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Chlormethiazole potentiates the discriminative stimulus effects of methamphetamine in rats

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Abstract

Chlormethiazole is a positive modulator of γ-aminobutyric acid $(GABA)_A$ receptors used in the treatment of alcohol withdrawal seizures. It recently has been reported to attenuate seizures engendered by acute and repeated exposure to cocaine in mice and neurotoxic effects of methamphetamine in rats. The aim of the present study was to determine whether chlormethiazole could also attenuate the discriminative stimulus effects of methamphetamine, a behavior predictive of the subjective effects of methamphetamine in humans. In Sprague–Dawley rats trained to discriminate 1.0 mg/kg methamphetamine [intraperitoneally (i.p.)] from saline under a fixed-ratio schedule of food delivery, the ability of chlormethiazole (i.p.) to (1) substitute for methamphetamine, (2) antagonize effects of methamphetamine and to (3) shift the methamphetamine dose–effect function was investigated. Chlormethiazole (18 and 30 mg/kg, i.p.) partially substituted for the discriminative stimulus effects of methamphetamine when administered alone (maximum group average, 60% responses on the methamphetamine-appropriate lever). Chlormethiazole did not attenuate effects of methamphetamine when coadministered with the training dose of methamphetamine. Instead, chlormethiazole potentiated the discriminative stimulus effects of methamphetamine as demonstrated by a significant (about 2.5-fold) leftward and upward shift in the methamphetamine dose–effect function in the presence of chlormethiazole (10 mg/kg). In conclusion, the present findings suggest that there is a behavioral interaction between methamphetamine and chlormethiazole. The profile of this interaction is qualitatively different from that of methamphetamine and classical GABAergic drugs (i.e., benzodiazepines and barbiturates), suggesting the involvement of non-GABAergic mechanisms in the effects produced by chlormethiazole.

Keywords: Chlormethiazole; Methamphetamine; Drug-discrimination; (Rat)

1. Introduction

Methamphetamine is a highly addictive drug that is widely abused (e.g., Cho and Melega, 2002). In addition to its addictive properties, chronic exposure to methamphetamine produces neurotoxic depletion of dopamine, serotonin and glutamate neurons in the central nervous system (Ohmori et al., 1996; Fleckenstein et al., 2000; Frost and Cadet, 2000; Davidson et al., 2001; Cho and Melega, 2002). Similar neurotoxic effects have been reported after exposure to the structurally similar drug of abuse methylene-dioxymethamphetamine (MDMA, "ecstasy") (Green et al., 1995; Kalant, 2001; Obrocki et al., 2002; Lyles and Cadet, 2003). Chlormethiazole is a positive allosteric modulator of the γ-aminobutyric acid $(GABA)_A$ receptor (Smith and Jewkes, 1995). Chlormethiazole is used in clinics to treat alcohol withdrawal seizures (e.g., Smith and Jewkes, 1995). It is also effective in attenuating methamphetamine- and MDMA-induced neurotoxicity in rodents (Green et al., 1992, 1995; Baldwin et al., 1993; Green, 1998) and in treating acute toxic complications of MDMA in humans and of cocaine in mice (Bedford Russell et al., 1992; Gasior et al., 2000).

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Despite modulating the same receptor, chlormethiazole shows a distinctly different pharmacological and clinical profile from other clinically used GABAergic drugs such as benzodiazepines or barbiturates (Smith and Jewkes, 1995; Green, 1998; Jarbe and Swedberg, 1998). For example, chlormethiazole is effective in stopping seizures and status epilepticus in patients unresponsive to barbiturates and benzodiazepines. It also appears superior in treating convulsive complications during ethanol withdrawal, pre-eclampsia and eclampsia (Morgan, 1995; Smith and Jewkes, 1995).

Although the effects of chlormethiazole on psychomotor stimulant-induced neurotoxic and convulsive effects have been studied, the influence of chlormethiazole on behavioral effects of methamphetamine has not been explored. The purpose of this study was to determine whether chlormethiazole can modify the discriminative stimulus effects of methamphetamine, an animal model predictive of the subjective effects of dopaminergic psychomotor stimulant drugs.

