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Reduction of Oral Ethanol Self-Administration in Rats by Monoamine Oxidase Inhibitors

CAROLINE COHEN, OLIVIER CURET, GHISLAINE PERRAULT AND DAVID J. SANGER

Synthelabo Recherche, 31 avenue Paul Vaillant-Couturier, 92220 Bagneux, France

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COHEN, C., O. CURET, G. PERRAULT AND D. J. SANGER. *Reduction of oral ethanol self-administration in rats by monoamine oxidase inhibitors.* PHARMACOL BIOCHEM BEHAV **64**(3) 535–539, 1999.—Evidence for a role of dopamine and serotonin in the control of ethanol intake in animals suggests that monoamine oxidase (MAO) inhibitors, which increase the synaptic availability of serotonin and dopamine by blocking their metabolism, might have efficacy in the treatment of alcohol dependence. The aim of the present study was, therefore, to evaluate several MAO inhibitors for their capacity to affect ethanol self-administration in rats trained to self-administer ethanol (10% v/v) orally in a free-choice two-lever operant task. The nonselective and irreversible MAO inhibitors, phenelzine (3–10 mg/kg), tranylcypromine (1–3 mg/kg), and nialamide (30 mg/kg), decreased rates of responding maintained by ethanol reinforcement. The reversible MAO-A inhibitor, befloxatone (0.3–3 mg/kg), and the irreversible MAO-A inhibitor, clorgyline (10–30 mg/kg), also reduced ethanol self-administration. However, befloxatone-induced effects leveled off at a 50% decrease. The irreversible MAO-B inhibitors, pargyline (30 mg/kg) and l-deprenyl (3–10 mg/kg) also decreased responding maintained by ethanol reinforcement; these results are consistent with previous findings that both drugs decreased ethanol intake in mice. In conclusion, the present results showing that several MAO inhibitors decreased ethanol self-administration in rats are consistent with previous findings that synaptic levels of serotonin and dopamine play a critical role in the control of ethanol self-administration. © 1999 Elsevier Science Inc.

Ethanol self-administration Monoamine oxidase inhibitors MAO-A and MAO-B activities

ALTHOUGH ethanol interacts with several neurotransmission systems (12,23,40), strong evidence suggests that dopamine and serotonin play central roles in the control of ethanol intake in animals.

The dopamine hypothesis of the reinforcing effects of ethanol is based on the finding that ethanol, like other drugs of abuse, activates the mesolimbic dopaminergic pathway (21,24,41), a brain neuronal circuit considered to be one of the major substrates for drug-induced reinforcement (25). Moreover, reduced dopaminergic function has been observed following the cessation of ethanol self-administration (14,15,42) and in strains of rats and mice with a spontaneous preference for ethanol (20,29), suggesting that dopaminergic deficiency may contribute to increased ethanol intake. The dopamine hypothesis of ethanol-induced reinforcement is also supported by findings that several D_1-like and D_2-like dopamine agonists and antagonists decrease ethanol intake in animals (7,8,16, 30,35).

Serotonin contributes to the regulation of many psychological functions, including anxiety, depression, aggression, and impulsivity, and evidence also exists for an involvement of serotonin in the control of ethanol intake (38). Ethanol increases serotonin release in the nucleus accumbens and ethanol withdrawal is associated with decreases in serotonin function (42). Reduced serotoninergic function is also observed in ethanol-preferring rats (26). A variety of treatments that increase the synaptic availability of serotonin, including serotonin releasers and reuptake inhibitors, decrease ethanol intake in animals (1,22,27).

Evidence for a role of serotonin and dopamine in the control of ethanol intake suggests that monoamine oxidase (MAO) inhibitors, which increase the synaptic availability of serotonin and dopamine by blockade of their metabolism, might have efficacy in the treatment of alcohol dependence. The purpose of the present study was, therefore, to evaluate several MAO inhibitors for their capacity to decrease ethanol self-administration, including the nonselective and irreversible MAO inhibitors, phenelzine, tranylcypromine, and nialamide, the reversible MAO-A inhibitor, befloxatone, the irreversible MAO-A inhibitor, clorgyline, and the irreversible

Requests for reprints should be addressed to C. Cohen, Synthélabo Recherche, 31 avenue Paul Vaillant-Couturier, 92220 Bagneux, France.

