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Effects of Monoamine Oxidase Inhibitors on Cocaine Discrimination in Rats

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Abstract

This study tested the time course of the discriminative stimulus effects of inhibitors of monoamine oxidase (MAO) alone or in combination with cocaine. Male Sprague-Dawley rats were trained to discriminate cocaine (10 mg/kg, i.p.) from saline using a two-lever choice methodology. The non-selective MAO inhibitors tranylcypromine (0.01 to 5 mg/kg) and phenelzine (1 to 25 mg/kg), the MAO-A selective compound clorgyline (1 to 25 mg/kg), and the MAO-B selective compounds pargyline (0.005 to 50 mg/kg) and selegiline (1 to 25 mg/kg) were tested for substitution 15 min or 24 hr following administration, and in combination with 10 mg/kg of cocaine 24 and 48 hr after administration. At 15 min, selegiline fully substituted for the discriminative stimulus effects of cocaine, whereas all other compounds partially substituted. At 24 hr, substitution of cocaine was diminished for all compounds except phenelzine, which produced a greater amount of substitution at 24 hr than at 15 min. When cocaine was administered 24 hr following clorgyline, selegiline, pargyline, and phenelzine, cocaine-appropriate responding was attenuated at intermediate doses of these drugs, whereas the highest doses did not alter cocaine-lever responding. All compounds except selegiline substantially decreased response rate and produced various adverse effects. At 48 hr, the effects of all compounds except phenelzine were markedly reduced. Selectivity for MAO-A or B did not predict the ability to substitute for or attenuate the subjective effects of cocaine. These findings suggest that MAO inhibitors can modulate the discriminative stimulus effects of cocaine for at least 24 hr, and may be useful for treatment of cocaine abuse.

Keywords

Cocaine; drug discrimination; dopamine receptors; monoamine oxidase inhibitors; rat

A number of pharmacological treatments have been used successfully for treating alcohol and opioid (e.g., heroin) abuse, but no analogous pharmacotherapies have been developed for cocaine abuse, a long-standing and serious social problem. Cocaine inhibits reuptake of dopamine, norepinephrine and serotonin, resulting in increased levels of these neurotransmitters in the synapse (Koob and Nestler, 1997). Although accumulation of dopamine is thought to play a principal role in the subjective and reinforcing effects of cocaine, both norepinephrine and serotonin play modulatory roles (Woolverton, 1990).

Irreversible inhibitors of monoamine oxidase (MAO), which prevent neuronal degradation of monoamine, are potentially useful as cocaine abuse therapeutics based on their ability to produce long-lasting modification of dopamine, norepinephrine, and serotonin

neurotransmission. Inhibitors may target different subtypes of MAO (MAO-A and MAO-B), that preferentially metabolize different neurotransmitters (Neff and Yang, 1974). MAO-A is selective for norepinephrine and serotonin, whereas MAO-B is selective for phenylethylamine, a naturally occurring compound that has mild stimulant-like effects that are thought to be mediated by the dopamine system. Dopamine, the neurotransmitter most involved with the subjective effects of cocaine, is metabolized non-preferentially by both MAO-A and MAO-B (Neff and Yang, 1974).

Selegiline, an irreversible MAO-B selective inhibitor (Salach et al., 1979), decreased the subjective effects of cocaine in human subjects (Bartzokis et al., 1999; Houtsmuller et al., 2004). Treatment with 10 to 20 mg of selegiline for 6 to 10 days reduced subjects' ratings of being "high" by 40% following 20 or 40 mg (i.v.) of cocaine. In addition, selegiline reversed the effects of cocaine on glucose utilization in the amygdala as measured by PET scans (Bartzokis et al., 1999) but did not alter metabolism of cocaine nor cocaine's effects on prolactin or growth hormone (Houtsmuller et al., 2004). Such findings suggest that MAO inhibitors might be good candidates as potential treatments of cocaine abuse and dependence.

