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Effects of Ethanol in a Putative Rodent Model of Tardive Dyskinesia

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STOESSL, A. J. *Effects of ethanol in a putative rodent model of tardive dyskinesia.* PHARMACOL BIOCHEM BEHAV **54**(3) 541–546, 1996.—The effects of acute challenge with ethanol were studied in a putative rodent model of tardive dyskinesia. Chronic administration of fluphenazine elicited vacuous chewing movements (VCMs) in the rat. Neuroleptic-induced VCMs were dose dependently suppressed by ethanol in a behaviorally specific fashion. Suppression by ethanol of neuroleptic-induced VCMs was reversed by pretreatment with the benzodiazepine inverse agonist Ro 15-4513 (2.5 mg/kg). These findings suggest that ethanol may acutely suppress neuroleptic-induced dyskinesias in humans via stimulation of $GABA_A$ receptors and are compatible with the previously reported clinical effects of alcohol consumption on the extrapyramidal system. Treatment strategies focussed on GABAergic stimulation deserve further investigation in the management of tardive dyskinesia.

Alcohol GABA Neuroleptics Tardive dyskinesia Vacuous chewing movements

TARDIVE dyskinesia (TD) is a disorder characterized by stereotypic involuntary movements that preferentially affect the orolingual musculature. TD is thought to affect approximately 20–30% of patients exposed to long-term neuroleptics (24), and treatment is frequently unsatisfactory. The pathogenesis of TD is poorly understood. The classical hypothesis is upregulation of D_2 dopamine receptors induced by chronic blockade (4) and the associated behavioral supersensitivity to dopamine agonists (56). In keeping with this hypothesis, TD may respond to increased doses of dopamine receptor antagonists or to dopamine depletion therapy (9,26). However, as reviewed by Fibiger and Lloyd (10), upregulation of dopamine receptors alone fails to account for a number of features of TD, including its restriction to a fraction of those individuals exposed to neuroleptics, its temporal course and (in some patients) irreversible nature, as well as the preferential involvement of orofacial musculature. Furthermore, neither positron emission tomographic (1) nor postmortem (28) studies have confirmed a relationship between D_2 dopamine receptor density and the development of TD. Fibiger and Lloyd (10) and others (14,15) have suggested that TD may reflect neuroleptic-induced suppression of GABA synthesis in the striatum and its efferent projections.

Neuroleptic therapy affects the expression of a number of neurotransmitters within the striatum and its outflow, including GABA (14), as well as many neuropeptides (8). We have used a putative rodent model of TD to explore the possible contribution of these changes to the development of TD. Rats chronically exposed to neuroleptics develop stereotyped vacuous chewing movements (VCMs) associated with tongue protrusion and jaw tremor (16,21,59). While some authors have suggested that neuroleptic-induced VCMs are more analogous to dystonia (46,47) or parkinsonian tremor (23,51), others have noted their utility as a model of TD, including late development, persistence (60) and suppression by acute challenge with dopamine receptor antagonists (52), or dopamine depletion (6).

We have previously demonstrated that systemically administered cholecystokinin octapeptide (CCK-8S) suppresses neuroleptic-induced VCMs in the rat (52,53). This observation correlates well with clinical studies that demonstrated efficacy of the CCK analog ceruletide in humans with TD (27) and other dyskinesias (19). In an effort to determine which CCK receptor subtype (A or B) mediated this effect, we undertook experiments in which we attempted to suppress the effects of systemically administered CCK by pretreatment with selective CCK-A (devazepide) or CCK-B (L-365,260) antagonists. However, the interpretation of our findings was hampered by an apparent effect of the vehicle for these agents. We used a vehicle of 10% (v/v) ethanol in 0.5% (w/v) carboxymethylcellulose, as described elsewhere (50). Although these authors found no effect of this vehicle in tests of anxiety, in our hands, it appeared to suppress neuroleptic-induced VCMs (independent of CCK administration). The experiments described here

were undertaken to confirm this effect and to determine its dependence upon an interaction of ethanol with the $GABA_A$-chloride ionophore complex.

A number of clinical observations also suggested that studies of ethanol in a model of TD might be of interest. Thus, chronic ethanol abuse is associated with a variety of movement disorders, including TD-like orofacial dyskinesias (5,39). Ethanol abuse may increase the risk of TD in neuroleptic-treated patients (7) and withdrawal from ethanol leads to dyskinesias (38).

