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European Journal of Pharmacology 357 (1998) 9–14

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Effects of cyclazocine on cocaine self-administration in rats

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Received 19 March 1998; revised 15 July 1998; accepted 21 July 1998

Abstract

Cyclazocine is a κ-opioid receptor agonist and μ-opioid receptor antagonist that was studied in the 1960s as a potential treatment for heroin addicts. Based on the evidence that opioid mechanisms modulate the reinforcing effects of cocaine, it has been suggested that cyclazocine be reconsidered for use in treating cocaine dependence. In the present study, the effects of orally administered (±)-cyclazocine, (+)-cyclazocine and (−)-cyclazocine on intravenous cocaine self-administration were assessed in rats. (±)-Cyclazocine produced a dose-related (2–8 mg/kg) decrease in cocaine intake without affecting bar-press responding for water. Neither enantiomer significantly altered responding for either cocaine or water. The efficacy of orally administered (±)-cyclazocine on cocaine self-administration was comparable to that previously observed using the intraperitoneal route. Distinct actions of the enantiomers of cyclazocine that might contribute to the unique efficacy of the racemate are discussed. Although the mechanistic basis for the results are not entirely understood, the data suggest that (±)-cyclazocine should be considered as a potential treatment for cocaine dependence.

Keywords: Cyclazocine; Cocaine; Drug self-administration

1. Introduction

Recent studies in animals have indicated that κ-opioid receptor agonists may be potentially useful as treatments for cocaine dependence. Such studies have focused both on neurochemical mechanisms mediating cocaine reinforcement and on behavioral correlates of cocaine's abuse liability.

An increase in extracellular dopamine levels in the nucleus accumbens has been associated with the reinforcing effects of cocaine as well as of most other addictive drugs (e.g., Di Chiara and Imperato, 1988). It has therefore been important to determine the receptor mechanisms that regulate or modulate nucleus accumbens dopamine release. Kappa opioid mechanisms have been of interest because the nucleus accumbens has high levels of both κ-receptors (cf. Mansour et al., 1988) and the endogenous κ-opioid receptor agonist peptide dynorphin (Hukfelt et al., 1984). Modulation of nucleus accumbens dopamine release by κ-opioid receptors has been demonstrated in several laboratories. Nucleus accumbens dopamine release in rats was decreased by κ-opioid receptor agonists and increased by κ-opioid receptor antagonists (e.g., Devine et al., 1993; Spanagel et al., 1992). Moreover, κ-opioid receptor agonists attenuated the increases in nucleus accumbens dopamine levels produced both by acute cocaine administration (Maisonneuve et al., 1994) and by withdrawal from repeated cocaine administration (Heidbreder and Shippenberg, 1994).

Several behavioral effects of cocaine in rats can be inhibited by κ-opioid receptor agonist administration. The locomotor hyperactivity produced by acute cocaine administration and the sensitized locomotor hyperactivity produced by repeated cocaine administration have both been attenuated by κ-opioid receptor agonist treatment (e.g., Crawford et al., 1995; Heidbreder et al., 1995; Shippenberg and Rea, 1997). Addressing cocaine's abuse liability more directly, κ-opioid receptor agonists were found to decrease cocaine-induced place preferences (Suzuki et al., 1992; Crawford et al., 1995) and the intravenous self-administration of cocaine (Glick et al., 1995). The intravenous self-administration of cocaine was also decreased by the administration of κ-opioid receptor agonists to rhesus monkeys (Negus et al., 1997). The discriminative stimulus effects of cocaine were not altered (Broadbent et al., 1995; Woolfolk and Holtzman, 1997) by κ- opioid

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0014-2999/98/$19.00
PII: S0014-2999(98)00548-2

receptor agonist administration in rats; however, the potentiating effect of morphine on the discriminative stimulus effect of cocaine was attenuated by κ-opioid receptor agonist administration (Suzuki et al., 1997) in rats, and in squirrel monkeys (Spealman and Bergman, 1992), the discriminative stimulus effects of cocaine alone were antagonized by κ-opioid receptor agonist administration. While, considered together, these results are mostly supportive of a κ-opioid receptor agonist approach to treating cocaine dependence, the side effects and limited specificity (e.g., Spealman and Bergman, 1992; Glick et al., 1995; Negus et al., 1997) of these agents have been cause for concern.

