Published in final edited form as:

Behav Pharmacol. 2005 July ; 16(4): 261–266.

GABAERGIC MODULATION OF THE DISCRIMINATIVE STIMULUS EFFECTS OF METHAMPHETAMINE

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Abstract

To assess whether GABA modulation of dopamine is important in mediation of the discriminative stimulus effects of methamphetamine, the GABA compounds chlordiazepoxide (benzodiazepine site agonist), pentobarbital (barbiturate site agonist), bicuculline and pentylenetetrazol (GABA_A receptor antagonists) were tested in Sprague-Dawley rats trained to discriminate methamphetamine (1 mg/kg, i.p.) from saline. Each of the compounds produced modest amounts of methamphetamine-appropriate responding (20–35%) when tested alone. When tested in combination with methamphetamine, the antagonists (bicuculline and pentylenetetrazol) failed to shift the methamphetamine dose-effect curve. In contrast, chlordiazepoxide (25 mg/kg, i.p.) reduced methamphetamine-appropriate responding at each dose of methamphetamine tested, and pentobarbital (10 mg/kg, i.p.) dose-dependently decreased the discriminative stimulus effects of 1 mg/kg methamphetamine. In conclusion, GABA_A antagonists and positive modulators likely do not produce methamphetamine-like stimulus effects. However, activation of GABA_A receptors can interfere with the discriminative stimulus effects of methamphetamine.

Keywords

Methamphetamine; GABA_A receptor; drug discrimination; rat

Methamphetamine has increasingly become an significant drug of abuse, as its use has increased in various regions of the US (National Institute on Drug Abuse, 2002). However, the behavioral effects of methamphetamine are not nearly as well-characterized as other psychostimulants. The drug discrimination studies that have been conducted in rats and monkeys have largely characterized the role of monoaminergic systems in mediating the discriminative stimulus effects of methamphetamine. Not surprisingly, given the well-known role of methamphetamine as a releaser of dopamine (Gerasimov et al., 1999), dopamine releasers, uptake inhibitors, and D1-like and D2-like receptor agonists all substitute for the discriminative stimulus effects of methamphetamine (Munzar et al., 1999a; Munzar and Goldberg, 2000; Tidey and Bergman, 1998). Conversely, antagonists of D1 and D2 receptors block the methamphetamine discriminative stimulus (Munzar and Goldberg, 2000; Tidey and Bergman, 1998).

The discriminative stimulus effects of methamphetamine seem to be most closely associated with dopaminergic neurotransmission, as adrenergic and serotonergic compounds have only modest effects. Indeed, adrenergic and serotonergic uptake inhibitors do not substitute for methamphetamine (Munzar et al., 1999a; Munzar and Goldberg, 1999; Tidey and Bergman,

1998), and beta adrenergic compounds fail to substitute or block the stimulus effects of methamphetamine (Munzar and Goldberg, 1999). Alpha-2 adrenergic compounds and various 5-HT agonists (5-HT_{1A}, 5-HT₂, 5-HT₃) produce at best partial substitution or small leftward-shifts in the dose response for methamphetamine discrimination (Munzar and Goldberg, 1999; Munzar et al., 2002; Munzar et al., 1999b).

To date, the role of GABA_A receptors in the mechanism for the discriminative stimulus effects of methamphetamine has not been studied. This is a potentially interesting line of investigation because GABA mediates/modulates the actions of dopamine receptors in the central nervous system. For example, the increase in dopamine release induced by methamphetamine is blocked by gamma-vinyl GABA (Gerasimov et al., 1999), and interneurons in the ventral tegmental area are known to regulate dopamine release in the nucleus accumbens (Rahman and McBride, 2002; Xi and Stein, 1998). Conversely, dopamine inhibits GABA transmission, and this effect is absent in D2 receptor knockout mice (Centonze et al., 2003). GABA_A and dopamine D₅ receptors can form a heteromeric complex in hippocampus, which suggests a co-regulatory role of these two receptors (Agnati et al., 2003). It is interesting to note that the GABA_B agonist baclofen failed to substitute for or block the stimulus effects of methamphetamine (Munzar et al., 2000). However, the failure of a GABA_B compound to alter the stimulus effects of methamphetamine does not preclude the possibility that GABA_A receptors may contribute. Clonazepam, which activates GABA_A receptors through its actions at the benzodiazepine receptor, prevents the development of sensitization to the locomotor effects of methamphetamine (Ito et al., 1997), which supports the possibility that GABA_A receptors may play a more active role in modulating the behavioral effects of dopaminergic compounds than GABA_B receptors.