METHOD

Animals

Male Sprague–Dawley rats (Charles River, Montreal) weighing 250 g at the start of the experiment were housed two per cage on a 12 L : 12 D cycle (lights on at 0700 h) and allowed standard rat chow and tap water ad lib. Rats were injected intramuscularly with fluphenazine decanoate (FLU, Squibb; 25 mg/kg) or an equivalent volume of vehicle (VEH; sesame oil, 1 ml/kg) every 3 weeks for 18–21 weeks. This duration and dose of treatment were chosen based on our previous work [e.g., (52)] and that of others (21,59). Allowing for pharmacokinetic differences between the human and the rat, this dose of FLU is comparable to that used in clinical practice. Although VCMs may emerge after a much shorter duration of neuroleptic treatment [(47,51); but see (16)], the responses to pharmacological challenges after such short-term treatment may be different and the analogy to TD is less secure (9a,58a).

Behavioral Observations

One to 3 weeks following the final injection of FLU or VEH, animals were allowed to habituate for at least 60 min to Plexiglas observation boxes (50 × 50 × 30 cm, with mirrors fixed to the rear walls). In the first set of studies, animals were then observed for 60 min immediately following administration of 1 ml/kg IP of 0, 2.5, 5, or 10% ethanol (v/v) IP. Each animal received all four doses of ethanol, with dose order varied according to a Latin square design and a minimum of 48 h between sessions. In the second set of studies, done in a different group of animals, observations were performed for 60 min immediately after the administration of 10% ethanol or 0.9% saline, following pretreatment (30 min) with the benzodiazepine inverse agonist Ro 15-4513 [(54); 1.25 mg/kg, 2.5 mg/kg IP; RBI, Natick, MA] or its vehicle (50% v/v methanol). Each animal received all four treatments (vehicle + vehicle; vehicle + ethanol; 1.25 mg/kg Ro 15-4513 + ethanol; 2.5 mg/kg Ro 15-4513 + ethanol) in randomized order, with a minimum of 48 h between sessions.

The frequency and duration of the following behavioral responses were recorded for 3 min out of each 6-min block for a total of 10 blocks (60 min), using a microcomputer with custom-designed software (BEBOP, Dr. M. T. Martin-Iverson, Univ. of Alberta): sniffing, locomotion (defined by visually dividing the test box into nine imaginary squares and recording forward movement from one square to another), rearing, grooming, and vacuous chewing movements (VCMs). VCMs were defined as all nondirected mouth movements and included tongue protrusions and jaw tremor, but excluded object-directed gnawing, yawning, and mouth movements associated with grooming.

Statistical Analysis

Data were analyzed separately for each behavioral response using a two-way (FLU × treatment) analysis of variance, followed by planned pair-wise comparisons where indicated by significant F-values.

RESULTS

Effects of Ethanol on Neuroleptic-Induced Behaviors

As previously described (21,52,53), fluphenazine induced a significant increase in VCMs. This was dose dependently suppressed to control levels by ethanol, $F(1, 27) = 7.89$, $p = 0.009$, FLU main effect, $F(3, 81) = 0.71$, ethanol dose main effect, $F(3, 81) = 3.36$, $p = 0.023$, FLU × dose interaction (Fig. 1). Locomotion, rearing, and grooming were unaffected by either fluphenazine or ethanol (Table 1). There was a small reduction of sniffing in the FLU-treated animals, but this was not significant following ethanol, $F(1, 27) = 4.14$, $p = 0.052$, FLU main effect; dose and FLU × dose interaction terms NS (Table 1).

Reversal by Ro 15-4513 of the Effects of Ethanol

As in the previous experiment, fluphenazine-induced VCMs were suppressed to control levels by 10% ethanol. This effect was reversed by both doses of Ro 15-4513, $F(1, 18) = 10.74$, $p = 0.004$, FLU effect; $F(3, 54) = 2.26$, $p = 0.092$, treatment effect; $F(3, 54) = 3.07$, $p = 0.035$, FLU × treatment interaction (Fig. 2). In these experiments, fluphenazine suppressed sniffing in the animals treated with ethanol alone, and this effect was also reversed by Ro 15-4513, $F(1, 18) = 5.53$, $p = 0.03$, FLU effect, $F(3, 54) = 4.65$, $p = 0.006$, treatment effect, FLU × treatment interaction, NS (Table 2). Locomotion, rearing, and grooming were unaffected by all treatments (Table 2).

DISCUSSION

Acute administration of ethanol dose dependently suppressed VCMs induced by chronic neuroleptic administration in the rat. The effects of ethanol and fluphenazine were behaviorally specific, as other motor responses were unaffected, apart from a small reduction in sniffing, consistent with