Cyclazocine, a compound synthesized by Archer in 1962, is a potent κ-opioid receptor agonist and μ-opioid receptor antagonist in both animals and humans (Archer et al., 1996). This compound was evaluated for use in treating opioid dependence 25–30 years ago (e.g., Martin et al., 1966; Resnick et al., 1971; Fink et al., 1972) and was eventually abandoned because of its side effects (e.g., dysphoria, hallucinations, irritability, insomnia). However, tolerance to these effects occurred when the dose was slowly increased and Fink et al. (1972) developed an induction protocol that was associated with minimal adverse symptoms. Archer et al. (1996) have argued that cyclazocine should be reconsidered for use in treating cocaine dependence. Cocaine abusers would not have to be detoxified prior to cyclazocine administration, and its μ-opioid receptor antagonist effect should be additive to its κ-opioid receptor agonist effect in preventing dopamine release in the nucleus accumbens (e.g., Devine et al., 1993; Spanagel et al., 1992) as well as possibly in decreasing cocaine intake (e.g., Kosten et al., 1989; Gerrits et al., 1995). A preliminary study showed that intraperitoneally administered cyclazocine would indeed decrease intravenous cocaine self-administration in rats (Archer et al., 1996). In the present study, using the same animal model, the effects of orally administered (via gavage) cyclazocine on cocaine self-administration were assessed and, in addition, the contribution of the (+) and (−) enantiomers of cyclazocine to the activity of the racemic compound was evaluated.

2. Materials and methods

2.1. Subjects and apparatus

All subjects were naive female Long–Evans (Charles River) rats, approximately 3 months old and weighing 230–250 g at the beginning of an experiment; female rats were used because they grow at much slower rate than male rats and are less likely than males to outgrow their intravenous cannulas. Rats were maintained on a normal light/dark cycle (lights on/off at 0700 h/1900 h).

All self-administration testing was conducted in Coulbourn Instruments operant test cages, each enclosed in a sound-attenuated cubicle. The intravenous self-administration procedure has been described previously (e.g., Glick et al., 1994, 1996). Briefly, responses on either of two levers (mounted 15 cm apart on the front wall of each operant test cage) were recorded on an IBM compatible 486 computer with a Med Associates interface. The intravenous self-administration system consisted of polyethylene–silicone cannulas constructed according to the design of Weeks (1972), Instech harnesses and commutators, and Harvard Apparatus infusion pumps (#55-2222).

2.2. Drugs

Cocaine hydrochloride was purchased from Sigma. The hydrochloride salts of (±)-cyclazocine, (+)-cyclazocine, and (−)-cyclazocine were provided by Albany Molecular Research, Albany, NY. All doses of drugs are expressed as the salts. Cocaine was dissolved in physiological saline while all the cyclazocines were dissolved in a lactic acid vehicle (3:2 ratio of 8.5% lactic acid/1.0 M NaOH solution).

2.3. Procedure

Shaping of the bar-press response was initially accomplished by training rats to bar-press for water. Cannulas were then implanted in the external jugular vein according to procedures described by Weeks (1972). Self-administration testing began with a 16-h nocturnal session followed by daily 1-h sessions, 5 days (Monday–Friday) a week; rats were tested about the same time each day, during the middle of the light cycle. A response on either lever (FR1 schedule) produced a 50 μl infusion of drug solution (0.1 mg of cocaine hydrochloride) in about 0.5 s. Since all rats generally weighed 250 ± 20 g, each response delivered approximately 0.4 mg/kg of cocaine; this dose is about twice the threshold dose required for maintaining self-administration behavior (Glick et al., 1987). One non-contingent drug infusion was administered at the beginning of each session. Each rat was gavaged daily, receiving 2 ml of physiological saline 30 min prior to each test session; this was done to ensure that rats were accustomed to the gavage procedure prior to drug administration. Experiments to assess the effects of racemic cyclazocine and its enantiomers were begun when baseline self-administration rates stabilized, usually after two weeks of testing. Drug treatments (2–8 mg/kg p.o. of each of the cyclazocines) were always made on Wednesdays, rats being gavaged as usual 30 min before a self-administration session; different groups of rats were used for each dose of each drug. To prevent clogging, intravenous cannulas were filled with heparin after each use. When blood could not be withdrawn, cannulas were tested by infusing a small dose (10 mg/kg) of methohexital (if the cannula was patent, a rat would immediately become ataxic).

In order to provide an indication of the specificity of the effects of the cyclazocines on cocaine self-administration, their effects on bar-pressing for water (0.01 ml) were assessed in other groups of rats. The operant chambers, reinforcement schedule (FR1), and session duration (1-h) were the same as those used for cocaine self-administration; however, these rats were maintained on a 23-h water deprivation schedule. The procedure of maintaining rats on a Monday–Friday 23-h water deprivation schedule, with daily 1-h operant test sessions (water reward), has been used in this laboratory for several years (e.g., Glick et al., 1996). As previously found, such rats exhibit small and gradual increases in body weight consistent with the asymptotic growth curves of normal female rats.