MAO-B inhibitors, pargyline and l-deprenyl (Table 1). Ethanol self-administration was induced in rats by using a modified version of the sucrose-fading operant procedure designed by Samson (34).

METHOD

All procedures described here are in compliance with the European Communities Council Directive of 24 November 1986 (86/609/EEC).

Oral Ethanol Self-Administration

Subjects. Seventeen male Wistar rats obtained from IFFA CREDO (l'Arbresle, France) were used. They weighed 180–200 g when obtained from the suppliers and were allowed to gain weight during the experiment so that by the end their weights averaged 630 g. Animals had free access to food and water with the exceptions noted. Housing was in individual cages under standard laboratory conditions with lights on between 0700 and 1900 h.

Apparatus. Operant chambers (MED-Associates, Inc. Georgia, VT) were equipped with two solenoid-operated liquid delivery devices and two associated drinking cups and response levers. The cups were mounted on opposite walls. One response lever was located to the right side of each drinking cup. Responses on either lever produced delivery of 0.1-ml fluid into the corresponding cup. All operant chambers were located in sound-attenuated and ventilated cubicles. The experiment was controlled and data recorded using MED-PC software (MED-Associates, Inc., Georgia, VT).

Oral ethanol self-administration training. The procedure for induction of oral ethanol self-administration was a modified version of the sucrose-fading procedure designed by Samson (34). A fixed-ratio (FR) 1 schedule of reinforcement was used. The animals were tested 5 days per week (Monday through Friday). Each session lasted for 30 min. To promote operant responding, the rats were initially deprived of water for 16–20 h before the start of each session. Both levers were operational, and every lever press initiated delivery of 0.1 ml of a saccharin solution (0.05% w/v). Following the session, the animal was returned to its home cage and the water bottle replaced. Two to three sessions with water deprivation and three to four sessions without water deprivation were required to establish lever pressing. The rats were then introduced to a two-lever, free-choice task in which presses on one lever produced a saccharin solution (0.05% w/v, 0.1 ml), while responses on the other lever resulted in delivery of water (demineralized water, 0.1 ml). The sides from which water and saccharin were available, were alternated daily. After 2–5 days under this schedule, ethanol self-administration was initiated by adding ethanol (5% v/v) to the saccharin solution five sessions). Subsequently, saccharin concentrations in the drinking solution were decreased from 0.05 to 0.01% w/v (four sessions). At this stage, ethanol concentrations were increased from 5 to 10% (10 sessions). Finally, saccharin was totally removed. Free choice between water and ethanol 10% (v/v) was continued for 30 sessions to allow the self-administration of both fluids to stabilize. Drug testing was then started.

Testing procedure. When ethanol preference had been established the rats were tested with several monoamine oxidase inhibitors, doses being given in a mixed order that was different for different animals. Rats that decreased or increased their rates of responding over several control sessions were not tested until the self administration of both fluids stabilized. One group of rats were tested with befloxatone ($n = 8$), nialamide ($n = 7$), and pargyline ($n = 8$). Another group of rats were tested with tranylcypromine ($n = 9$), clorgyline ($n = 8$), phenelzine ($n = 8$), and l-deprenyl ($n = 8$). Testing sessions were usually conducted on Tuesdays and Fridays, and control data were taken on the days preceding the testing sessions. Saline was injected on all nondrug days.

Data analysis. The number of lever presses was recorded during each 30-min session. Responses obtained from the sessions preceding the drug sessions served as control values. Drug effects on rates of lever pressing were analyzed statistically using one-way analyses of variance (ANOVA) for repeated measures followed by Dunnett's tests.

Drugs. Ethanol (100%) was diluted with demineralized water to concentrations of 5 and 10% v/v. Saccharin hydrochloride was diluted in demineralized water to concentrations of 0.05 and 0.01% (w/v). Drugs used were befloxatone, clorgyline hydrochloride, nialamide, phenelzine sulfate, tranylcypromine hydrochloride, pargyline hydrochloride, and l-deprenyl hydrochloride. They were obtained from commercial sources or synthesized at Synthelabo Recherche. Drugs were injected as solutions in saline or suspensions in saline containing two drops of Tween 80. All injections were given at a volume of 1 or 2 ml/kg. Injections were given IP 30 min before the start of the sessions. All doses are expressed as the bases.