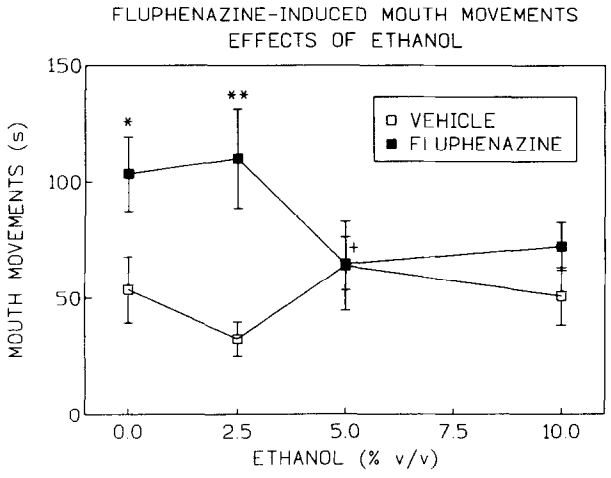

FIG. 1. Effects of ethanol on vacuous chewing movements in rats treated chronically with vehicle ($n = 15$) or fluphenazine ($n = 14$). Each bar is the means ± SEM duration of VCMs recorded over 10 blocks of 3 min immediately following administration of ethanol. $^*p < 0.05$, $^{**}p < 0.01$, fluphenazine vs. vehicle; $^+p < 0.05$, vs. 0% ethanol.

TABLE 1

EFFECTS OF ETHANOL AND FLUPHENAZINE ON MOTOR BEHAVIORS

	Ethanol (% v/v)			
	0	2.5	5	10
Locomotion				
Vehicle	21.4 (8.0)	21.0 (5.5)	10.4 (3.4)	12.3 (3.9)
Fluphenazine	5.6 (1.7)	19.3 (6.2)	10.9 (4.0)	19.7 (10.2)
Rearing				
Vehicle	22.9 (8.6)	31.5 (9.6)	15.7 (6.8)	19.4 (9.0)
Fluphenazine	3.4 (1.6)	17.3 (4.9)	25.0 (13.8)	11.8 (7.1)
Sniffing				
Vehicle	211.7 (37.3)	205.7 (34.2)	157.7 (35.0)	167.4 (24.5)
Fluphenazine	90.1 (15.5)*	173.5 (36.4)	128.0 (24.3)	131.1 (35.3)
Grooming				
Vehicle	77.1 (16.3)	98.4 (21.1)	66.0 (17.0)	74.3 (15.3)
Fluphenazine	90.6 (18.7)	66.5 (19.6)	61.2 (18.0)	53.2 (13.2)

Values are the means (±SEM) duration of behavior in seconds, scored over 10 blocks of 3-min duration.

*Significantly different, vehicle vs. fluphenazine.

blockade by FLU of striatal dopamine receptors. As discussed above, although controversy exists, chronic neuroleptic-induced VCMs are considered by many to be analogous to TD in humans [see (58a) for review]. Thus, our findings are compatible with a number of uncontrolled clinical observations. Alcohol intake can be associated with a number of movement disorders, including tremor and parkinsonism, as well as dyskinesias (5,39). Mullin et al. (38) described transient dyskinesias in chronic alcoholics, often associated with withdrawal, but a number of their patients had associated Wernicke's encephalopathy. Acute administration of ethanol was found to precipitate akathisia and dystonia in young patients on neuroleptics (33). Chronic ethanol abuse has been associated with TD-like orofacial dyskinesias (11,32) and with increased risk of TD in patients on neuroleptics (7). Halliday (17) recently reported an instructive case in which a chronic alcoholic woman on neuroleptics for bipolar affective disorder suffered precipitation of TD following withdrawal from alcohol. The dyskinesias were suppressed by resumption of ethanol and returned when she abstained. Conversely, ethanol is well known to suppress tremor, particularly essential tremor. In contrast, ethanol has relatively little effect on Parkinsonian tremor (27a), so one other possible interpretation of our findings [i.e., that neuroleptic-induced VCMs are analogous to parkinsonian tremor (23), which is suppressed by ethanol] is not strongly supported by clinical evidence.

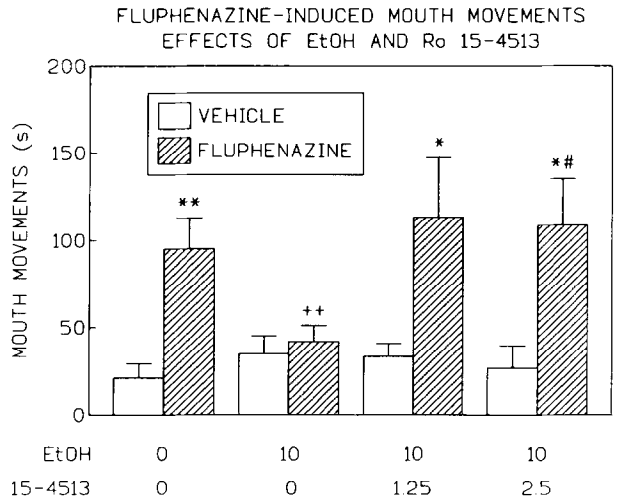

FIG. 2. Effects of Ro 15-4513 on suppression by ethanol of neuroleptic-induced VCMs. Each bar is the means ± SEM duration of VCMs recorded over 10 blocks of 3 min, immediately following administration of ethanol (10% v/v IP) or 0.9% saline, 30 min after Ro 15-4513 (1.25 or 2.5 mg/kg IP) or its vehicle (XXX). $n = 10$ per group. $*p < 0.05$, $**p < 0.01$, fluphenazine vs. vehicle; $^{++}p < 0.01$, 10% vs. 0% ethanol; $\#p < 0.05$, Ro 15-4513 2.5 mg/kg vs. 0 mg/kg.

