric drugs might then become available for the treatment of drug addiction and other disorders of impulse control.
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