2. Material and methods

2.1. Subjects

Nine male Sprague–Dawley rats (Charles River; Wilmington, MA) experimentally naive at the start of the study and initially weighing 280 to 350 g were housed individually. Their body weights were gradually reduced to approximately 80% of free feeding weight relative to age-matched rats. Water was available ad libitum. All rats were housed in a temperature- and humidity-controlled room and were maintained on a 12-h light/dark cycle (lights on at 6:45 A.M.). Experiments were conducted daily, approximately at the same time of the light phase.

Animals used in the present study were maintained in facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC). All experiments were conducted in accordance with the guidelines issued by the Institutional Care and Use Committee of the National Institute on Drug Abuse, National Institutes of Health and included in the Guide for Care and Use of Laboratory Animals (National Research Council, 1996).

2.2. Apparatus

Standard operant conditioning chambers (Coulbourn Instruments; Lehigh Valley, PA) located singly in sound-attenuating plastic cubicles were used. Each chamber was equipped with two response levers separated by a recessed tray into which a pellet dispenser could deliver 45-mg food pellets (F0021, Bioserv; Frenchtown, NJ). Each chamber was also equipped with a white houselight that was centrally mounted on the front wall below the ceiling, and with a white-noise generator to mask extraneous sounds. Each press of a lever, with a force exceeding 0.4 N through 1 mm, produced an audible click of a relay and was recorded as a response. The operant chambers were controlled by microcomputers using MED-PC software (MED Associates; East Fairfield, VT).

2.3. Drug discrimination procedure

The drug discrimination procedure used in the present study has been described previously (Munzar and Goldberg, 1999; Munzar et al., 1999). Briefly, rats were trained under a fixed-ratio 10 (FR10) schedule of food delivery to respond on one lever (“drug lever”) after an injection of a training dose of methamphetamine [1.0 mg/kg, intraperitoneally (i.p.)] and on the other lever (“saline lever”) after an injection of an equivalent volume of saline (i.p.). Methamphetamine and saline were injected i.p. 15 min before the start of the session. After the 15 min has elapsed, the rats were put into the operant chambers. Illuminating the white houselight signaled the beginning of the session. Once the session started, the rats were required to make 10 consecutive responses (FR10 schedule of food delivery) on the lever appropriate to the presession treatment. The completion of 10 consecutive responses on the correct lever produced delivery of one food pellet and initiated a 45-s timeout during which the white houselight was dimmed and lever pressing had no programmed consequences. After each timeout, the white houselight was again illuminated and 10 consecutive responses on the correct lever produced delivery of a food pellet. Each session ended after the completion of 20 trials or after 30 min elapsed, whichever occurred first.

Discrimination training was conducted in daily sessions, Monday to Friday, under a double alternation schedule of methamphetamine and saline pretreatments. Training continued until there were eight consecutive training 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 prior to the delivery of the first food pellet. Once the rats met these criteria of stimulus control, the test phase of the experiment with methamphetamine and chlormethiazole began.

2.4. Test sessions

Test sessions were identical to training sessions with the exception that 10 consecutive responses on either one of the two levers resulted in delivery of a food pellet. There were no more than two test sessions conducted per week that were separated by at least two days. There were regular training sessions with either methamphetamine or saline conducted on the other days. Test sessions were conducted only if the criterion of 90% accuracy and not more than four incorrect responses during the first trial was maintained in the two preceding training sessions.

Chlormethiazole was tested in three separate experiments. Experiment 1: a range of doses of chlormethiazole

was substituted for the training dose of methamphetamine to assess its ability to produce methamphetamine-like discriminative stimulus effects. Experiment 2: a range of doses of chlormethiazole was coadministered with the training dose of methamphetamine to assess its ability to block the discriminative stimulus effects of the training dose of methamphetamine. Experiment 3: a single dose of chlormethiazole was coadministered with a range of doses of methamphetamine to assess its ability to enhance the discriminative stimulus effects of low doses of methamphetamine and to shift the dose–effect function for the discriminative stimulus effects of methamphetamine. The selected dose of chlormethiazole did not produce any level of responding on the methamphetamine-appropriate level and had no significant effect on rates of responding when administered alone as determined in Experiment 1.