3. Results

Fig. 1 shows the effects of (±)-cyclazocine on cocaine self-administration and on bar-pressing for water; percent baseline values were obtained by comparing each dose to its own baseline (average of responding during two preceding test sessions). (±)-Cyclazocine produced a dose-related decrease in cocaine intake: all doses, from 2–8 mg/kg, had significant effects (analysis of variance (ANOVA) across doses, $P < 0.001$ and paired *t*-tests comparing cyclazocine to saline baseline, $P < 0.05$–0.005). At the same doses, (±)-cyclazocine did not affect responding for water (ANOVA across doses, $P > 0.05$).

Fig. 2 shows the effects of (+)- and (−)-cyclazocine: neither enantiomer had a significant effect on cocaine intake or on responding for water (ANOVA across doses, $P > 0.05$ in each case).

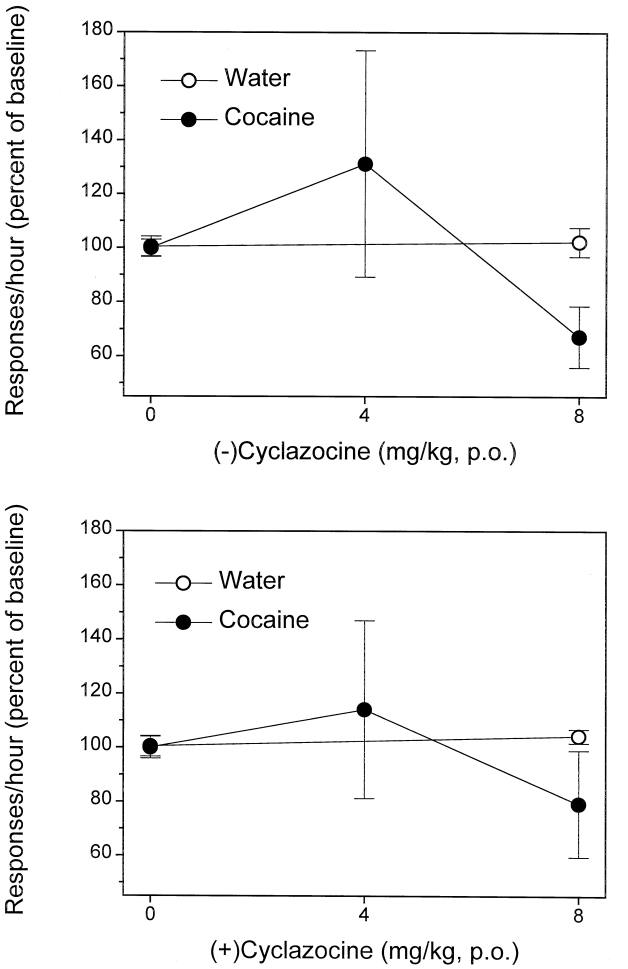

Fig. 2. Effects (mean ± SEM) of cyclazocine enantiomers on cocaine self-administration (for each enantiomer, $n = 3$ and 7–9 at 4 and 8 mg/kg, respectively) and on bar-press responding for water ($n = 4$ for each enantiomer).