The present experiments examined the actions of GABA_A receptor selective compounds on the discriminative stimulus effects of methamphetamine in rats. The GABA_A receptor antagonists pentylenetetrazol and bicuculline, and the allosteric GABA_A receptor agonists chlordiazepoxide and pentobarbital, were tested alone and in combination with methamphetamine in rats trained to discriminate methamphetamine (1 mg/kg) from saline.

METHODS

Subjects

Male Sprague-Dawley rats were obtained from Harlan-Sprague Dawley (Indianapolis, IN). All rats were housed individually and were maintained on a 12:12 light/dark cycle (lights on at 7:00 AM). Body weights were maintained at 320–350 g by limiting food to 20 g/day, which included the food received during operant sessions. Water was freely available. All housing and procedures were in accordance with the guidelines of the Institute of Laboratory Animal Resources, National Research Council (Institute of Laboratory Animal Resources, 1996) and were approved by the University of North Texas Health Science Center Animal Care and Use Committee.

Discrimination training

Standard operant chambers (Coulbourn Instruments, Allentown, PA) were connected to IBM-PC compatible computers via LVB interfaces (Med Associates, East Fairfield, VT). The computers were programmed in MED-PC 1.15 (Med Associates, East Fairfield, VT) for the operation of the chambers and collection of data.

Rats were trained to discriminate methamphetamine (1 mg/kg) from saline using a two-lever choice methodology. Food (45 mg food pellets; Bio-Serve, Frenchtown, NJ) was available as a reinforcer under a fixed ratio 10 schedule when responding occurred on the injection appropriate lever. There was no consequence for incorrect responses. The rats received

approximately 60 training sessions before use in any behavioral experiment. Animals were selected for use in experiments when they had met the criteria of emitting 85% of responses on the injection-correct lever for both the first fixed-ratio and during the remainder of the session during their last 10 training sessions.

Training sessions occurred in a double alternating fashion (D-D-S-S-D, etc.), and tests were conducted between pairs of identical training sessions (i.e., between either two saline or two methamphetamine training sessions). Rats were tested only if they had achieved 85% drug-lever responding for both first fixed-ratio and total session on the two prior training sessions. Before each session, the rats received an injection of either saline or methamphetamine. Ten minutes later, the rats were placed in an operant chamber. Each training session lasted a maximum of 10 min, and the rats could earn up to 20 food pellets.

Test procedures

For all test sessions, intraperitoneal injections of the test compounds or vehicle occurred 15 min prior to the start of the test session. Intraperitoneal injections of the training dose of methamphetamine occurred 10 min prior to the start of the test session. In contrast with training sessions, both levers were active, such that 10 consecutive responses on either lever led to reinforcement. Data was collected until the first reinforcer was obtained, or for a maximum of 20 min. At least three days elapsed between test sessions. Groups of 9 or 10 rats were tested with each test compound. A repeated measures design was used, such that each rat was tested at all doses in ascending order.

During substitution testing, bicuculline (0.5, 1.0, 2.5, 5.0 mg/kg), pentylenetetrazol (1.0, 2.5, 5.0, 10 mg/kg), chlordiazepoxide (1.0, 2.5, 5.0, 10, 25, 50 mg/kg), pentobarbital (5, 10, 25 mg/kg), or methamphetamine (0.1, 0.25, 0.5, 1 mg/kg) were tested for the ability to substitute for the discriminative stimulus effects of 1 mg/kg methamphetamine.