The immediate effects of the MAO inhibitors appear to be psychostimulant-like, as they substitute for the discriminative stimulus effects of cocaine (Colpaert et al., 1980; Johanson and Barrett, 1993; Yasar et al., 1994), and of amphetamine (Porsolt et al., 1984; Yasar et al., 1993). Selegiline (17 mg/kg) fully substituted in rats trained to discriminate 10 mg/kg cocaine from saline (Yasar et al., 1994). A number of other MAO inhibitors fully substituted for the discriminative stimulus effects of 5 mg/kg cocaine, including pargyline [MAO-B selective, (Edwards and Pak, 1979)], and tranlylcypromine, nialamide, pheniprazine (non-selective, Neff and Yang, 1974), whereas clorgyline [MAO-A selective (Salach et al., 1979)] failed to fully substitute (Colpaert et al., 1980). In addition, selegiline produced small increases in the effects of low doses of cocaine (Yasar et al., 1994).

The main purpose of the present study was to characterize the time course of MAO inhibitors in rats trained to discriminate cocaine from saline, testing the compounds alone for substitution and in combination with cocaine across a number of time points. Substitution of these compounds for cocaine shortly after administration has been well studied. However, given that these compounds are irreversible inhibitors of MAO (Standaert and Young, 1996) that can produce long-lasting behavioral changes (Timar, 1989; Turkish et al., 1988), it is important to also characterize the time course of their effects on the subjective effects of cocaine. The ability of MAO inhibitors to substitute for the discriminative stimulus effects of cocaine 15 min and 24 hr after administration were tested. In addition, the effects of MAO inhibitors in combination with cocaine were tested 24 and 48 hr after their administration to assess their usefulness as potential long-term blockers of the subjective effects of cocaine.

A second purpose was to assess the role of MAO-subtype selectivity, as one earlier study had suggested that only MAO-B inhibitors substituted for cocaine (Colpaert et al., 1980). To this end, the effects of the nonselective MAO inhibitors tranlylcypromine and phenelzine (Neff and Yang, 1974), the MAO-A selective compound clorgyline (Salach et al., 1979), and the MAO-B selective compounds selegiline and pargyline (Edwards and Pak, 1979; Salach et al., 1979) were selected for testing.

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 cocaine (10 mg/kg) from saline using a two-lever choice methodology. Food (45 mg food pellets; Bio-Serve, Frenchtown, NJ) was available as a reinforcer when responding occurred on the injection appropriate lever. Half of the rats were trained with cocaine as the cue on the right lever; half were trained with cocaine on the left lever. Animals received approximately 60 training sessions in total before use in any behavioral experiment. Animals were selected for use in experiments when they had achieved 85% drug-lever responding on both first reinforcer and total 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 cocaine training sessions). Rats were tested only if they had achieved 85% drug-lever responding for both first reinforcer and total session on the two prior training sessions. During each session, the rats received an injection of either saline or cocaine. 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. Because of the long-acting effects of the test compounds, training sessions were not conducted for five days after administration of a test compound.

Test Procedures

Test sessions lasted for a maximum of 20 min. In contrast with training sessions, both levers were active, such that 10 consecutive responses on either lever led to reinforcement. Data were collected until the first reinforcer was obtained, or for a maximum of 20 min. At least 5 days elapsed after administration of a test compound. Six rats were tested for each test compound. A repeated measures design was used, such that each rat was tested at all doses in ascending order.

For substitution tests, intraperitoneal injections (1 ml/kg) of saline, clorgyline (5 to 100 mg/kg), selegiline (1 to 10 mg/kg), pargyline (10 to 50 mg/kg), tranilcypromine (0.25 to 5 mg/kg) and phenelzine (1 to 25 mg/kg) occurred 15 min prior to the start of the test session. In separate groups of rats, clorgyline (5 to 50 mg/kg), selegiline (5 to 50 mg/kg), pargyline (10 to 50 mg/kg), tranilcypromine (1 to 10 mg/kg) and phenelzine (1 to 25 mg/kg) were also tested for substitution 24 and 48 hr after administration.