The basis for these clinical observations as well as the findings described here is unclear. Ethanol interacts with a number of neurotransmitter systems, including dopamine and adenosine, calcium channels, and ligand-gated ion channels, such as the $GABA_A$-chloride ionophore, NMDA, and 5-HT_3 receptors (13,40). Chronic administration of ethanol enhances the behavioral responses to intraaccumbens or intrastriatal dopamine (31) or systemically administered apomorphine (30,31). Such treatment may induce a small (12%) increase in the concentration of striatal D_2 dopamine receptors (30). This increase in D_2 binding might conceivably contribute to the emergence of dyskinesias, but seems unlikely to account for the considerably more marked alteration in behavioral responses to dopamine agonists. More recently, Torres (58) found that acute ethanol suppressed cocaine-induced striatal c-*fos* immunoreactivity. This finding implies an effect on dopamine release or an interaction with D_1 dopamine receptor mechanisms (44), which are also known to be important for the induction of VCMs (45,52) and might conceivably explain the suppression of neuroleptic-induced VCMs reported here following acute ethanol.

A considerable body of evidence exists for an agonist-like effect of ethanol at the $GABA_A$-chloride ionophore (13,29, 40). This effect is site selective, with actions demonstrated in

TABLE 2

EFFECTS OF Ro 15-4513 AND ETHANOL ON MOTOR BEHAVIORS

	Treatment			
	Vehicle Vehicle	EtOH Vehicle	EtOH Ro 1.25	EtOH Ro 2.5
Locomotion				
Vehicle	2.5 (1.2)	15.2 (6.7)	14.0 (9.2)	22.1 (8.9)
Fluphenazine	9.4 (3.6)	7.2 (5.9)	16.0 (7.1)	14.9 (6.6)
Rearing				
Vehicle	1.9 (1.2)	23.1 (7.9)	26.6 (10.7)	26.3 (9.3)
Fluphenazine	9.2 (5.2)	6.1 (6.0)	5.7 (2.6)	11.8 (4.8)
Sniffing				
Vehicle	129.2 (27.9)	222.0 (50.7)	199.9 (33.1)	246.9 (51.6)
Fluphenazine	103.4 (23.2)	54.8 (8.2)*	131.0 (28.2)	195.5 (34.9)†
Grooming				
Vehicle	62.3 (18.1)	93.9 (29.7)	62.5 (23.5)	47.2 (20.4)
Fluphenazine	93.9 (20.7)	56.6 (28.4)	86.5 (15.8)	73.3 (15.9)

Values are the means (±SEM) duration of behavior in seconds, scored over 10 blocks of 3-min duration.

*Significantly different, vehicle vs. fluphenazine.

†Significantly different from EtOH/vehicle.

the substantia nigra pars reticulata (41), among other sites. In the studies described here, the benzodiazepine inverse agonist Ro 15-4513 completely reversed the effects of ethanol on neuroleptic-induced behaviors, at a dose that is devoid of behavioral effects when given alone (22,42). Ro 15-4513 antagonizes some, but not all of the behavioral effects of ethanol (2,18, 54), consistent with interactions between ethanol and multiple neurotransmitter receptors. The effect of Ro 15-4513 in the experiments described here suggests that suppression of neuroleptic-induced VCMs by acute ethanol is predominantly mediated by an interaction with the $GABA_A$ receptor. This conclusion is also consistent with the efficacy of rather low doses of ethanol used here, which preferentially act at $GABA_A$ sites (43), and with previous neurochemical (14,15,57) and behavioral (12,25,49) evidence pointing to a role for $GABA_A$ mechanisms in neuroleptic-induced VCMs and TD.

Chronic use of ethanol may lead to sensitization of the responses to dopamine (30,31), as well as desensitization of $GABA_A$ receptors (20,36,37,48), probably reflecting altered expression of receptor subunits (3,34,35). For these reasons and others, ethanol cannot be recommended for long-term management of TD. Indeed, the clinical observations noted above suggest that the effects of ethanol may be analogous to those of neuroleptics, in that acute challenge may suppress dyskinesias, whereas chronic use may elicit or exacerbate TD. Nevertheless, our findings do support previous suggestions that treatment strategies aimed at GABAergic mechanisms are worth pursuing [see (55) for review]. Our data furthermore emphasize the caution required in interpreting nervous system effects of drugs when even low doses of ethanol are used as a vehicle.

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