Bicuculline (2.5 g/kg), pentylenetetrazol (10 mg/kg), chlordiazepoxide (5, 10, 25 mg/kg), and pentobarbital (10, 25 mg/kg) were also tested for the ability to antagonize the discriminative stimulus effects of the training dose of methamphetamine (1 mg/kg). The maximum dose of each compound was also tested in combination with the full dose range of methamphetamine (0.1 to 1 mg/kg). Test compounds were administered 15 min before testing, and methamphetamine (1 mg/kg) was administered 10 min before testing.

Drugs

Pentylenetetrazol (PTZ), bicuculline, chlordiazepoxide and pentobarbital sodium were purchased from Sigma Chemical Co (St. Louis, MO). (+)-Methamphetamine hydrochloride was obtained from the National Institute on Drug Abuse. Bicuculline was dissolved in deionized water. All remaining drugs were dissolved in 0.9% saline. All drugs were administered i.p. in a volume of 1 ml/kg.

Data Analysis

Drug discrimination data were expressed as the mean percentage of responses made on the methamphetamine-appropriate lever prior to completion of the first fixed ratio. Percent methamphetamine-appropriate responding and response rate were plotted as a function of the dose of the test compound (log scale). Percent methamphetamine-appropriate responding was calculated for a given dose only if at least 3 rats completed the first fixed ratio. Full substitution was defined as >80% methamphetamine-appropriate responding, and partial substitution as 40% and <80% methamphetamine-appropriate responding. Rates of responding were expressed as a function of the number of responses made divided by the total session time. Comparison of the effects of various doses of pentobarbital and

chlordiazepoxide in combination with methamphetamine was performed by one-way analysis of variance. Individual differences were compared using Duncan's Multiple Range Test. Criterion for significance was set a priori at $p < 0.05$.

RESULTS

Substitution Tests

GABA_A antagonists pentylenetetrazol (N=9) and bicuculline (N=10) each failed to substitute for the discriminative stimulus effects of methamphetamine (Fig. 1). Pentylenetetrazol produced a plateau of methamphetamine-appropriate responding at 30 to 35% methamphetamine-appropriate responding between 2.5 to 10 mg/kg. Seizures were observed in 3 of 9 rats following 10 mg/kg pentylenetetrazol. Bicuculline produced an increase in methamphetamine-appropriate responding to a maximum of 27% at a dose (5.0 mg/kg) that also produced seizures in 2 of 10 rats. There was no effect of either compound on response rates at the doses tested. Higher doses were not tested due to risk of seizures.

Pentobarbital (N=10), a GABA_A barbiturate-site agonist, produced no methamphetamine-appropriate responding at the doses tested (Fig. 2). A dose-dependent decrease in response rates was observed, and the largest dose of pentobarbital (25 mg/kg) substantially decreased response rates such that only 1 of 10 rats completed the first fixed ratio. Chlordiazepoxide (N=10), a GABA_A benzodiazepine-site agonist, produced methamphetamine-appropriate responding which fluctuated between 17 to 33% in a dose range of 2.5 to 50 mg/kg (Fig. 2). Chlordiazepoxide dose-dependently decreased response rates and progressively fewer rats completed the first fixed ratio, such that only 3 of 10 rats completed the first fixed-ratio following 50 mg/kg chlordiazepoxide.

Combination Tests

Pentylenetetrazol (N=10) and bicuculline (N=10) both failed to modify the methamphetamine dose-effect curve (Fig. 1). The maximum dose of PTZ (10 mg/kg) did not alter responding at any dose of methamphetamine. The maximum dose of bicuculline that did not produce seizures (2.5 mg/kg) also did not alter responding at any dose of methamphetamine (N=10). Response rates after methamphetamine alone were not different from those when PTZ and bicuculline were combined with methamphetamine.

As shown in figure 2, pentobarbital (10 mg/kg) decreased the effects of 0.25 and 1 mg/kg methamphetamine. In contrast, chlordiazepoxide (25 mg/kg, i.p.) reduced methamphetamine-appropriate responding at each dose of methamphetamine tested, except for the lowest dose of methamphetamine (0.1 mg/kg). Neither compound altered the response rate dose-effect curve produced by methamphetamine. Table 1 shows the effects of increasing doses of chlordiazepoxide or pentobarbital on the discriminative stimulus effects of the training dose of methamphetamine (1 mg/kg). There was an overall effect of dose [$F(6,60)=6.91$, $P<0.001$]. Pentobarbital dose-dependently reduced the discriminative stimulus effects of methamphetamine to 63.6% ($p<0.05$). Chlordiazepoxide produced a dose-dependent reduction to 42.5% ($p<0.05$).

