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Ethanol Suppression of Schedule-Controlled Responding: Interactions With Ro 15-4513, Ro 15-1788 and CGS 8216

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WOUDENBERG, F. AND J. L. SLANGEN. *Ethanol suppression of schedule-controlled responding: Interactions with Ro 15-4513, Ro 15-1788 and CGS 8216.* PHARMACOL BIOCHEM BEHAV **31**(2) 375–380, 1988.—Rats (N=14) were trained to respond under a five seconds differential reinforcement of low rate (DRL 5″) schedule and under a fixed ratio 10 (FR10) schedule of reinforcement. Ro 15-1788 did not influence the number of responses in the DRL 5″ schedule, but increased responding in the FR10 schedule. Ethanol (ETOH, 1250 mg/kg) and CGS 8216 (5 mg/kg) suppressed responding in both schedules and these effects were not antagonized by Ro 15-1788. The response suppressing effects of ETOH in both schedules were not influenced by CGS 8216. These results indicate that the response suppressing effects of ETOH and CGS 8216 are not mediated by the BDZ receptor. Ro 15-4513 suppressed responding strongly in the FR10 schedule. The response suppressing effects of Ro 15-4513 were additive with the response suppressing effects of ETOH. In rats (N=11) trained to respond under a variable interval 40 seconds-fixed ratio 10 (VI 40″-FR10) schedule Ro 15-4513 dose-dependently suppressed responding. These results indicate that Ro 15-4513 has sedative effects and is not able to antagonize all the behavioral actions of ETOH.

Schedule-controlled behavior Ethanol Ethanol antagonist Ro 15-4513 Benzodiazepine antagonist Ro 15-1788 CGS 8216 Rat

DEPENDING on dose and time after administration, ethanol (ETOH) can have anxiolytic, stimulating and depressing effects (22,26). Among the depressing effects of ETOH are discoordination (in rat measured as an impairment of performance in the horizontal wire test and in the rotorod test) and sedation (in rat measured as reduced motility and as a decreased response rate in schedule-controlled behavior). The impairment of rotorod performance induced by 1600 mg/kg of ETOH is not antagonized by 20 mg/kg of CGS 8216 (3). Sedative effects of 2000 mg/kg of ETOH are not antagonized by 10 mg/kg of Ro 15-1788 (26).

The selective benzodiazepine (BDZ) antagonist Ro 15-1788 was originally thought to be devoid of intrinsic activity (17), but was subsequently found to have various effects (6, 11, 12, 20). With respect to schedule-controlled behavior, response rate increasing as well as response rate decreasing effects of Ro 15-1788 have been reported (1, 2, 8–10, 23, 27, 28). Response increasing effects have been reported over a dose range of 0.01 mg/kg (28) to 30 mg/kg (23). Response decreasing effects have been reported over a dose range of 0.1 mg/kg (23) to 80 mg/kg (10). In general, response increasing effects tend to be associated with lower doses and response decreasing effects with higher doses of Ro 15-1788. Unexpectedly it was found in a pilot experiment that 10 mg/kg of Ro 15-1788 antagonized the response depressing effect of 1500 mg/kg of ETOH in a food reinforced fixed ratio 10 (FR10) schedule of 45 minutes duration (unpublished observations). Since there was also an indication of a response stimulating effect of Ro 15-1788 on FR10 responding, the antagonizing effect of Ro 15-1788 on ETOH-induced suppression could be ascribed to the response enhancing effect of Ro 15-1788. In order to further investigate effects of Ro 15-1788 on response suppression caused by ETOH, the present experiment compares the effects of Ro 15-1788 with effects of CGS 8216 and Ro 15-4513.

CGS 8216 is a mixed BDZ antagonist/inverse agonist that has been found to decrease response rate in various schedule- and in different species (23–25, 27). The response rate depressing effects of CGS 8216 are neither antagonized by Ro 15-1788 (23,25) nor by BDZs (23). Because CGS 8216 has a response decreasing effect itself, the reduction of ETOH-induced response suppression by CGS 8216 could not be explained by a response enhancing effect of CGS 8216 and would therefore suggest a pharmacological antagonism.

