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# Attenuation of the Biphasic Effects of Ethanol on Avoidance Extinction by RO 15-4513 in Rats

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GALIZIO, M. *Attenuation of the biphasic effects of ethanol on avoidance extinction by RO 15-4513 in rats.* PHARMACOL BIOCHEM BEHAV **34**(3) 585–589, 1989.—Ethanol had biphasic effects on jump-up avoidance extinction with low doses (1 g/kg) increasing, and high doses (2.5 g/kg) decreasing number of trials to extinction criterion. In Experiment 1 these doses of ethanol were studied alone, and in combination with RO 15-4513 (0.3, 3 or 6 mg/kg). The stimulation of responding produced by low ethanol doses was reversed by 3 and 6 mg/kg doses of RO 15-4513 which had intrinsic suppressive effects, but the depressed responding produced by higher ethanol doses was not attenuated by RO 15-4513. Experiment 2 analysed the interaction between ethanol and benzodiazepine antagonists RO 15-1788 and CGS 8216. RO 15-1788 did not have intrinsic action and did not interact with ethanol. CGS 8216 showed an intrinsic suppressive action much like RO 15-4513, and also reversed the stimulation produced by low dose ethanol, but not the effects of the high dose. Experiment 3 showed that the benzodiazepine agonist, chlordiazepoxide, had effects much like low dose ethanol which were reversed by CGS 8216 and RO 15-4513. The major conclusions were that RO 15-4513 and CGS 8216 possess inverse agonist properties which may cancel out the effects of alcohol under certain circumstances.

Ethanol RO 15-4513 CGS 8216 RO 15-1788 Chlorpromazine Benzodiazepines Avoidance Extinction Rats

RECENT analyses of the mechanism of ethanol's action have emphasized the commonalities in the effects of barbiturates, benzodiazepines (BZ's), and ethanol and implicated the GABA-BZ receptor complex as a possible common mechanism of action for these effects (8, 12, 30). Support for such a notion has come from the finding by Suzdak *et al.* (26) that RO 15-4513, an imidazobenzodiazepine that acts as a partial inverse agonist of BZ receptors, reversed some effects of ethanol. Suzdak *et al.* (26) found that RO 15-4513 antagonized ethanol-induced chloride uptake into brain vesicles, and also reversed behavioral effects of ethanol, as measured by the Vogel conflict test and by rater's judgements of intoxication.

The Suzdak *et al.* report has already generated a number of follow-up studies and several issues have emerged with regard to the nature of the interaction between RO 15-4513 and ethanol. One major issue involves the question of just which effects of ethanol can be reversed by RO 15-4513. RO 15-4513 has been shown to reverse a number of behavioral effects of ethanol including loss of motor control and righting reflex (6, 17, 29), "disinhibited" performances on the staircase test and light/dark choice procedure (4), depression of positively reinforced operant behavior (27), and locomotor stimulation (23). In addition, RO 15-4513 can block the discriminative stimulus properties of ethanol (24) and reduces ethanol-reinforced lever pressing (25). However, some effects of ethanol apparently are not reversed or reduced by RO 15-4513, including ethanol's hypothermic effects (17,29) and the sedation and sleep induced by high doses (3 g/kg or more) of ethanol (16, 23, 27, 28).

A second major issue concerns whether the ethanol antagonist properties of RO 15-4513 are shared by other BZ antagonists and inverse agonists. Most studies have not been able to demonstrate reversal of ethanol effects by other BZ-receptor ligands. Several studies have failed to observe reversal of ethanol effects by the BZ antagonist, RO 15-1788 (1, 7, 19, 26, 28), although Chan *et al.* (10) recently found ethanol-stimulation of runway responding to be reversed by RO 15-1788. CGS 8216, a BZ antagonist with some inverse agonist properties, did not reverse behavioral effects of ethanol (14). Studies of full inverse agonists such as FG 7142, beta-CCM, and beta-CCE, have been mixed. Suzdak *et al.* (26–28) reported that FG 7142 and beta-CCE failed to reverse the effects of ethanol that were reversed by RO 15-4513. However, in some studies inverse agonists such as FG 7142 have reversed ethanol effects (9, 18, 20, 21, 23). One explanation for these findings is that the intrinsic behavioral effects of FG 7142 may have simply summated with the opposite behavioral effects of ethanol which had the effect of canceling out one another's actions. Indeed, FG 7142 has been shown to reverse ethanol effects primarily when those effects are opposite to its intrinsic action [(9, 21, 23); but see (20) for an exception].