During interaction studies, intraperitoneal injections (1 ml/kg) of saline, clorgyline (1 to 20 mg/kg), pargyline (0.03 to 60 mg/kg), selegiline (2.5 to 25 mg/kg), tranylcypromine (1 to 8 mg/kg), and phenelzine (1 to 30 mg/kg) occurred 24 or 48 hr prior to the start of the test session. Intraperitoneal injections of the training dose of cocaine occurred 10 minutes prior to the start of the test session. For the saline control, saline was administered at 24 or 48hr before testing, and again 15 min before testing.

Drugs

(-)-Cocaine HCl was provided by the National Institute on Drug Abuse. Tranylcypromine, phenelzine, clorgyline, pargyline, and selegiline were obtained through the Cocaine Treatment Discovery Program of the National Institute on Drug Abuse. Clorgyline and phenelzine were dissolved in deionized water. All remaining drugs were dissolved in 0.9% saline. All drugs were administered i.p. Dose increments were based either on doublings, or by 1/3 logs.

Data Analysis

Drug discrimination data are expressed as the mean percentage of cocaine-appropriate responses occurring in each test period. Rates of responding were expressed as a function of the number of responses made divided by the total session time. Graphs for percent cocaine-appropriate responding and response rate were plotted as a function of dose of test compound (log scale). Percent cocaine-appropriate responding was shown only if at least 3 rats completed the first fixed ratio. Full substitution was defined as ≥80% cocaine-appropriate responding, and partial substitution as ≥40% and <80% cocaine-appropriate responding, or two or more consecutive doses produced ≥20% and <40% cocaine-appropriate responding (i.e., a plateau). Full antagonism was defined as <20% cocaine-appropriate responding, and partial antagonism was defined as ≥20% and <60% cocaine-appropriate responding, or two or more consecutive doses produced ≥60% and <80% cocaine-appropriate responding.

RESULTS

Substitution Studies

Fifteen minute pretreatment—Effects of cocaine and MAO inhibitors 15 min following injection are shown in Figure 1. Cocaine produced dose-dependent increases in cocaine-appropriate responding to a maximum of 95% at 10 mg/kg. Selegiline (10 mg/kg) fully substituted for the discriminative stimulus effects produced by 10 mg/kg of cocaine, producing 87% cocaine-appropriate responding. Neither compound produced an effect on response rate at the doses tested.

Clorgyline, pargyline, tranylcypromine, and phenelzine partially substituted for the discriminative stimulus effects produced by 10 mg/kg of cocaine (Fig. 1). Clorgyline produced a maximum of 67% cocaine-appropriate responding following 100 mg/kg, pargyline 54% following 40 mg/kg, tranylcypromine 68% following 5 mg/kg, and phenelzine 63% following 25 mg/kg. Dose-dependent decreases in response rates precluded testing higher doses of these compounds, except for pargyline which was not tested at doses higher than 50 mg/kg to avoid the lethality observed following 60 mg/kg in the interaction study.

Twenty-four hour pretreatment—Clorgyline, tranylcypromine, and phenelzine partially substituted for the discriminative stimulus effects produced by 10 mg/kg of cocaine (Fig. 2). Clorgyline produced a maximum of 41% cocaine-appropriate responding following 25 mg/kg, tranylcypromine 48% following 10 mg/kg, and phenelzine 78% following 25 mg/kg. In

contrast, selegiline and pargyline failed to substitute for cocaine. Selegiline produced a maximum of 33% cocaine-appropriate responding at 25 mg/kg, but a higher dose (50 mg/kg) produced only 16%. Pargyline produced 37% cocaine-appropriate responding following 25 mg/kg. Selegiline did not produce an effect on response rate, whereas the other compounds produced dose-dependent decreases. Higher doses of the other compounds were not tested due to either low response rates or anticipated adverse effects. Pargyline produced lethality in 2 of 4 rats following 50 mg/kg, and phenelzine produced tremors in 3 of 3 rats following 50 mg/kg.