In contrast to Ro-1788 and CGS 8216 the newly discovered imidazobenzodiazepine Ro 15-4513 (14) antagonizes

intoxication and impairment in the rotorod test induced by 2000 mg/kg of ETOH (16,26) as well as impairment in the horizontal wire test and reduction in motility induced by 3000 mg/kg of ETOH (5,21). Ro 15-4513 also antagonizes the anticonflict activity of 1000 mg/kg of ETOH (26). The ETOH antagonizing effects of Ro 15-4513 are blocked after administration of Ro 15-1788 and CGS 8216 (16,26). Effects of Ro 15-4513 on schedule-controlled responding have not yet been reported.

Because FR10 schedules of reinforcement usually generate high rates of responding, the stimulating effect of a drug could be obscured by a ceiling effect. Therefore, animals were also tested in a five seconds differential reinforcement of low rate schedule (DRL 5″) of 10 minutes duration.

Under the FR10 and DRL 5″ schedule only one dose of each drug was tested. In order to broaden the information on the effect of Ro 15-4513 on schedule-controlled responding, a range of doses was tested in animals trained to respond under a variable interval 40 seconds-fixed ratio 10 (VI 40″-FR10) schedule of 15 minutes duration.

METHOD

Animals

Twenty-five male rats of an outbred Wistar strain (CPB:WU, CPB-TNO, Zeist, The Netherlands) weighing approximately 250 g at the beginning of the experiment were individually housed under a nonreversed 12 hr light-dark cycle and a room temperature of 20–22°C. Tap water was freely available. Rats were maintained at approximately 85% of their free-feeding weight by giving a diet of 13 g laboratory food 1 hr after each daily session. Food was freely available from Friday afternoon until Sunday morning.

Apparatus

Eight ventilated rat chambers, equipped with two retractable levers, were used. A pellet dispenser delivered 45 mg pellets (Noyes) in a tray placed between the levers. A Digital Equipment Corporation PDP-8 and PDP-11 microcomputer and software (SKED) supplied by State Systems Incorporated (Kalamazoo, MI) was used to control schedule contingencies and to record and analyse data.

Procedure

Fourteen rats were trained to press the left lever under a differential reinforcement of low rate (DRL) 5″ schedule of 10 minutes duration. In this schedule a lever press 5 seconds or longer after the previous one produced a food pellet. Lever presses before 5 seconds had elapsed resulted in resetting of the clock. Drug conditions under this schedule were: Control, ETOH, Ro 15-1788, CGS 8216, Ro 15-1788 + ETOH and CGS 8216 + ETOH. After testing in the DRL 5″ schedule was completed, the rats were retrained to press the lever under a fixed ratio 10 (FR10) schedule of 45 minutes duration. In this schedule every tenth response produces a food pellet. Under this schedule two series of tests were run. Tests with ETOH, Ro 15-1788 and CGS 8216 (control, ETOH, Ro 15-1788, CGS 8216, Ro 15-1788 + ETOH, CGS 8216 + ETOH, Ro 15-1788 + CGS 8216 and Ro 15-1788 + CGS 8216 + ETOH) were performed first. After these tests were completed, tests including Ro 15-4513 (Ro 15-4513, Ro 15-4513 + ETOH, Ro 15-1788 + Ro 15-4513 + ETOH and CGS 8216 + Ro 15-4513 + ETOH) were done. During all sessions in both schedules the left lever was present in the chamber and the central houselight was illuminated. Sessions were conducted Monday through Friday. After response rates had stabilized testing was begun. For half the animals the drug test day was Wednesday, for the other half Friday. On other days animals were injected with physiological saline 15 minutes prior to the session. For all drugs one dose was administered. The dose of ETOH (1250 mg/kg) was chosen to obtain a reliable, but not complete response depression. The dose of CGS 8216 (5 mg/kg) was chosen to obtain a level of response suppression less than that of ETOH and at the same time antagonism of ETOH-induced sedation. The dose of Ro 15-1788 (10 mg/kg) was chosen because in pilot experiments this dose antagonized the response suppression caused by 1500 mg/kg of ETOH. Higher doses of Ro 15-1788 were less effective in antagonizing ETOH-induced response suppression. The dose of Ro 15-4513 (5 mg/kg) was chosen on the basis of the literature, showing this dose to be able to antagonize a 1250 mg/kg ETOH discoordination and to be sensitive to the antagonizing effect of 10 mg/kg Ro 15-1788. As control substance the Ro 15-1788, Ro 15-4513 and CGS 8216 vehicle (distilled water to which Tween 80 (2 drops/10 ml) was added) was chosen. The order of the drug conditions was counterbalanced. The tests with Ro 15-4513 in the FR10 schedule were conducted separately after it was shown that baseline responding had not changed. In this part of the experiment the order of the drug conditions was also counterbalanced. After the tests with Ro 15-4513 were completed, eleven different animals were trained to respond under a tandem variable interval 40 seconds-fixed ratio 10 (VI 40″-FR10) schedule. Under this schedule the following doses of Ro 15-4513 were tested: 0.625, 1.25, 2.5, 5 and 10 mg/kg. The order of the doses was counterbalanced. As a control substance the Ro 15-4513 vehicle (see above) was taken. Sessions were conducted Monday through Friday. Testing was begun