Such findings raise another question involving RO 15-4513: to what extent can *its* effects be attributed to intrinsic behavioral effects opposing those of ethanol rather than specific antagonism? Several studies have found RO 15-4513 to reverse ethanol effects only when they were opposite in direction to intrinsic actions of RO 15-4513 (9, 21, 23). However, Suzdak *et al.* (27) showed that RO 15-4513 reversed effects of ethanol at doses that were low

enough to be without observable intrinsic action, and similar findings have been reported by Belzung *et al.* (4). Thus, one position is that RO 15-4513's interaction with ethanol involves a unique and specific activity that is independent of the drug's intrinsic behavioral actions (antagonism). The alternative model holds that the interaction involves behavioral effects which are opposite those of ethanol and, although presumably acting at a different site, cancel out one another (summation).

The present study sought to address the above issues by extending the analysis of RO 15-4513 and ethanol to a behavioral procedure involving negative reinforcement—the extinction of avoidance behavior. The effects of ethanol on avoidance extinction have been studied previously and have been shown to be biphasic: low doses of ethanol facilitate, and high doses depress, responding in extinction (2, 3, 15). This procedure was chosen because there have been no previous studies of RO 15-4513 on extinction of negatively reinforced behavior, and because the biphasic nature of ethanol effects with this procedure permits analysis of RO 15-4513 reversal of ethanol effects in both directions in a single study. This is significant because accounts of RO 15-4513's interaction with ethanol that stress summation predict that reversal should only be possible in the direction opposite the intrinsic action of RO 15-4513. The present study used two doses of ethanol, 1 and 2.5 g/kg, because 1 g/kg had previously been shown to reliably increase trials to extinction criterion and 2.5 was the lowest dose that reliably decreased responding (15). In one experiment, three different doses of RO 15-4513 were studied, 0.3, 3 and 6 mg/kg. The highest dose was one that often produces intrinsic action, while the lowest was chosen on the basis of Suzdak *et al.* (27) who found reversal of ethanol, but no intrinsic action at this dose of RO 15-4513. In a second study the interaction of the weak inverse agonist, CGS 8216, with ethanol was observed in order to compare its effects with those of RO 15-4513. In a final experiment the BZ agonist chlordiazepoxide (CDZ) was studied to compare its effects with those of ethanol and to determine whether these effects could be reversed by RO 15-4513 and CGS 8216.

## METHOD

### *Subjects*

Subjects were 250 male, Sprague-Dawley-derived, specific-pathogen-free rats. All were obtained from the Holtzman Co. (Madison, WI) and tested when they were between 80–120 days old. They were housed individually with ad lib food and water, and maintained on 12/12-hr light-dark cycle.

### *Apparatus*

An automated jump-up box (Lafayette Instrument Co.) was used. The box had Plexiglas sides and top, and a stainless steel grid floor through which scrambled constant current shock (0.5 mA) was delivered by a shock generator (Lafayette Instrument Co.). The front and back walls of the box were metal and the front wall contained a unit that could be retracted revealing a 12 × 20 × 20-cm ledge, 8 cm above the floor. White noise (80 dB) was presented through a wall speaker throughout the duration of the experiment. Timing and control of the retractable ledge was accomplished with electro-mechanical equipment.

### *Drugs*

Ethanol was mixed as a 10% weight/volume concentration in isotonic saline and administered in volumes sufficient to produce 1.0 or 2.5 g/kg doses. Isotonic saline was administered in volumes equivalent to the 1.0 g/kg group to control rats. RO 15-4513 and RO 15-1788 were donated by Hoffmann-La Roche Co., Basel, Switzerland, and CGS 8216 was a donation from Ciba-Geigy Co., Summit, NJ. Chlordiazepoxide hydrochloride was obtained from Sigma Co., St. Louis, MO. RO 15-4513, RO 15-1788 and CGS 8216 were suspended in isotonic saline and dispersed with ultrasound, with 1 drop of Tween 20 added to each ml of saline. Solutions were prepared such that injections of 1 ml/kg body weight provided the dose indicated. Tween vehicle was used as a control injection for these conditions.

### *Procedure*

The procedures were divided into three phases: acquisition, drug administration, and extinction. During acquisition and extinction phases, all rats were treated identically regardless of experiment or condition. Differential treatment involved the assignment of subjects to drug conditions which was randomly determined within each experiment.