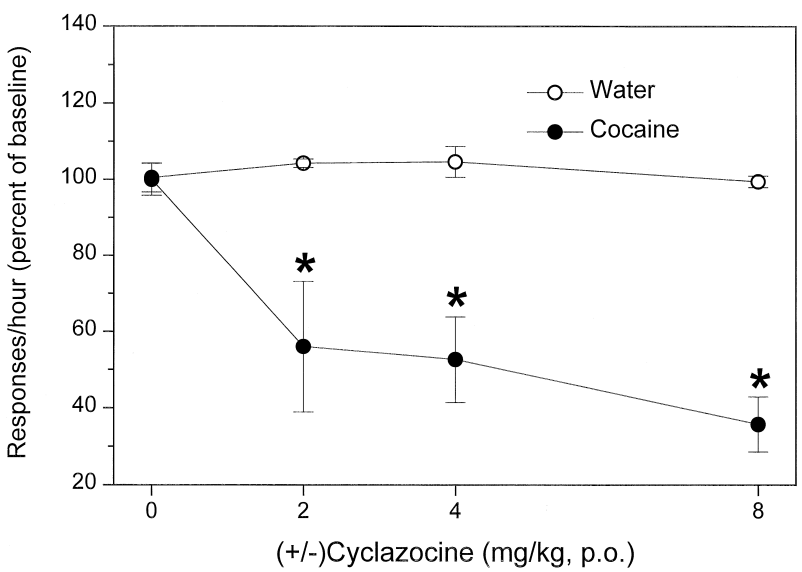

Fig. 1. Effects (mean ± SEM) of (±)-cyclazocine on cocaine self-administration ($n = 3$, 7 and 9 for 2, 4 and 8 mg/kg, respectively) and on bar-press responding for water ($n = 4$, 4 and 8 for 2, 4 and 8 mg/kg, respectively). Asterisks indicate significant differences from saline baseline (0 dose; $P < 0.05$–0.005, paired *t*-tests).

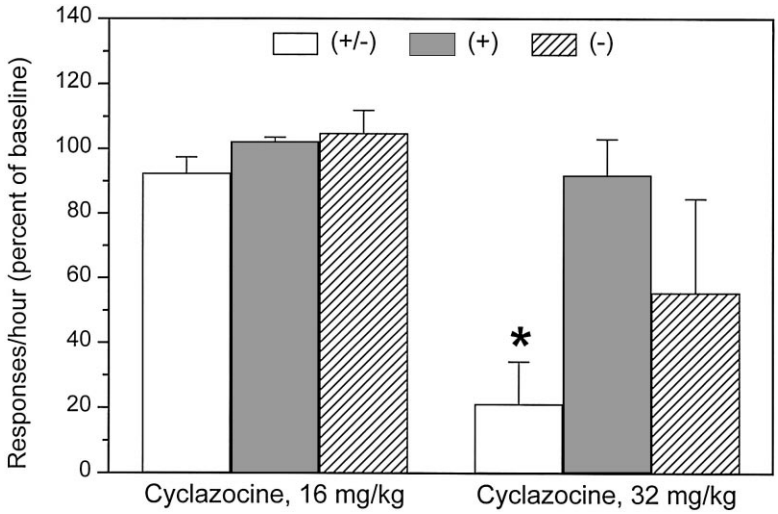

Fig. 3. Effects (mean ± SEM) of high doses of racemic cyclazocine and its enantiomers on bar-press responding for water ($n = 8$ at both doses for the racemate; $n = 4$ at both doses for each enantiomer). Asterisk indicates significant difference from saline ($P < 0.05$, paired t-test).

The results shown in Fig. 2 indicated that both enantiomers of cyclazocine contributed to racemic cyclazocine's effects on cocaine self-administration (Fig. 1). And the latter effects appeared to be selective inasmuch as (±)-cyclazocine, in the same dose range, had no effect on bar-pressing for water. It was therefore of interest to determine the extent of this selectivity by assessing whether higher doses of (±)-cyclazocine would affect responding for water; the enantiomers were also tested at higher doses in this context in order to determine their relative contribution to what might be considered an indication of a potential side effect. Accordingly, Fig. 3 compares the effects of (±)-, (+)- and (−)-cyclazocine, at doses of 16 and 32 mg/kg, on bar-press responding for water. Only (±)-cyclazocine significantly decreased rates of responding, and only at 32 mg/kg ($P < 0.05$, paired t-test with saline control).

4. Discussion

The results of the present study confirm previously reported preliminary results showing that i.p. administered (±)-cyclazocine decreased cocaine self-administration in rats (Archer et al., 1996). Comparison of the two sets of data suggests that (±)- cyclazocine is less potent but no less selective when administered orally than when administered intraperitoneally. In the previous study, (±)-cyclazocine, 0.5 mg/kg i.p., decreased cocaine self-administration to about 35% of baseline without affecting bar-press responding for water; at 2.0 mg/kg i.p., (±)-cyclazocine decreased responding for both cocaine and water. In the present study, (±)-cyclazocine, 8.0 mg/kg p.o., decreased cocaine self-administration to about 35% of baseline and without affecting bar-press responding for water; only at 32 mg/kg p.o. did (±)-cyclazocine produce a comparable decrease in responding for water. Thus, (±)-cyclazocine appears to be about 16-fold less potent when administered by gavage than by intraperitoneal injection but, by both routes, there is approximately fourfold selectivity regarding its effects on responding for cocaine versus water.

