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Dopamine partial receptor agonists reduce ethanol intake in the rat

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Abstract

Dopamine neurotransmission is an important neuropharmacological component of ethanol reinforcement in rodents. A recently characterized class of compounds, dopamine partial receptor agonists, appears to possess a unique pharmacological profile on dopamine neurotransmission. The aim of the present study was to test the effects of systemic administration of terguride and SDZ 208-911 (*N*-[(8α)-2,6-dimethylergoline-8-yl]-2,2-diethylpropanamide), two prototype dopamine partial receptor agonists, in free-feeding, non-deprived rats trained to drink ethanol (10% w/v) and water in 'free-choice' limited access conditions. Both acute and chronic administration of terguride and SDZ 208-911 significantly reduced ethanol intake while water intake was not significantly affected, thus ruling out possible non-specific effects of these drugs on fluid intake. These results suggest that dopamine partial receptor agonists reduce the reinforcing properties of ethanol in the rat, an effect similar to that previously observed with cocaine. Therefore, the pharmacological profile of dopamine partial receptor agonists and their effects in animal models of dependence provide preclinical support to the hypothesis that these compounds may represent a novel pharmacological strategy for intervention in various forms of drug addiction.

Keywords: Ethanol; Dopamine receptor agonist; Dependence; Partial receptor agonist

1. Introduction

Ethanol is a widely abused substance which interacts with several neurotransmitters within the central nervous system (CNS) including γ-aminobutyric acid (GABA), serotonin, catecholamines and opiates (for review, see Weiss and Koob, 1991). Recently, however, many studies have indicated that the interaction of ethanol with dopamine neurotransmission within the limbic system of the basal forebrain may be of particular functional importance concerning ethanol reinforcement. Specifically, electrophysiological studies indicated that systemic administration of ethanol in rats selectively stimulates the firing of the dopamine-containing cells of the ventral tegmental area (A10) projecting to the nucleus accumbens of the ventral striatum (Gessa et al., 1985; Brodie et al., 1990). In addition, microdialysis studies suggest that ethanol administration increases dopamine overflow in the nucleus accumbens in freely moving rats (Di Chiara and Imperato, 1988; Yoshimoto et al., 1991) and voluntary ethanol self-administration stimulates dopamine neurotransmission within the rat nucleus accumbens (Fadda et al., 1989; Weiss et al., 1993). Finally, the behavioral significance of these observations is supported by the reduction of ethanol self-administration observed in rats following systemic administration of dopamine receptor antagonists (Samson et al., 1993) or local blockade of dopamine receptors within the nucleus accumbens (Rassnick et al., 1992).

Recently, a new class of drugs which possess a unique pharmacological profile on dopamine neurotransmission has been characterized, namely dopamine partial receptor agonists. These drugs bind to the dopamine receptor with high affinity but low intrinsic activity (Hoyer and Boddeke, 1993). The functional consequence is that these compounds act as *antago-*

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nists under conditions of high dopamine tone, but, in contrast, in conditions of low dopamine tone as after denervation or during functional depletion of the neurotransmitter, partial receptor agonists show *agonistic* properties (Clark et al., 1985; Pulvirenti and Koob, 1994).

The compounds with dopamine partial receptor agonist activity characteristics include preclamol, terguride, SDZ 208-911 and SDZ 208-912, all active at the dopamine D_2 receptor site (Hjorth et al., 1983, Kehr, 1984). Biochemical studies have revealed that SDZ 208-911 and terguride reduced the accumulation of l-dopa in reserpinized rats, an effect similar to that of the full agonist quinpirole, but produced the opposite effect in non-reserpinized rats (Svensson et al., 1991). Similarly, behavioral studies showed that SDZ 208-911 and terguride reduced amphetamine-induced locomotor activity and stereotypy, but induced controlateral turning in rats with unilateral striatal 6-hydroxydopamine lesions (Clark et al., 1991), reflecting their agonistic properties in conditions of denervation supersensitivity.