TABLE 1

EFFECTS OF MONOAMINE OXIDASE INHIBITORS ON EX VIVO INHIBITION OF MAO-A AND MAO-B ACTIVITY IN RAT BRAINS

Drug	ED_{50} (mg/kg, po*)		Selectivity Ratio A vs. B
	MAO-A	MAO-B	
Befloxatone	0.02	1.2	60
Clorgyline	3.4	>20	>6
Nialamide	13	57	4.4
Phenelzine	6	12	2
Tranylcypromine	0.5	0.24	0.5
Pargyline	9.3	1.4	0.15
l-Deprenyl	>30	1.5	<0.05

Data taken from Curet et al. (11).
*Drugs were administered orally.

RESULTS

All 17 rats trained to self-administer ethanol developed a preference for ethanol (10% v/v) over water. During the 30-min control sessions that preceded the drug sessions, total ethanol intake exceeded 0.5 g/kg, as estimated from the mean number of responses emitted by rats on the ethanol lever (Table 2).

The effects of nonselective MAO inhibitors on the rates of responding maintained by ethanol or water reinforcement are presented in Fig. 1. Phenelzine (3–10 mg/kg), tranylcypromine (1–3 mg/kg) and nialamide (30 mg/kg) decreased rates of responding maintained by ethanol reinforcement [phenelzine, $F(3, 21) = 18.88, p < 0.01$; tranylcypromine $F(3, 24) = 7.31, p < 0.01$; nialamide, $F(4, 24) = 8.85, p < 0.01$]. In contrast to ethanol, the MAO inhibitors did not modify water self-administration [phenelzine, $F(3, 21) = 18.88, p < 0.01$; tranylcypromine, $F(3, 24) = 7.31, p < 0.01$; nialamide, $F(4, 24) = 8.85, p < 0.01$].

TABLE 2

ETHANOL PREFERENCE AND TOTAL ETHANOL INTAKE ESTIMATED FROM THE MEAN NUMBER OF RESPONSES DURING THE 30-MIN CONTROL SESSIONS THAT PRECEEDED THE DRUG SESSIONS

	Mean (± SEM) Ethanol Lever Presses	Total Ethanol Intake (g/kg)	Mean (±SEM) Ethanol Preference (%)
Befloxatone ($n = 8$)	75 ± 7	1.04 ± 0.08	93 ± 1
Clorgyline ($n = 8$)	86 ± 17	1.12 ± 0.20	93 ± 2
Nialamide ($n = 7$)	60 ± 6	0.74 ± 0.06	91 ± 1
Phenelzine ($n = 8$)	80 ± 8	1.04 ± 0.09	94 ± 2
Tranylcypromine ($n = 9$)	82 ± 12	1.11 ± 0.15	93 ± 1
Pargyline ($n = 8$)	54 ± 5	0.68 ± 0.07	92 ± 1
l-Deprenyl ($n = 8$)	80 ± 13	1.02 ± 0.15	92 ± 2

Figure 2 shows the effects of MAO-A inhibitors on ethanol and water self-administration. Befloxatone (0.3–3 mg/kg) and clorgyline (10–30 mg/kg) decreased responding maintained by ethanol reinforcement [befloxatone, $F(5, 35) = 5.26$, $p < 0.01$; clorgyline $F(3, 21) = 9.73$, $p < 0.01$]. However, in contrast to clorgyline, befloxatone-induced effects leveled off at a 50% decrease. Although the MAO-A inhibitors tended to increase rates of responding maintained by water reinforcement, the differences from control values were not statistically significant.

Effects displayed by MAO-B inhibitors are represented in Fig. 3. l-deprenyl (3–10 mg/kg) and pargyline (30 mg/kg) also reduced ethanol self-administration [l-deprenyl, $F(3, 21) = 17.66$, $p < 0.01$; pargyline, $F(4; 28) = 4.34$, $p < 0.01$]. Like the other MAO inhibitors, pargyline and l-deprenyl did not produce statistically significant effects on water self-administration.