Interaction Studies

Twenty-four hour pretreatment—Figure 3 shows the effects of MAO inhibitors in combination with 10 mg/kg of cocaine. Tranylcypromine failed to alter the discriminative stimulus effects produced by 10 mg/kg of cocaine, producing 86 to 100% cocaine-appropriate responding. Clorgyline, selegiline, pargyline, and phenelzine each altered the discriminative stimulus effects produced by 10 mg/kg cocaine. Selegiline (10 mg/kg) and pargyline (0.5 and 8 mg/kg) each reduced cocaine-appropriate responding to 50%, whereas higher doses produced little or no effect (83 to 100% cocaine-appropriate responding). Phenelzine and clorgyline each reduced cocaine-appropriate responding below 80% at two consecutive doses. Phenelzine produced maximal effects of 67 and 62% at 2 and 4 mg/kg, and clorgyline produced maximal effects of 74 and 67% at 2.5 and 5 mg/kg.

Selegiline produced no effect on response rates 24 hr following administration, whereas each of the other compounds produced large decreases in response rates at the highest doses tested. In addition, tremors occurred immediately after administration of cocaine 24 hr following administration of the highest doses of clorgyline, phenelzine, and tranylcypromine. Lethality occurred in 2/6 rats within 24 hours following 60 mg/kg pargyline, and 2 of the 4 remaining rats failed to complete testing. Lethality increased to 3/6 within 48 hours. The 40 mg/kg dose was evaluated in the 3 rats surviving following 60 mg/kg.

Forty-eight hour pretreatment—Pargyline and phenelzine each reduced cocaine-appropriate responding to 50% at a single dose. Clorgyline, selegiline, and tranylcypromine all failed to alter the discriminative stimulus effects of cocaine 48 hr after treatment. Effects on response rate were similar to those observed at 24 hr.

DISCUSSION

Short-term effects

All of the MAO inhibitors at least partially substituted for the discriminative stimulus effects of 10 mg/kg cocaine in rats. Selegiline was the only compound that fully substituted. These findings are in contrast to an earlier study in which a number of MAO-B or non-selective MAO inhibitors fully substituted for the discriminative stimulus effects of 5 mg/kg cocaine (Colpaert et al., 1980), including two that only produced partial substitution in the present study (tranylcypromine and pargyline). In that study, only clorgyline, a MAO-A selective inhibitor failed to fully substitute.

Selegiline has also fully substituted for the discriminative stimulus effects of cocaine in rats (Colpaert et al. 1980; Yasar et al. 1994) and pigeons (Johanson and Barrett, 1993). These findings raise the question of why selegiline was more efficacious at producing cocaine-like subjective effects than other MAO inhibitors. Given that selegiline is selective for MAO-B (Salach et al., 1979), it is possible that MAO subtype selectivity is responsible. Colpaert and colleagues (1980) reported substitution for the discriminative stimulus effects of 5.0 mg/kg

cocaine only in compounds with MAO-B activity (MAO-B selective or non-selective compounds). Clorgyline, which is selective for MAO-A (Salach et al., 1979), did not substitute for this low dose of cocaine (Colpaert, 1980). However, in the present study clorgyline partially substituted for the discriminative stimulus effects of a larger dose of cocaine (10 mg/kg). Further, pargyline, which is also MAO-B selective (Edwards and Pak, 1979), only partially substituted for cocaine in the present study. Pargyline may have fully substituted at doses higher than those tested in the present study, but this possibility was not tested as these doses produced lethality. Alternatively, it is quite possible that the doses of MAO inhibitors tested in the present study were not selective for MAO-A or MAO-B. For example, it is possible that the doses of clorgyline tested in the present study were high enough to inhibit both MAO-A and MAO-B. Moreover, it is doubtful that the highest doses of selegiline were MAO-B selective. In summary, given that both MAO-A and MAO-B compounds produced at least partial substitution, and that the doses tested may not have been selective, it is possible that inhibition of either MAO-A and MAO-B is sufficient to produce cocaine-like stimulus effects, or that inhibition of both is necessary for full effects.