*Acquisition.* Rats were initially placed on the grid floor facing the open ledge and 10 sec later the grid was electrified. Shock remained on until the animal jumped onto the ledge. The animal's weight on the ledge closed a microswitch which initiated a 15-sec intertrial interval. After the intertrial interval, the wall was inserted, which pushed the rat off the ledge back onto the grid floor. The wall was then immediately retracted once again exposing the ledge. If the animal jumped back onto the ledge within 10 sec, no shock was administered and an avoidance response was recorded on that trial. If no response occurred within 10 sec, shock was delivered until a response was made. These procedures were continued until the animal had made 10 consecutive avoidance responses at which time the rat was removed from the box, and received the appropriate drug injections.

*Drug administration.* Immediately after reaching the acquisition criterion, rats in Experiment 1 were exposed to an intraperitoneal injection of ethanol (1.0 g/kg, 2.5 g/kg, or saline control) followed 5 min later by a second IP injection of one of various doses of RO 15-4513 (0.3, 3.0, or 6 mg/kg or Tween vehicle). Ten min after the second injection rats were placed back in the box for the extinction phase (see below). Ten rats were studied in each of the 12 conditions of Experiment 1 forming a 3 × 4 factorial design.

Experiment 2 focused on RO 15-1788 and CGS 8216 alone and in combination with ethanol. As in Experiment 1 the first injection (1 or 2.5 g/kg ethanol or saline control) was administered immediately after the acquisition criterion was attained. Five min after the first, a second injection was given of CGS 8216 (5 mg/kg) or RO 15-1788 (10 mg/kg) or Tween vehicle. Ten min after the second injection the extinction phase was begun. Ten rats were studied in each of the 9 conditions of Experiment 2.

A third experiment involved CDZ effects and their reversal by CGS 8216 and RO 15-4513. Immediately after acquisition, rats were injected with CDZ (2.5 mg/kg) or saline, and this was followed with a second injection five min later of CGS 8216 (5 mg/kg) or RO 15-4513 (3 mg/kg), or Tween vehicle. The extinction phase began 10 min later, and 10 rats were studied in each of the 4 conditions of Experiment 3 (Tween + Saline; Tween + CDZ; CGS 8216 + CDZ; RO 15-4513 + CDZ).

*Extinction.* Extinction procedures were essentially the same as those in acquisition except that the shock was turned off. These procedures continued until a trial occurred where the animal failed to jump to the ledge for 3 min. The major dependent variable of the study was the number of trials required by animals in the various conditions to reach the 3-min extinction criterion. In order to avoid excessive variance due to declining drug levels, if a subject failed to meet the 3-min extinction criterion after 2 hr of

testing, the session was terminated and the number of responses made during the 2-hr period was recorded.

## RESULTS

The jump-up avoidance response was acquired rapidly by most animals. In Experiment 1, the mean number of trials to acquisition criterion was 16.1 (including the 10 consecutive avoidance responses) and the mean number of shocks received 2.7. The groups were treated identically during acquisition and there were no significant differences between groups on trials to reach the acquisition criterion or shocks received ($p>0.05$).

The major findings of Experiment 1 are presented in Fig. 1 which shows the mean number of trials to the extinction criterion. As the leftmost bars of Fig. 1 clearly show, there was a biphasic response to ethanol when it was injected in combination with Tween vehicle. The 1 g/kg dose produced a large increase in responding, while the 2.5 g/kg dose nearly eliminated responding. In contrast, consider the effects of the highest dose of RO 15-4513 (6.0 mg/kg, rightmost bars). There was a marked intrinsic action at this dose (white bar) which was accompanied by a reversal of ethanol-induced stimulation at the 1 g/kg dose (striped bar). However, the decrease induced by the 2.5 g/kg ethanol was not reversed by 6 mg/kg RO 15-4513 (black bar). The 3 mg/kg dose also decreased behavior as an intrinsic effect (white bar), and reversed the effects of the 1 g/kg ethanol dose (striped bar), and in addition, appeared to somewhat increase responding at the high ethanol dose, although there was considerable variability here (black bar). Finally, the 0.3 mg/kg dose was low enough to be without intrinsic depressive effects, but there was only a slight tendency to antagonize the effects of 1 g/kg ethanol, and no apparent effect at the 2.5 g/kg dose. Statistical analysis with a $3\times4$ factorial ANOVA revealed a significant interaction, $F(6,108)=5.47$, $p<0.01$. Simple main effects tested indicated a significant main effect of RO 15-4513 without ethanol, reflecting the intrinsic suppressive effects of the 3 and 6 mg/kg doses of RO 15-4513 ($p<0.01$). There was also a significant simple main effect at the 1 g/kg ethanol level ($p<0.01$) which supports the observation that the 3 and 6 mg/kg doses of RO 15-4513 reversed the effects of the 1 g/kg ethanol dose. Pairwise comparisons (Tukey HSD) confirmed these observations with the 3 and 6 mg/kg groups (which did not differ from one another) showing significantly ($p<0.05$) lower numbers of responses than the 0.3 mg/kg or 0 mg/kg groups (which did not differ from one another). However, simple main effects tests of RO 15-4513 at the 2.5 g/kg ethanol level were not significant ($p>0.05$), indicating that the trend toward reversal noted in the 3 mg/kg RO 15-4513-2.5 g/kg ethanol group was not reliable.