Compared with pure dopamine receptor blockers these compounds seem to be devoid of the extrapyramidal side effects which greatly limit the clinical use of classical antipsychotic drugs (Coward et al., 1990). This has prompted much attention into the preclinical evaluation of dopamine partial receptor agonists in conditions of altered brain dopamine neurotransmission including movement disorders and dependence. Regarding the latter, two prototype partial receptor agonists, SDZ 208-911 (Pulvirenti et al., 1994) and terguride (Pulvirenti and Koob, unpublished results), have already been shown to reduce the rewarding properties of cocaine in rodents and they have been proposed as novel treatment strategies for psychostimulant dependence (Pulvirenti and Koob, 1994).

The aim of the present study was therefore to examine the effects of acute and chronic administration of two dopamine partial receptor agonists, SDZ 208-911 and terguride, on voluntary oral ethanol intake in non-fluid-deprived rats in 'free-choice' limited access conditions.

2. Materials and methods

Male albino Wistar rats (Charles River) weighing 100–120 g at the beginning of training, were housed individually and exposed to a normal 12-h light-dark cycle (lights on 7:00 a.m.–7:00 p.m.). Rats were initially water deprived for 3 days only (22 h/day) to motivate drinking during the 2 h of daily exposure to ethanol. Food and water were then available ad libitum throughout subsequent training and testing periods. All training and testing was conducted in the home cages.

Animals were trained to drink ethanol using a variant of the sucrose fading technique previously described by Samson (1986) and modified by Rassnick et al. (1992). In the present study, saccharin was added to the ethanol solution to increase the palatability of the ethanol solution and to overcome ethanol's aversive taste. Initially rats were trained for 3 days in 120-min daily sessions to drink from either of two bottles containing water or 0.2% (w/v) saccharin reinforcement. Then rats were exposed daily for 120 min to a free-choice condition where one bottle contained water, the other 0.2% (w/v) saccharin + ethanol, with the ethanol side alternated daily. During training days 4–10 rats were trained to drink from either of two bottles con-

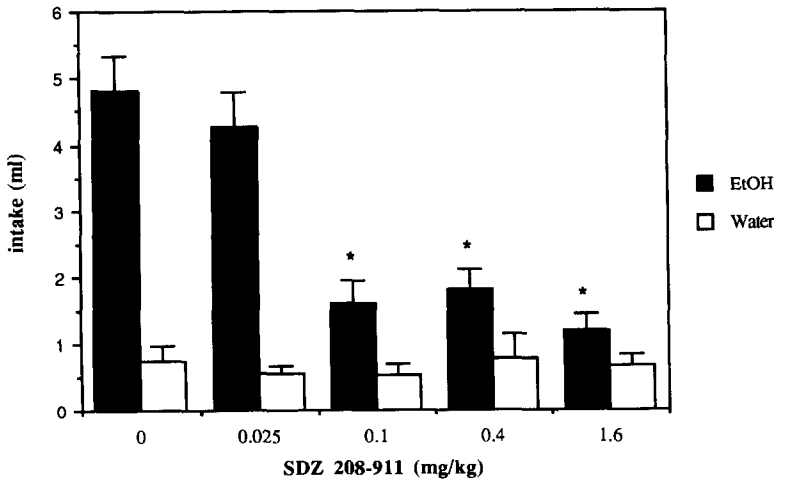

Fig. 1. Effects of acute treatment with SDZ 208-911 on ethanol intake (2-h). Values represent means ± S.E.M. of 11 animals. $^{*}P < 0.01$ Newman-Keuls' test.

Table 1
Effects of chronic treatment with SDZ 208-911 (0.2 mg/kg) on ethanol and water intake

	Day of treatment									
Baseline	1	2	3	4	5	6	7	8	9	10
Ethanol										
5.61	3.11 [a]	2.56 [a]	2.24 [a]	3.12 [a]	2.91 [a]	3.23 [a]	2.22 [a]	3.71 [a]	2.03 [a]	2.43 [a]
±0.81	±0.73	±0.54	±0.82	±0.58	±0.57	±0.67	±0.44	±0.89	±0.41	±0.74
Water										
1.09	0.62	0.52	1.76	0.60	0.49	0.82	0.57	2.03	0.33	0.18
±0.36	±0.40	±0.18	±0.89	±0.26	±0.19	±0.31	±0.36	±0.76	±0.17	±0.10

Daily intake of ethanol and water (ml) expressed as means ± S.E.M. of eight animals. [a] $P < 0.05$ Newman-Keuls' test vs. baseline.

taining water or ethanol 5% (w/v) + saccharin 0.2% (w/v). On training days 10–12 rats were given access to two bottles containing water or ethanol 5% (w/v). Thereafter, the concentration of ethanol was increased to 8% with 3 days of access to an ethanol-saccharin solution and 1 day of access to 8% ethanol without saccharin. Ethanol at 10% was then introduced in the presence of saccharin and training to respond for this concentration was conducted for 3 days. The concentration of saccharin was then gradually faded out and animals were exposed daily to 10% ethanol or water free-choice procedure in the absence of water or food deprivation and without sweeteners in the ethanol solution.