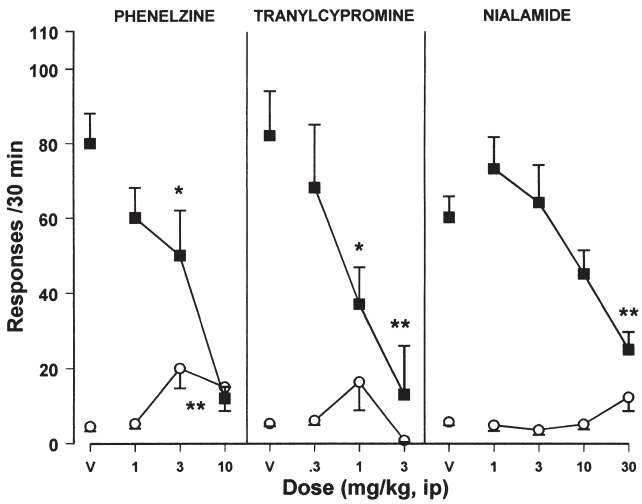

FIG. 1. Effects of the nonselective MAO inhibitors, phenelzine, tranylcypromine, and nialamide, on the rates of responding maintained by ethanol (■) and by water (°) reinforcement. Values are means (±SEM) of the number of lever press responses emitted in a 30-min session based on seven to nine rats. Control values are obtained from the sessions preceeding the drug sessions. *$p < 0.05$; **$p < 0.01$ compared to saline control values.

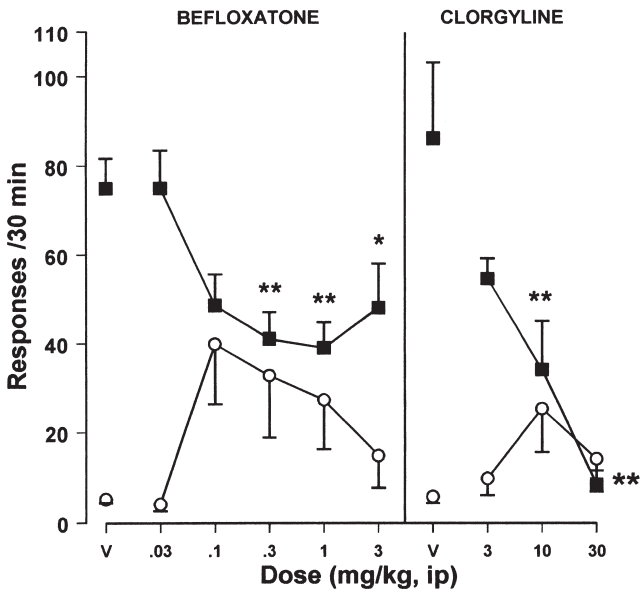

FIG. 2. Effects of the MAO-A inhibitors, befloxatone and clorgyline, on the rates of responding maintained by ethanol (■) and by water (°) reinforcement. Values are means (±SEM) of the number of lever press responses emitted in a 30-min session based on eight rats. Control values are obtained from the sessions preceeding the drug sessions. *$p < 0.05$; **$p < 0.01$ compared to saline control values.

DISCUSSION

Sweetener-fading operant procedures have proved useful to promote rapid ingestion of large amounts of ethanol in animals (34). In the present experiment, total ethanol intake exceeded 0.5 g/kg in 30-min sessions, a dose of ethanol that has been shown to produce pharmacological effects, including increased cerebral glucose utilization (31), dopamine and serotonin release (42), and discriminative stimulus effects (39).

The nonselective MAO inhibitors, phenelzine, tranylcypromine, and nialamide, produced dose-related decreases in ethanol self-administration. At doses active in the present study, these MAO inhibitors have been shown to increase dopamine and serotonin levels and to reduce levels of their metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), and 5-hydroxyindoleacetic acid (5-HIAA) (2,18,28,43). Despite their therapeutic potential, the clinical use of nonselective and irreversible MAO inhibitors has been limited by fear of the so-called "cheese effect," i.e., the hypertensive crises resulting from ingestion of foods with a high tyramine content (32). To allow the deamination of tyramine to a certain degree, drugs with selective inhibition of one MAO isoform have been developed.