2.5. Drugs

S-(+)-methamphetamine HCl (D-methylamphetamine) was purchased from Research Biochemicals International (Natick, MA). Chlormethiazole edisylate (also called clomethiazole, Heminevrin; 5(2-chloroethyl)-4 methylthiazole) was obtained from AstraZeneca (Södertälje, Sweden). Doses of both drugs refer to their salt forms. Both methamphetamine and chlormethiazole were dissolved in 0.9% NaCl and were injected i.p. in a volume of 1.0 ml/kg 15 min before the session. The doses and pretreatment time for chlormethiazole were based on information on biological activity from the literature and confirmed in the present. Chlormethiazole was tested up to doses that produced a marked suppression of response rate.

2.6. Data analysis

Results were expressed as the percentage of the total responses emitted on the methamphetamine-appropriate lever. Rate of responding (responses per second) was calculated by dividing the total number of responses on both levers by the total elapsed time (in seconds), excluding responses and time during timeout periods. Experimental results are presented as group means (± S.E.M.).

Where appropriate, dose–effect data were analyzed by estimating doses of drugs that (1) produced 50% responses on the methamphetamine-appropriate lever (ED_{50}) or (2) that decreased response rates by 50% from their control values. ED_{50} values were calculated by linear regression analysis of the linear portion of the dose–effect function in individual rats and then averaging the results across rats to derive a mean ED_{50} with 95% confidence limits (CL). Group data were also analyzed by using repeated measures analysis of variance (ANOVA). For comparisons within the same group, one-way repeated measures ANOVA was used, followed, where appropriate, by Dunnett's test for multiple comparisons versus control performance (vehicle instead of chlormethiazole). For between-group comparisons, two-way repeated measures ANOVA was used, followed, where appropriate, by Tukey's test on specific dose comparisons.

Changes were considered statistically significant when the P value was <0.05. A shift in the dose–effect function was considered statistically significant when two-way ANOVA revealed significant difference ($P<0.05$) and 95% CL of methamphetamine's ED_{50} in the studied groups did not overlap.

3. Results

3.1. Maintenance of discrimination baseline

Once the training criterion for the methamphetamine discrimination was reached (range of 40–80 sessions), discrimination performance after pretreatments with saline or the training dose of methamphetamine (1.0 mg/kg) was maintained at high accuracy during subsequent training sessions. Specifically, rats responded almost exclusively on the saline-appropriate lever (99.7 ± 0.3%) after pretreatment with saline and on the methamphetamine-appropriate lever (98.9 ± 1.1%) after pretreatment with the training dose of methamphetamine. Rates of responding after saline pretreatment (1.9 ± 0.2 responses/s) were higher ($P<0.05$) than during sessions with methamphetamine pretreatment (1.3 ± 0.1 responses/s).

3.2. Generalization and pretreatment tests

Chlormethiazole produced a dose-dependent substitution to the methamphetamine training stimulus in the group of nine rats, with a maximal group effect of about 60% at 30 mg/kg [(○), Fig. 1]. Statistically significant increases in responding on the methamphetamine-appropriate lever were produced by the two highest doses of chlormethiazole (18 and 30 mg/kg; $F(4,32)=13.148$, $P<0.001$). Partial (between 20% and 79%) or full (>80%) substitution was observed in five rats after pretreatment with 18 mg/kg of chlormethiazole and in nine rats tested after the highest dose of chlormethiazole. Dose–effect functions of chlormethiazole were amenable to ED_{50} calculation in six rats. In this subset of rats, the ED_{50} value of chlormethiazole was 19.5 mg/kg (95% CL: 13.0–25.9). Chlormethiazole also dose-dependently decreased rates of responding in eight of nine rats (ED_{50}, 95% CL: 17.0 mg/kg, 12.7–21.2).

In contrast, the same range of doses of chlormethiazole failed to alter the discriminative stimulus effects of the 1.0 mg/kg training dose of methamphetamine when both compounds were administered together [$F(4,31)=1.612$, $P=0.196$; (●), Fig. 1]. Like in the generalization study, however, there were significant and dose-dependent decreases in rates of responding in eight of nine rats after coadministration of methamphetamine and chlormethiazole. The ED_{50} value of chlormethiazole in the presence of 1.0 mg/kg of methamphetamine was 18.8 mg/kg (95% CL: 14.8–22.7)