The entire training period generally required 20–30 days. At the end of the training, a stable baseline intake was reached, defined as ±20% of intake for 3 consecutive days. All training and testing sessions consisted of 120-min daily sessions conducted between 9:00 a.m. and 12:00 p.m.

Ethanol solutions were prepared from 100% ethyl alcohol and diluted with tap water for concentrations of 5, 8 and 10% (w/v). SDZ 208-911 (*N*-[(8α)-2,6-dimethylergoline-8-yl]-2,2-diethylpropanamide, a generous gift of Sandoz, Basel, Switzerland) and terguride (a generous gift of Schering AG, Berlin, Germany) were dissolved in sterile saline solution with a drop of HCl 1 N and administered in a volume of 1 ml/kg. Based on previous behavioral effects, SDZ 208-911 was administered at the doses of 0; 0.025; 0.1; 0.4 and 1.6 mg/kg intraperitoneally (i.p.) and terguride was administered at the doses of 0; 0.025; 0.1; 0.2 and 0.4 mg/kg i.p. Following results of the acute treatment, the dose of 0.2 mg/kg was chosen for both drugs for the chronic treatment and intake during treatment was compared with baseline intake (mean of 3 days before treatment).

Prior to the first drug injection, rats were habituated to the injection procedure. For the acute treatment experiments, vehicle was administered as the first injection; thereafter the order of drug injection was counterbalanced using a Latin square design between all animals and all doses including vehicle. Each experiment was conducted with a separate group of rats serving as subjects ($n = 11$ for SDZ 208-911; $n = 15$ for

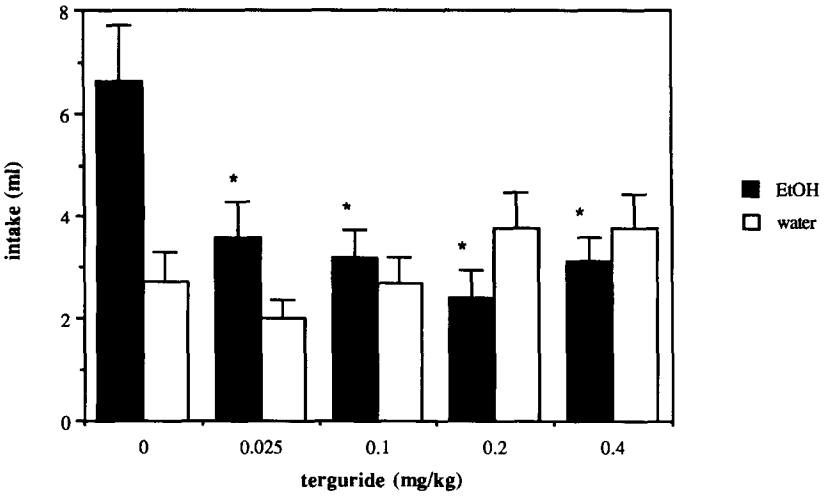

Fig. 2. Effects of acute treatment with terguride on ethanol intake (2-h). Values represent means ± S.E.M. of 15 animals. *$P < 0.01$ Newman-Keuls' test.