Figure 2 shows the extinction data for Experiments 2 and 3. The leftmost bars replicated the biphasic effects of ethanol observed in Experiment 1—increased trials to criterion at 1 g/kg and reduced responding at the 2.5 g/kg doses. The next set of bars shows the effects of CGS 8216, and reveals that CGS 8216 had an intrinsic depressive action when given without ethanol similar to that of RO 15-4513. The combination of CGS 8216 and 1 g/kg ethanol also resulted in a reversal of the ethanol effect, but CGS 8216 did not reverse the effects of the high ethanol dose. A $3\times2$ factorial ANOVA revealed a significant main effect for Ethanol, $F(2,54)=24.3$, $p<0.01$, and a significant main effect for CGS 8216, $F(1,54)=10.16$, $p<0.01$, but no significant interaction ($p>0.05$).

The next set of bars reveals that RO 15-1788 was without intrinsic action, and did not reverse ethanol effects at either dose level. A $3\times2$ factorial ANOVA revealed a significant main effect for ethanol, $F(2,54)=43.11$, $p<0.01$, but no main effect for RO 15-1788 and no significant interaction ($p>0.05$).

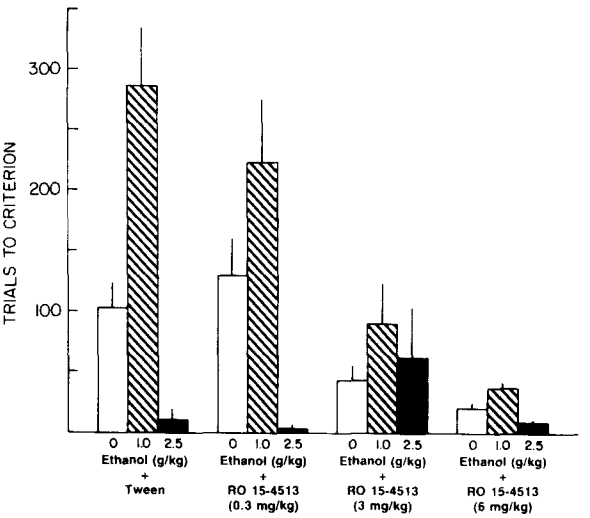


FIG. 1. Interaction between the various doses of RO 15-4513 (abscissa) and 0 (white bars), 1.0 (striped bars) and 2.5 (black bars) g/kg ethanol (Experiment 1). Mean trials to the extinction criterion are plotted on the ordinate and vertical lines represent SEM.

Finally, the last set of bars in Fig. 2 show the effects of CDZ in combination with Tween, CGS 8216, RO 15-4513, and a Tween-saline control group. CDZ increased the number of trials to criterion, much like the effects of 1 g/kg ethanol, and this effect was reversed by both RO 15-4513 and CGS 8216. One-way ANOVA confirmed the significance of these findings, $F(3,36)=5.52$, $p<0.01$, and post hoc tests (Tukey's HSD) revealed that the