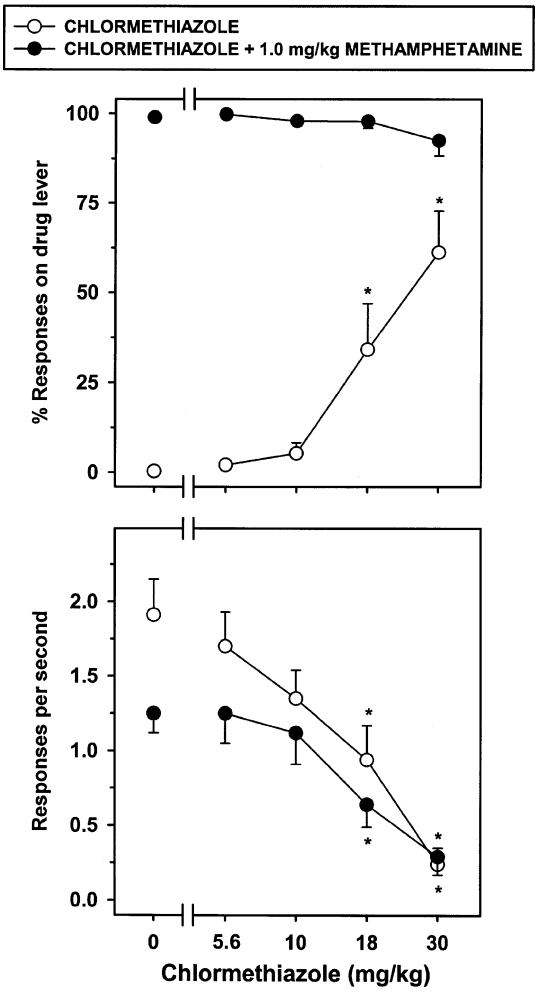

Fig. 1. Effects of chlormethiazole in rats trained to discriminate 1.0 mg/kg of methamphetamine from saline. Data are means (± S.E.M.) from $n=9$ subjects. The percentage of methamphetamine-appropriate responding (%; top) and response rates (responses/s; bottom) are shown as a function of chlormethiazole dose during substitution test sessions with chlormethiazole alone (○) or in combination with the training dose of methamphetamine (●). *$P<0.05$, within group comparison with the vehicle pretreatment (zero points) using Dunnett's test after significant main effect in one-way repeated measures ANOVA.

and it did not differ from that of methamphetamine alone ($P>0.05$).

3.3. Effects of chlormethiazole on the dose–effect function of methamphetamine

A dose of 10 mg/kg chlormethiazole was selected as the dose that did not produce any level of methamphetamine-appropriate responding and did not have significant effects on rates of responding when administered alone. Coadministration of 10 mg/kg of chlormethiazole with methamphetamine produced a statistically significant, leftward and upward shift in the methamphetamine dose–effect function [$F(1,24)=49.789$, $P<0.001$]. Doses of methamphetamine (0.1–0.3 mg/kg), that alone resulted in responding on the saline-appropriate lever, produced over 50% responding on the methamphetamine-appropriate lever when coadministered with 10 mg/kg of chlormethiazole ($P<0.05$, Tukey's test). Consequently, there was a statistically significant ($P<0.05$), 2.5-fold increase in the potency of methamphetamine (ED_{50}, 95% CL: 0.20 mg/kg, 0.11–0.29) in combination with 10 mg/kg of chlormethiazole relative to the potency of methamphetamine alone (ED_{50}, 95% CL: 0.50 mg/kg, 0.38–0.62).

Combined drug effects were more than additive because the dose of chlormethiazole used in combination experiments (10 mg/kg) did not produce any generalization to methamphetamine's training stimulus when given alone (compare Figs. 1 and 2).