Table 2
Effects of chronic treatment with terguride (0.2 mg/kg) on ethanol and water intake

	Day of treatment									
Baseline	1	2	3	4	5	6	7	8	9	10
Ethanol										
4.30	2.81 [a]	1.73 [b]	2.65 [b]	2.07 [b]	2.01 [b]	1.91 [b]	1.14 [b]	2.03 [b]	1.44 [b]	1.00 [b]
±0.58	±0.51	±0.32	±0.56	±0.50	±0.57	±0.35	±0.38	±0.53	±0.56	±0.29
Water										
1.03	0.90	1.39	3.43	1.60	2.21	1.67	0.66	3.64 [a]	2.26	0.87
±0.23	±0.29	±0.48	±0.94	±0.40	±0.65	±0.56	±0.45	±0.68	±0.79	±0.26

Daily intale of ethanol and water (ml) expressed as means ± S.E.M.of six animals. [a] $P < 0.05$; [b] $P < 0.01$ Newman-Keuls' test vs. baseline.

terguride). For the chronic treatment experiments, each rat was treated with daily injections of either vehicle or one dose of the drug for 10 days. All injections were performed 15 min before the beginning of the 120-min session.

The intake of liquid was calculated using specifically designed precision bottles (Tecniplast, Buguggiate, Italy) after the 120-min daily sessions with the approximation of 100 μl. Ethanol and water intakes were analyzed using separate one-way analyses of variance (ANOVA) each with a within-subject factor for dose or day, as appropriate. Differences among individual means were subsequently determined by Newman-Keuls' post-hoc test.

3. Results

Fig. 1 shows the effects of acute pretreatment with SDZ 208-911 on ethanol and water intake. ANOVA revealed that SDZ 208-911 significantly reduced ethanol intake [$F(4,40) = 12.15$ $P < 0.0001$], but did not modify water intake [$F(4,40) < 1$ NS]. Newman-Keuls' post-hoc test showed that statistical significance was reached at the doses of 0.1; 0.4 and 1.6 mg/kg (Fig. 1).

Table 1 shows the effect of chronic treatment with the intermediate dose of 0.2 mg/kg of SDZ 208-911 for 10 days on ethanol and water intake. ANOVA revealed that SDZ 208-911 significantly reduced ethanol intake [$F(10,80) = 2.52$ $P < 0.05$] throughout the 10-day treatment period. Statistical significance compared with baseline intake was reached every day of treatment (Table 1). ANOVA also revealed that water intake was marginally affected by chronic treatment with SDZ 208-911 [$F(10,80) = 1.96$ $P = 0.049$], an effect due to the high daily variability of water intake together with a trend towards a compensatory increase in water intake observed on days 3 and 8 (Table 1).

Fig. 2 shows the effects of acute pretreatment with terguride on ethanol and water intake. ANOVA revealed that terguride significantly reduced ethanol intake [$F(4,56) = 6.03$ $P < 0.001$], but did not modify water intake [$F(4,56) = 1.05$ NS]. Newman-Keuls' post-hoc test showed that statistical significance was reached at all the doses (Fig. 2). Water intake in this experiment appeared consistently higher compared with water intake in the experiment shown in Fig. 1: this is due to the spontaneous high variability of water intake shown by non-fluid-deprived rats under the present experimental conditions.

Table 2 shows the effect of chronic treatment with the intermediate dose of 0.2 mg/kg of terguride for 10 days on ethanol and water intake. ANOVA revealed that terguride significantly reduced ethanol intake [$F(10,60) = 4.97$ $P < 0.001$] throughout the 10-day treatment period. Statistical significance compared with baseline intake was reached each day of the treatment (Table 2). ANOVA also revealed that water intake was affected by chronic treatment with terguride [$F(10,60) = 3.10$ $P = 0.01$], an effect due to the high daily variability of water intake together with a trend towards a compensatory increase in water intake observed on days 3, 5, 8 and 9: however, statistical significance as revealed by Newman-Keuls' post-hoc test, was reached on day 8 only (Table 2).

The average basal ethanol intake in the present experiments ranged from approximately 4.5 to 6.5 ml. Although blood alcohol levels were not measured in this study, blood alcohol levels of the same strain of rats (Wistar) following similar daily ethanol intake have been previously determined in our laboratory in other populations of rats (Rassnick et al., 1993). Based on these results ethanol intakes of 4.5–6.5 ml corresponding approximately to 0.7–0.9 g/kg produced blood ethanol concentrations of approximately 45–60 mg% which did not induce overt, gross intoxication.

4. Discussion

The results reported here show that acute and chronic administration of dopamine partial receptor agonists reduce ethanol intake in non-deprived rats. In a free-choice paradigm ethanol intake was significantly decreased by systemic administration of SDZ 208-911

and terguride, while water intake was unaffected or slightly increased, thus ruling out possible non-specific effects of these drugs on motor performance of consummatory behavior in general.