In the present experiment, the MAO-A inhibitors, befloxatone and clorgyline, decreased ethanol self-administration at doses that have been shown to increase levels of dopamine and serotonin and to decrease levels of their respective deaminated metabolites in the rat brain (3,4,6,9, 10,19). In contrast to the other MAO inhibitors, befloxatone-induced effects leveled off at a 50% decrease. Befloxatone is

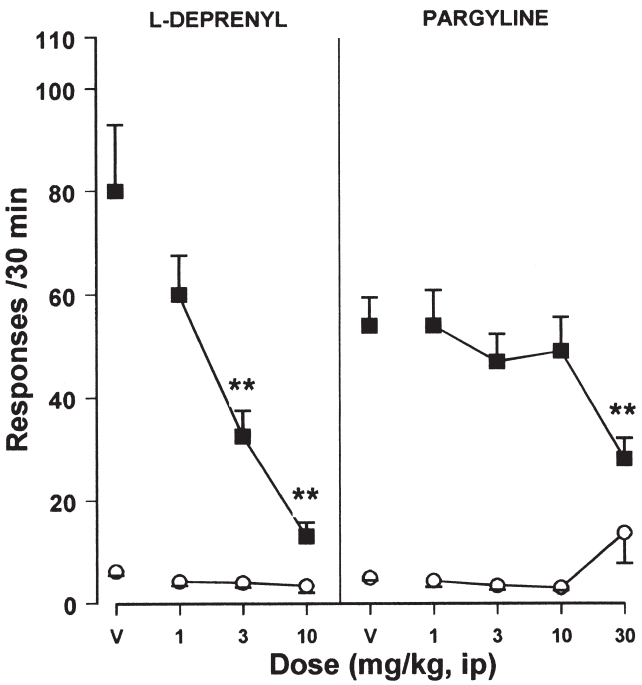

FIG. 3. Effects of the MAO-B inhibitors, pargyline and l-deprenyl, on the rates of responding maintained by ethanol (■) and by water (○) reinforcement. Values are means (±SEM) of the number of lever press responses emitted in a 30-min session based on eight rats. Control values are obtained from the sessions preceeding the drug sessions. $^{**}p < 0.01$ compared to saline control values.

a novel reversible MAO inhibitor (5,9) whose reversibility may explain its differential profile of action.

Pretreatment with the MAO-B inhibitors, pargyline and l-deprenyl, also decreased ethanol self-administration. These results extend those from previous studies that have found that I-deprenyl (20) and pargyline (36,37) decreased ethanol intake in mice. However, pargyline decreased ethanol self-administration in the present study at a dose (30 mg/kg) that is not selective for the MAO-B form (see Table 1), suggesting that the reduction of ethanol self-administration by pargyline is mediated by an inhibition of the MAO-A form. This finding is consistent with evidence suggesting that dopamine is mainly deaminated by MAO-A in the rat brain (3,4). In the case of l-deprenyl, the doses that decreased ethanol self-administration (3 and 10 mg/kg) selectively inhibit the MAO-B form (see Table 1). However, amphetamine-like metabolites of the drug could also account for its effects (17,33). The present finding that MAO-A rather than MAO-B form might be involved in the effects of MAO inhibitors on ethanol self-administration in rats is further confirmed by correlational analyses. Thus, there is a significant correlation between the potency (minimal effective dose) for decreasing rates of ethanol self-administration and the ED_{50} (data taken from Table 1) for inhibiting MAO-A activity ($r = 0.89$, $p < 0.05$) but not for inhibiting MAO-B activity ($r = 0.60$, $p > 0.1$). Because both dopamine and serotonin are metabolized by the MAO-A form in the rat brain, the present results do not allow an evaluation of the relative contribution of these neurotransmitters in the regulation of ethanol intake.

The present results showing that several MAO inhibitors decreased ethanol self-administration in rats are consistent with previous findings that serotonin and dopamine play a critical role in the control of ethanol self-administration (7,8,38). The effects of the MAO inhibitors may be due to an elevation of synaptic levels of serotonin and dopamine prior to the onset of ethanol self administration or to an enhancement of the effects of ethanol on these neurotransmission systems. In contrast to ethanol reinforcement, the rates of responding on the lever associated with water were very low in the present study. The specificity of the effects of the MAO inhibitors on ethanol self-administration should, therefore, be investigated using another reinforcer. However, by increasing levels of serotonin and dopamine, MAO inhibitors might decrease self-administration of other drugs. It is also possible that the MAO inhibitors interact with ethanol metabolism and, thus, the aversive effects of acetaldehyde could mediate the effects of the MAO inhibitors on ethanol intake. However, this effect does not appear to be important as, although pargyline has been shown to increase blood acetaldehyde levels in ethanol-treated mice, l-deprenyl and clorgyline give modest elevations and nialamide and tranylcypromine are only weakly active (13).

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