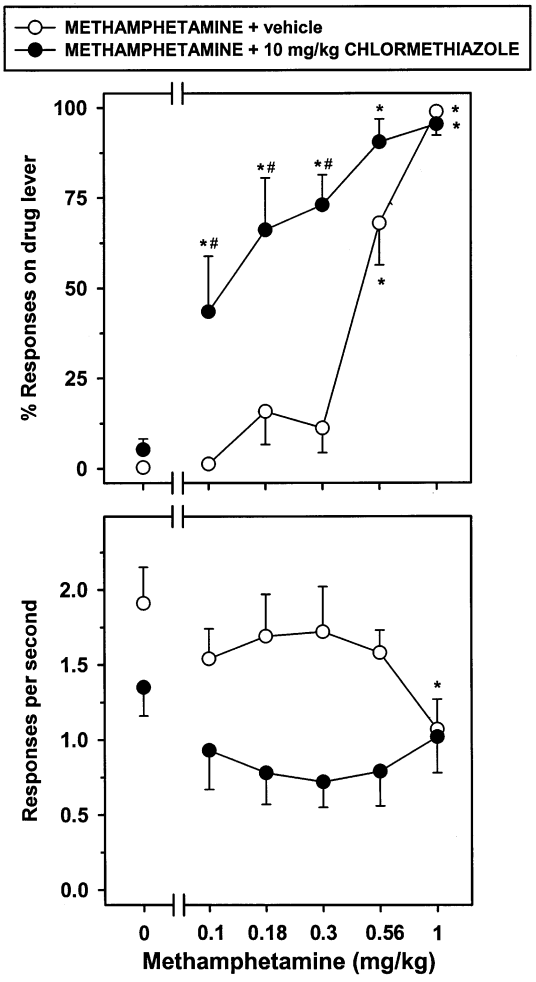

Fig. 2. Methamphetamine dose–effect function after pretreatments with vehicle [(●); 1.0 ml/kg saline] and 10 mg/kg chlormethiazole (○). Data are means (± S.E.M.) from $n=9$ subjects. The percentage of methamphetamine-appropriate responding (top) and response rates (responses/s; bottom) are shown as a function of methamphetamine dose. *$P<0.05$, within group comparison with the vehicle pretreatment (zero points) using Dunnett's test after significant main effect in one-way repeated measures ANOVA. #$P<0.05$, between group comparison of the corresponding doses using Tukey's test after significant main effect in two-way repeated measures ANOVA.

In contrast, coadministration of 10 mg/kg of chlormethiazole with methamphetamine had inconsistent effects on rates of responding. Rates of responding after coadministration of both compounds decreased relative to the rates of responding after methamphetamine alone, but the difference did not reach statistical significance as revealed by two-way ANOVA for repeated measures ($P>0.05$). Finally, the magnitude of this decrease was comparable to the decrease in response rates after 10 mg/kg chlormethiazole alone.

4. Discussion

The main finding of the present study is that chlormethiazole partially substituted for the discriminative stimulus effects of methamphetamine and shifted the dose–effect function for methamphetamine up and to the left when given at a dose without effects of its own. This drug interaction resulted in a 2.5-fold increase in the potency of methamphetamine. In contrast to the predictions based upon its ability to prevent neurotoxic effects of methamphetamine, chlormethiazole did not block the discriminative stimulus effects of methamphetamine.

Chlormethiazole also decreased the overall response rates when it was substituted for or administered prior to the training dose of methamphetamine. The response rate–decreasing effect of chlormethiazole, however, could not explain its methamphetamine-like discriminative stimulus effects because no significant changes in response rates were observed when chlormethiazole augmented the discriminative stimulus effects of lower doses of methamphetamine. Also, it is unlikely that sedative effects of chlormethiazole disrupted the ability of rats to appropriately select levers since, in that case, coadministration of higher doses of chlormethiazole with the training dose of methamphetamine would have resulted in intermediate lever selection which did not happen. Thus, the effects of chlormethiazole appear to be pharmacologically specific.

Chlormethiazole binds to the $GABA_A$ receptor and has no appreciable affinity to any other receptors measured (Smith and Jewkes, 1995; Green, 1998). Consistent with this action, chlormethiazole shares discriminative stimulus effects with some (but not all) positive modulators of the $GABA_A$ receptor (Evenden et al., 1998). However, the ability of chlormethiazole to substitute for and augment the discriminative stimulus effects of methamphetamine revealed in the present study sharply contrasts with the findings with other modulators of the $GABA_A$ receptor. Firstly, neither benzodiazepines (e.g., triazolam, imidazenil or diazepam) nor barbiturates (e.g., pentobarbital) substituted for the discriminative stimulus effects of cocaine or amphetamine (Evans and Johanson, 1987; de la Garza and Johanson, 1985, 1987; Negus et al., 2000). Secondly, they also either attenuated or had no effect on the discriminative stimulus effects of cocaine or amphetamine when administered as pretreatments (Nencini and Woolverton, 1988; Negus et al., 2000; Nader and Woolverton, 1994). In addition, discriminative stimulus effects of methamphetamine and cocaine were not modulated by baclofen, another GABAergic compound (Munzar et al., 2000; Negus et al., 2000). Finally, positive GABAergic modulators like benzodiazepines generally attenuate but not potentiate behavioral effects of psychomotor stimulants under other experimental paradigms such as self-administration (e.g., Goeders et al., 1993). Thus, it is unlikely that the observed potentiation of methamphetamine's effects by chlormethiazole might be attributed to its GABAergic component of action because no GABAergic drugs evaluated under the same or similar experimental paradigms exerted comparable effects.