Ethanol is known to interact with several neurotransmitters within the CNS and many neuronal systems may mediate the different behavioral effects of alcohol including GABA, serotonin, catecholamines and opiates (for review, see Weiss and Koob, 1991). However, dopamine has been proposed as a key neurochemical mediator of specific CNS effects of ethanol on the basis of electrophysiological and biochemical evidence (Gessa et al., 1985; Di Chiara and Imperato, 1988; Brodie et al., 1990; Yoshimoto et al., 1991). In particular, the significance of these observations for the reinforcing effects of ethanol and for ethanol-seeking behavior has been emphasized by a number of behavioral observations. Voluntary ethanol consumption in the rat has been shown to selectively stimulate dopamine turnover in brain limbic regions (Fadda et al., 1989) and an increase in dopamine overflow in the nucleus accumbens as measured by in-vivo brain microdialysis has been reported (Weiss et al., 1993). Also, systemic administration of dopamine receptor antagonists (Samson et al., 1993) and local blockade of dopamine receptors within the nucleus accumbens reduced the reinforcing properties of ethanol in rats trained to orally self-administer ethanol (Rassnick et al., 1992).

Dopamine partial receptor agonists possess a unique pharmacological profile since their net effect appears to depend upon the level of existing synaptic activity such as the degree of receptor occupancy by the endogenous transmitter (Clark et al., 1985). Interestingly, both SDZ 208-911 (Pulvirenti et al., 1994) and terguride (Pulvirenti and Koob, unpublished results) have been shown to act as dopamine receptor antagonists in rats trained to self-administer cocaine intravenously. In these conditions, systemic administration of both partial receptor agonists reduced the reinforcing properties of cocaine in rats. The results of the present study is consistent with these observations and the reduction of ethanol intake induced by SDZ 208-911 and terguride closely resembles the reduction induced by drugs acting at the dopamine receptor site (Samson et al., 1993). Furthermore, the specificity of the effects of these drugs on ethanol but not water intake rules out possible non-specific effects including motor effects, malaise or general suppression of fluid intake.

One important property of partial receptor agonists is their effect as agonists in conditions of low receptor occupancy by the neurotransmitter. This is of importance for ethanol dependence since electrophysiological and biochemical evidence suggests that a rebound reduction of dopamine activity within mesolimbic areas may be associated with ethanol withdrawal (Diana et al., 1993; Smith et al., 1994). A heuristic hypothesis is therefore that dopamine partial receptor agonists may provide a means to reverse the functional dopamine hypoactivity observed during ethanol withdrawal, as suggested for psychostimulant withdrawal (Pulvirenti and Koob, 1994). The impulse-regulating activity of SDZ 208-911 and terguride which reduced the firing rates of dopamine neurons in naive animals, but reversed the inhibitory effect of dopamine receptor agonists (Ackerman et al., 1993, Piercey et al., 1987) may be relevant in this respect.

It should also be noted that a role for dopamine receptor agonists in operant responding for ethanol has been proposed. Systemic administration of both indirect (amphetamine) and direct (apomorphine) dopamine receptor agonists reduced oral ethanol self-administration in the rat (Pfeffer and Samson, 1985, 1988). Considering that SDZ 208-911 and terguride in rats consuming ethanol orally interact with a dopamine system which may be stimulated by the presence of ethanol, it is possible that the effect of these drugs may reflect their dopamine receptor antagonistic action. However, since one cannot directly determine the level of stimulation of the dopamine system in these animals the possibility that these compounds may be acting as dopamine receptor agonists cannot be ruled out. Similarly, SDZ 208-911 and terguride also showed adrenoceptor and serotonergic activity at high doses (Svensson et al., 1991): therefore the possibility that the reduction in ethanol intake induced by these compounds may be in part due to effects on neuronal systems other than dopamine cannot be excluded.

In conclusion, the unique pharmacological profile of dopamine partial receptor agonists further supports the hypothesis that these drugs may represent a novel potential therapeutic strategy for normalizing dopamine neurotransmission during the various phases of the natural history of drug dependence including alcoholism.

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