DISCUSSION

No substitution for the discriminative stimulus effects of 1.0 mg/kg methamphetamine occurred with the GABA_A antagonists (bicuculline and pentylenetetrazol) or the allosteric positive modulators of GABA_A receptors (pentobarbital and chlordiazepoxide). Small increases in methamphetamine-appropriate responding occurred in all 4 compounds, but none reached the criterion for partial substitution of 40% drug-appropriate responding. These findings suggest that neither GABA_A antagonists nor positive modulators produce

methamphetamine-like stimulus effects. However, these two types of compounds differed in their effects when they were tested in combination with methamphetamine. The largest non-toxic doses of the GABA_A antagonists failed to alter the methamphetamine dose-effect curve, showing neither antagonism nor facilitation of methamphetamine-lever responding. In contrast, pentobarbital and chlordiazepoxide both antagonized the discriminative stimulus effects of methamphetamine. Pentobarbital produced a small, but dose-dependent decrease in the discriminative stimulus effects of the training dose of methamphetamine (1 mg/kg), whereas chlordiazepoxide produced substantial decreases in methamphetamine-lever responding following 0.25 to 1 mg/kg methamphetamine.

The effects of these GABA_A compounds on methamphetamine are different from those reported for cocaine-trained rats and monkeys (Gatch et al., 2003; Negus et al., 2000). In rats, GABA_A compounds had no effect on the discriminative stimulus effects of cocaine, although diazepam may have produced a small facilitation of the effects of low doses of cocaine. They did, however, decrease response rates following administration of cocaine. In contrast, in the present study, comparable doses of the GABA_A compounds produced no change in the response rate dose-effect curve of methamphetamine. It is of potential interest that in rats, GABA_A positive modulators are more effective at modifying the discriminative effects of methamphetamine, but more effective at modifying the rate effects of cocaine. In monkeys, GABA_A agonists and positive modulators also failed to substitute for cocaine (Negus et al., 2000). In that study, high doses of pentobarbital and triazolam did produce a right shift in the cocaine dose-effect curve, but did not alter the discriminative stimulus effects of d-amphetamine. The monkeys were less sensitive to the rate-decreasing effects of the GABA_A compounds than the rats (Gatch et al., 2003; Negus et al., 2000). It is possible a comparable effect would have been seen in rats had higher doses not completely suppressed responding (Gatch et al., 2003). It is interesting to note that the GABA reuptake inhibitor tiagabine and the positive modulator triazolam failed to alter the subjective effects of cocaine in human studies (Haga et al., 2003; Lile et al., 2004).

GABA modulates the actions of dopamine receptors in the central nervous system. For example, the increase in dopamine release induced by methamphetamine is blocked by gamma-vinyl GABA, which irreversibly inhibits degradation of GABA (Gerasimov et al., 1999), and interneurons in the ventral tegmental area are known to regulate dopamine release in the nucleus accumbens (Adell and Artigas, 2004; Rahman and McBride, 2002; Xi and Stein, 1998). These findings suggest that release of GABA from GABA-interneurons or by activating GABA receptors on dopamine neurons in the ventral tegmental area or their terminals in the nucleus accumbens decreases the activity of those neurons. This would lead to a decrease in dopamine-mediated effects, such as the methamphetamine discriminative stimulus. However, blockade of GABA receptors would decrease the amount of inhibition, with a concomitant increase in dopamine activity, but this may not be enough to mimic the increase in dopamine activity produced by methamphetamine.