The explanation for neurochemical mechanisms underlying the observed findings remains speculative at present and explicit investigations will be needed to clarify the mechanisms underlying these observations. Several neurochemical systems might be involved. The effects of chlormethiazole on the discriminative stimulus effects of methamphetamine resemble those produced by noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonists. Like chlormethiazole, NMDA receptor ion channel blockers such as dizocilpine, phencyclidine and magnesium chloride each partially substituted for and augmented the discriminative stimulus effects of cocaine (Kantak et al., 1998). Dizocilpine similarly affected the discriminative stimulus effects of amphetamine and methamphetamine (Liang and Zheng, 2000; Gaiardi et al., 2001). Finally, dizocilpine partially substituted for the discriminative stimulus effects of chlormethiazole (Evenden et al., 1998), further supporting a role of NMDA receptors in the effects of chlormethiazole. That functional NMDA receptor blockade may underlie some of the pharmacological effects of chlormethiazole is supported by its anticonvulsant effects against acute and repeated cocaine administration (Gasior et al., 2000), an effect shared by NMDA receptor antagonists (Karler et al., 1989; Itzhak and Stein, 1992; Witkin et al., 1999). This idea is further supported by comparable effects of dizocilpine and chlormethiazole on NMDA-induced sensory-evoked potentials (SEPs; Thoren and Sjolander, 1993) and methamphetamine- and MDMA-induced neurotoxicity (Green et al., 1995; Green, 1998).

In addition to the functional block of NMDA receptors, there may be other mechanisms underlying interactions between chlormethiazole and methamphetamine observed in the present study. For example, chlormethiazole can act as a monoamine oxidase B antagonist after higher doses (Morinan, 1987). Furthermore, clinical effects of chlormethiazole closely resemble those of the α_2-adrenoceptor agonist clonidine. These two mechanisms might contribute to observed interaction because monoamine oxidase B inhibitors and α_2-adrenoceptor agonists both partially substitute for methamphetamine and potentiate the discriminative stimulus effects of methamphetamine or amphetamine when administered in combination (e.g., Yasar et al., 1993; Munzar and Goldberg, 1999).

In conclusion, chlormethiazole partially substituted for and potentiated the discriminative stimulus effects of methamphetamine by a mechanism, that although not known at present, is distinct from that of its interactions with the $GABA_A$ receptor. Nonetheless, the present findings have several important implications. The interaction of chlormethiazole with methamphetamine is similar to the interactions observed with methamphetamine and neuroprotective drugs from other classes under the same experimental paradigm (e.g., dizocilpine or selegiline; Yasar et al., 1993; Koek et al., 1995; Kantak et al., 1998; Liang and Zheng, 2000;). These data thus lend support to the potential use of chlormethiazole in the treatment of neurodegenerative disorders, as proposed previously based upon neurochemical studies. Second, overlapping effects of chlormethiazole and methamphetamine suggest a potential application of chlormethiazole in the treatment of acute psychiatric complications produced by methamphetamine or other psychomotor stimulants without aggravating their withdrawal symptoms. Chlormethiazole has long been used to treat similar emergency complications of the alcohol withdrawal syndrome (Smith and Jewkes, 1995; Green, 1998). Third, modified behavioral effects of methamphetamine are expected in humans using chlormethiazole, and coadministration of these two compounds may lead to potentially clinically relevant drug interactions. Finally, methamphetamine-like effects of chlormethiazole under the drug-discrimination paradigm predict that chlormethiazole may have some abuse liability as suggested by early clinical reports (Gregg and Akhter, 1979).

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