Another possible reason selegiline may be relatively more effective at substituting for cocaine than the other compounds is that it may directly inhibit uptake and/or promote release of dopamine and norepinephrine (Gerlach et al., 1992) and may thereby produce cocaine-like stimulus effects. However, recent studies have demonstrated that modulation of intracellular calcium is necessary for selegiline-induced release of dopamine and conclude that selegiline does not directly induce release of dopamine, but increases dopamine and phenylethylamine levels in the axon terminal via MAO inhibition (Finberg et al., 2000; Lamensdorf et al., 1999; Perez et al., 2000). Phenylethylamine does not likely play an important role in mediating the substitution of selegiline for cocaine. The doses of phenylethylamine necessary to produce stimulant effects of its own (Dourish and Cooper, 1984) result in brain concentrations much higher than those seen in normal physiology, and are greater than those following administration of selegiline (Bergman et al., 2001). Taken together, these findings suggest that release of dopamine and/or phenylethylamine by selegiline would not be sufficient to account for the cocaine-like stimulus effects.

The most likely reason selegiline fully substitutes for cocaine is that it is rapidly metabolized into amphetamine and methamphetamine (Heinonen et al., 1994; Lajtha et al., 1996), both of which fully substitute for the discriminative stimulus effects of cocaine in rats (Colpaert et al., 1979; Ho and McKenna, 1978). There is no evidence that the other MAO inhibitors tested in this study are metabolized to amphetamine analogues (DeMaster et al., 1986; McKenna et al., 1990; Sherry et al., 2000).

Effects 24 to 48 hours after administration

In combination with cocaine, phenelzine, clorgyline, pargyline, and selegiline all produced U-shaped dose-effect curves 24 hr after administration such that they reduced cocaine-appropriate responding at some dose range, whereas higher doses failed to alter the discriminative stimulus effects of cocaine. These effects largely disappeared by 48 hr after administration of the MAO inhibitors. Only tranylcypromine, a non-selective MAO inhibitor, failed to produce any reduction in cocaine-appropriate responding. The magnitude of the effects were small, in agreement with earlier studies in humans in which selegiline attenuated the subjective and/or discriminative stimulus effects of cocaine (Bartzokis et al., 1999; Houtsmuller et al., 2004). The present study used a fairly large training dose of cocaine, so it is possible that these compounds could fully block the discriminative stimulus effects of lower doses of cocaine.

However, the U-shaped curves suggests that competing mechanisms may interfere with the blockade of the discriminative stimulus effects of cocaine at higher doses in rats. When

administered alone, each of the compounds produced increases in cocaine-appropriate responding 24-hr after administration in the same dose ranges as the upturn in the dose-effects of these compounds when administered with cocaine. All but phenelzine produced smaller maximal levels of cocaine-appropriate responding 24 hr after administration than at 15 min. Although the effects were small and variable, the compounds other than phenelzine produced dose-dependent ascending curves which reached a plateau. For example, clorgyline yielded a plateau of partial substitution over the range of 10 to 20 mg/kg. This suggests that the compounds still had some effect 24 hr after administration. Selegiline and tranylcypromine produced smaller effects over the same dose range after 24 hr, and even increasing the dosage failed to produce comparable peak effects. Unfortunately, the doses of clorgyline and pargyline which produced peak effects at 15 min (100 and 50 mg/kg, respectively) could not be tested at 24 hr because of decreased response rates, which precludes drawing strong conclusions about their time courses. In contrast, phenelzine produced a greater effect at 24 hr than at 15 min after administration, which is not surprising as it has a very slow onset and long-lasting inhibition of MAO (Parent et al., 2000).