This interpretation leads to the prediction that GABA_A receptor agonists/positive modulators would at least partially block the discriminative stimulus effects of methamphetamine, whereas GABA_A receptor antagonists/negative modulators would produce small or no substitution for the methamphetamine discriminative stimulus. This is, in fact, what we report in the present study. Similarly, the benzodiazepine clonazepam prevents the development of sensitization to the locomotor effects of methamphetamine (Ito et al., 1997). In contrast, chlormethiazole, which is usually characterized as a GABA_A positive modulator, potentiated the discriminative stimulus effects of methamphetamine (Gasior et al., 2004). However, the authors suggest that these effects were not mediated by GABA receptors, and chlormethiazole indeed has effects at NMDA receptors (Usala et al., 2003), glycine and purinergic receptors (Pilip et al., 2000), and acts as a protein kinase inhibitor

(Simi et al., 2002). In the present study, methamphetamine blocks the rate-decreasing effects of GABA_A receptor positive modulators and these compounds in turn block the subjective effects of methamphetamine. Taken together, these findings indicate that GABA_A receptors play a contributing role in modulating the behavioral effects of methamphetamine.

The data from the present study do not provide direct evidence of an interaction of GABAergic compounds at dopaminergic neurons. There is a possibility that the presence of chlordiazepoxide or pentobarbital decrease the perceptibility of methamphetamine through unrelated mechanisms, a phenomenon termed “perceptual masking” (Gauvin and Young, 1989). There is a possibility that the GABA compounds, which are anxiolytic, reduce acute anxiety produced by the methamphetamine at a mechanism unrelated to GABAergic modulation of dopamine release. Currently, there is no clear-cut evidence that methamphetamine produces anxiety. The locomotor activating effects of methamphetamine obscure the results of several anxiety assays, which are activity based (Shimada et al., 1995). On the other hand, there is a plausible mechanism for a GABA/dopamine interaction. Until there is more direct evidence that the modulation of the behavioral effects of methamphetamine is mediated by GABA positive modulators or by alterations of anxiety-related effects, or some other neural mechanism, the mechanism for these behavioral effects is speculative.

Acknowledgments

Supported by NIH N01DA-7-8076.

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Figure 1.

Effects of GABA_A antagonists on the discriminative stimulus and response rate effects of methamphetamine (1 mg/kg, i.p.). Left panels show the effects of pentylenetetrazol and bicuculline alone. The right panels show the effects of pentylenetetrazol (10 mg/kg, i.p.) and bicuculline (2.5 mg/kg, i.p.) in combination with increasing doses of methamphetamine (0.1 to 1 mg/kg, i.p.). Each point shows the average of 10 rats unless otherwise shown. Error bars show standard error of the mean. (+)-Meth indicates the methamphetamine control.

Figure 2.

Effects of GABA_A positive modulators on the discriminative stimulus and response rate effects of methamphetamine (1 mg/kg, i.p.). Left panels show the effects of pentobarbital and chlordiazepoxide alone. The right panels show the effects of pentobarbital (10 mg/kg, i.p.) and chlordiazepoxide (25 mg/kg, i.p.) in combination with increasing doses of methamphetamine (0.1 to 1 mg/kg, i.p.). Each point shows the average of 10 rats unless otherwise shown. Error bars show standard error of the mean. (+)-Meth indicates the methamphetamine control.

Table 1

Effects of GABA_A receptor positive modulators on the discriminative stimulus effects of methamphetamine (1 mg/kg). MAR indicates methamphetamine-appropriate responding, SEM indicates standard error of measurement. Response rates are expressed as responses per second. Asterisks indicate values different from methamphetamine alone ($p < 0.05$).

Compound	Test Dose (mg/kg)	Meth Dose (mg/kg)	N Test	N Not complete first fixed ratio	Methamphetamine-appropriate responding (%)	MAR SEM	Rate (res/sec)	Rate SEM
Saline	0	0	10	0	0	0	0.46	0.09
Methamphetamine	1	0	10	0	100.0	0	0.40	0.07
Chlordiazepoxide	1	1	10	0	90.0	10.0	0.66	0.13
Chlordiazepoxide	5	1	10	0	53.8 *	15.8	0.54	0.12
Chlordiazepoxide	25	1	10	1	42.5 *	14.8	0.32	0.05
Pentobarbital	5	1	10	0	80.0	13.3	0.64	0.09
Pentobarbital	10	1	10	2	63.6 *	17.8	0.35	0.10