Both (+) and (−) enantiomers of cyclazocine appear to contribute to, and to be necessary for, the efficacy of the racemic compound on cocaine self-administration. While a significant decrease in cocaine self-administration was produced by (±)-cyclazocine at 2 mg/kg, neither enantiomer had any effect even at 8 mg/kg. This apparently unique activity of the racemate is a novel finding. In radioligand binding studies, it has been shown that (−)-cyclazocine has much higher affinity than (+)-cyclazocine at μ-opioid and κ-opioid receptors (Zukin, 1982) and at NMDA receptors (Largent et al., 1984; Lockhart et al., 1995) while (+)-cyclazocine has a higher affinity than (−)-cyclazocine at σ receptors (Su, 1982; Weber et al., 1986; Vilner et al., 1995). In drug discrimination studies, the (−) enantiomer has been reported to have much greater potency than the (+) enantiomer in generalizing to both NMDA receptor antagonists and σ receptor agonists (Herling et al., 1983; Shannon, 1982, 1983; Steinfels et al., 1987). Although the discrepancy between σ receptor binding and σ receptor agonist generalization is puzzling, the affinities and potencies of racemic cyclazocine have generally been in between those of the two enantiomers in all these studies. In contrast, the results of the present study suggest that the (+) and (−) enantiomers of cyclazocine have distinct actions, and that these actions have equivalent roles in mediating the effects of (±)-cyclazocine on cocaine self-administration. Based on the results of the aforementioned binding studies, it would appear that the unique efficacy of the racemate is attributable to a combination of the μ- and κ-opioid receptor activity and possi-

bly NMDA receptor activity of the (−) enantiomer and the σ receptor activity of the (+) enantiomer.

While substantial evidence (see introduction) suggests that cocaine dependence might be ameliorated by κ-opioid receptor agonists and μ-opioid receptor antagonists, the available data regarding involvement of NMDA receptors and σ receptors are less clear. Although it has been reported that the NMDA receptor antagonist dizocilpine (MK-801) blocks sensitization to cocaine-induced locomotor stimulation (e.g., Karler et al., 1989) in rats, this effect has not been uniformly found (e.g., Haracz et al., 1995); and it has also been reported that dizocilpine enhances the acute locomotor stimulant effect of cocaine (Wolf et al., 1994). In self-administration studies in rats, it has been reported that dizocilpine either reduces (Schenk et al., 1993) or enhances (Pierce et al., 1997) the reinforcing effect of cocaine; and both effects of dizocilpine may occur as a function of dose (Ranaldi et al., 1996). Neurochemical results have also been discrepant, with NMDA receptor antagonists attenuating (Moghaddam and Bolinao, 1994; Pap and Bradberry, 1995) or having no effect (Pierce et al., 1997) on cocaine-induced increases in extracellular dopamine levels in the striatum and nucleus accumbens.

There are relatively few reports that bear on the issue of whether the σ receptor activity of cyclazocine should affect cocaine dependence. It has been reported (Gudelsky, 1995) that several σ receptor ligands, both agonists and antagonists, enhance dopamine release from nigrostriatal and mesocorticolimbic neurons in rats. However, σ receptor antagonists have been found to block the development of behavioral sensitization to cocaine in rats (Ujike et al., 1996), and σ receptor agonists have been shown to attenuate both cocaine-induced convulsions (Ritz and George, 1997a) and cocaine-induced lethality (Ritz and George, 1997b) in mice. Cocaine itself has micromolar affinity for σ receptors, and it has been suggested that interactions with σ receptors may mediate cocaine's dysphoric and psychotomimetic properties (Sharkey et al., 1988). A σ receptor agonist action has also been suggested to mediate some of the psychotomimetic effects of phencylidine (e.g., Shannon, 1983). Based on the findings that, in drug discrimination studies, cyclazocine generalizes to both σ receptor agonists and phencyclidine (Shannon, 1982, 1983; Slifer and Balster, 1988; Steinfels et al., 1987), it might be speculated that the σ receptor agonist activity of (+)-cyclazocine would enhance cocaine's dysphoric/aversive effects. This action of (+)-cyclazocine might potentiate the consequences of (−)-cyclazocine's actions (κ-opioid receptor agonist, μ-opioid receptor antagonist, NMDA receptor antagonist) that directly modulate cocaine reinforcement, and this might explain why, in the present study, only the racemic compound was effective in decreasing cocaine self-administration.

In summary, racemic cyclazocine, but not either of its enantiomers, selectively decreased cocaine self-administration in rats; the efficacy of orally administered (±)-cyclazocine was comparable to that previously observed using the intraperitoneal route. Although the mechanistic basis for these results are not entirely understood, the data suggest that (±)-cyclazocine should be considered as a potential treatment for cocaine dependence. The fact that a well-documented history of cyclazocine use (albeit for another purpose) in humans is available should encourage such a trial.

Acknowledgements

This research was supported by NIDA grant DA 03817 and by Albany Molecular Research.

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