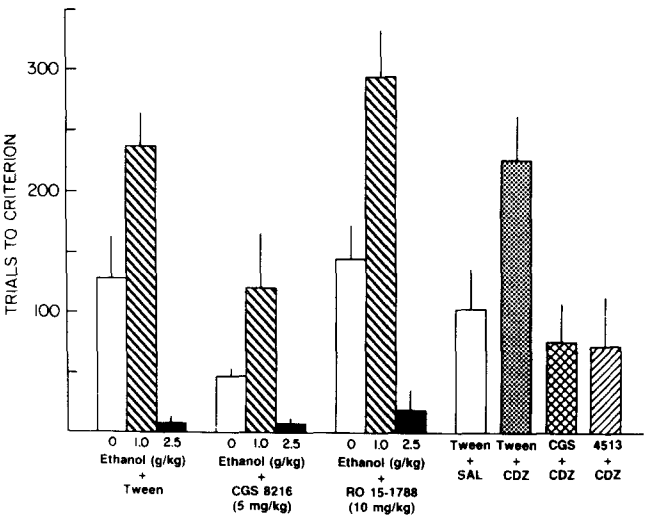


FIG. 2. Results of Experiments 2 and 3 are shown with mean trials to the extinction criterion plotted on the ordinate (vertical lines represent SEM). The leftmost bars show the effects of the ethanol doses in combination with Tween vehicle. The second group of bars show the results of ethanol in combination with CGS 8216, and the third group shows results of ethanol in combination with RO 15-1788. The rightmost bars show the results of Experiment 3 with the white bar presenting data after vehicle, stippled bar showing after chlordiazepoxide and vehicle, the cross-hatched bar shows the chlordiazepoxide-CGS 8216 combination and the striped bar the chlordiazepoxide-RO 15-4513 combination.

CDZ-Tween Group differed from the other three groups which did not differ from one another ($p<0.05$).

## DISCUSSION

Consistent with previous studies (2, 3, 15) ethanol produced a biphasic effect on avoidance extinction with low doses (1 g/kg) stimulating and high doses (2.5 g/kg) depressing number of trials to criterion. RO 15-4513 attenuated the effects of 1 g/kg ethanol, but only at doses that produced an intrinsic depressive action on extinction responding (3 and 6 mg/kg). The low dose of RO 15-4513 (0.3 mg/kg) did not affect responding, and also failed to significantly attenuate the effects of alcohol. These findings were thus consistent with the interpretation that reversal of ethanol effects by BZ inverse agonists is due to their intrinsic effects opposing those of ethanol (9, 21, 23). RO 15-1788, a BZ antagonist without inverse agonist properties, did not affect extinction when presented alone, and also did not reverse ethanol effects. Finally, CGS 8216 produced an intrinsic decrease in trials to avoidance extinction, and also consistent with a summation account, attenuated the stimulation of responding produced by 1 g/kg ethanol. A summation account of the interaction between RO 15-4513 and ethanol would generally predict that no reversal would be seen when the effects of ethanol are the same as the intrinsic actions of RO 15-4513. Thus, the failure of RO 15-4513 to significantly attenuate the suppressive effects of the 2.5 g/kg ethanol dose is consistent with the summation model.

The replication of biphasic effects of ethanol in Sprague-Dawley derived rats is of some interest in its own right, since rats of this strain do not show stimulation of general locomotor behavior by ethanol (13). Of further interest was the finding that CDZ (2.5 mg/kg) also stimulated responding during avoidance extinction. This outcome replicates an earlier study by Ziskind *et al.* (31) that showed biphasic effects of benzodiazepines on avoidance extinction. These findings appear somewhat contrary to theories emphasizing the role of fear or anxiety in avoidance. Such accounts would seem to predict that anxiolytic drugs like benzodiazepines or ethanol would decrease anxiety-motivated behavior, not stimulate it. However, as Mineka (22) has noted, many factors other than fear reduction may result in avoidance extinction. For example, a rat that still shows a strong conditioned fear reaction to the stimuli of the jump-up box may "freeze" on the grids and thus meet the extinction criterion (5). Anxiolytic drugs may elevate extinction responding by lowering fear levels and breaking up freezing or other fear-elicited behaviors that are incompatible with responding. Such an account would also help explain the intrinsic actions of CGS 8216 and RO 15-4513 on avoidance extinction. Both of these drugs are said to be partial inverse agonists and are thus thought to produce effects opposite those of benzodiazepines. For example, in certain procedures both CGS 8216 and RO 15-4513 have been claimed to produce anxiogenic effects (11, 21, 23). Perhaps in the context of avoidance extinction these effects were manifest as enhanced freezing or other behavior incompatible with responding. Thus, the intrinsic suppression of avoidance responding produced by RO 15-4513 and CGS 8216 might reflect their anxiogenic properties. Whatever the basis for the intrinsic actions of these drugs seen in the present study, it does seem valid to describe them as inverse agonist effects, since they were opposite in form to the effects of BZ agonist, CDZ.

In conclusion, both RO 15-4513 and CGS 8216 (but not RO 15-1788) were capable of attenuating the enhancement of responding induced by low doses of ethanol, but only at doses that decreased responding when administered alone. These interactions are best explained by a summation account which posits a suppressive action of the inverse agonist subtracting from the response-enhancing effect of ethanol. Although more specific mechanisms of antagonism may be required for reversal of some ethanol effects by RO 15-4513, no such mechanisms need to be posited to explain the interaction between BZ antagonists and the effects of ethanol on avoidance extinction.

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