MAO inhibitors are assumed to be prolong the effects of dopamine in the central nervous system by irreversible inhibition of the MAO-A and -B enzymes (Standaert and Young, 1996). Most studies have examined the effects of the MAO inhibitors when given over several days or weeks. Maximal inhibition is seen in humans in a few days, and altered metabolism of catecholamines may last as long as two weeks after discontinuing the compounds (Baldessarini, 1996). Similarly, studies in rats have shown that MAO-A and -B inhibitors prolong the electrophysiological effects of dopamine and produce a compensatory decrease in number of dopamine D₂ receptors (Martin et al., 1995; Mercuri et al., 1997). Even single doses of selegiline produce behavioral effects for as long as 5 days, which parallels the time course of changes in MAO activity (Turkish et al., 1988). It is important to note that different behaviors are affected differently. Selegiline enhanced phenylethylamine-induced stereotypies for more than 24 hr, but locomotor activity was enhanced for less than 24 hr. These studies suggest that the long-lasting effects of the MAO inhibitors seen in the present study may be due to their irreversible inhibition of MAO-A and MAO-B.

In the present study, MAO inhibitors produced at least some cocaine-like stimulus effects shortly after administration. At 24 hr after administration, intermediate doses of the MAO inhibitors attenuated the discriminative stimulus effects of cocaine in about 50% of the rats. This profile is similar to that of buprenorphine, which has been used successfully to treat opioid abuse and dependence (Resnick, 2003; Robinson, 2002). Buprenorphine, like selegiline, has short-term agonist effects that are thought to help reduce withdrawal and craving, as well as long-term reductions of the subjective effects which helps to reduce the likelihood of administering the illicit drug. These reductions may be comparable to the reduction in the discriminative stimulus and reinforcing effects of cocaine produced by cross-tolerance from long-term exposure to compounds that increase dopamine levels (Peltier et al., 1996). The adverse effects produced by the other MAO inhibitors suggests that selegiline is the best candidate of the group for treatment of cocaine abuse. Selegiline does not maintain self-administration and does not alter self-administration of cocaine or methamphetamine when given prior to the session. These findings suggest that selegiline would not produce relapse of cocaine addicts or produce dependence to its own effects. Given the results that selegiline can attenuate the subjective effects of cocaine 24 or more hours after administration, further studies on the long-term effects of selegiline on self-administration of cocaine and other abused stimulants are warranted.

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Figure 1.

The effects of MAO inhibitors on cocaine-appropriate responding 15 min after administration (N=6, except where shown). The upper panels show the mean ($\pm$ SEM) percentage of responses emitted on the cocaine-appropriate lever during the total session as a function of dose, for doses with three or more rats completing the first fixed ratio. The lower panels show the mean response rate ($\pm$ SEM) as a function of dose for all subjects tested. To the left of the axis break, control (Ctrl) data are shown for the vehicle (0.9% saline) and for the training dose of cocaine (10 mg/kg).

Figure 2.

The effects of MAO inhibitors on cocaine-appropriate responding 24 hr after administration ($N=6$, except where shown). The upper panels show the mean ($\pm$ SEM) percentage of responses emitted on the cocaine-appropriate lever during the total session as a function of dose, for doses with three or more rats completing the first fixed ratio. The lower panels show the mean response rate ($\pm$ SEM) as a function of dose for all subjects tested. To the left of the axis break, control (Ctrl) data are shown for the vehicle (0.9% saline) and for the training dose of cocaine (10 mg/kg).

Figure 3.

The effects of cocaine (10 mg/kg) when tested 24 hr after administration of MAO inhibitors (N=6, except where shown). The upper panels show the mean ($\pm$ SEM) percentage of responses emitted on the cocaine-appropriate lever during the total session as a function of dose, for doses with three or more rats completing the first fixed ratio. The lower panels show the mean response rate ($\pm$ SEM) as a function of dose for all subjects tested.

Figure 4.

The effects of cocaine (10 mg/kg) when tested 48 hr after administration of MAO inhibitors n (N=6, except where shown). The upper panels show the mean ($\pm$ SEM) percentage of responses emitted on the cocaine-appropriate lever during the total session as a function of dose, for doses with three or more rats completing the first fixed ratio. The lower panels show the mean response rate ($\pm$ SEM) as a function of dose for all subjects tested.