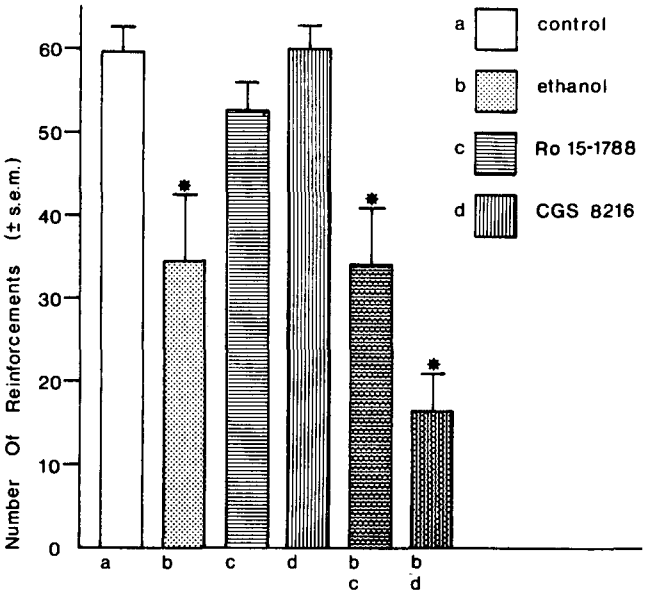

FIG. 1. Effects of Tween-vehicle, ethanol (1250 mg/kg), Ro 15-1788 (10 mg/kg), CGS 8216 (5 mg/kg) and the effects of ethanol after pretreatment with Ro 15-1788 or CGS 8216 on the number of reinforcements under the DRL 5″ schedule of food presentation. Asterisks indicate the significance of differences from control ($^*p<0.05$).

after response rates had stabilized. Animals were tested on Wednesday and Friday. On other days animals were injected with physiological saline 15 minutes prior to the session.

Drugs

Ro 15-1788 (Hoffmann-La Roche, Basle, Switzerland), Ro 15-4513 (Hoffmann-LaRoche, Basle, Switzerland) and CGS 8216 (Ciba-Geigy, Basle, Switzerland) were suspended in vehicle [distilled water to which Tween 80 (2 drops/10 ml) was added]. Ro 15-4513 and CGS 8216 were suspended ultrasonically. Ethyl alcohol (ETOH, 99.8%, Merck, Darmstadt, BRD) was diluted with saline to a concentration of 12% (w/v) and doses were adjusted by changing the volumes administered. Ro 15-1788, Ro 15-4513 and CGS 8216 were administered in an injection volume of 2 ml/kg. Ro 15-1788 was given 30 min, CGS 8216 20 min, Ro 15-4513 18 min and ETOH and vehicle 15 min prior to testing. All drugs were administered intraperitoneally.

Data Analysis

In the DRL 5″ schedule three response classes were measured: total number of responses with an interresponse-time greater than or equal to 5 seconds (=total number of reinforcements), total number of responses with an interresponse-time between 1 and 5 seconds and total number of responses with an interresponse-time smaller than or equal to 1 second (=burst-responding). Each response class was analyzed separately, with the different conditions constituting one within factor, by means of multivariate ANOVA. If the overall effect was significant, paired comparisons with univariate F-tests were performed to determine differences between conditions.

In the FR10 schedule total number of responses was measured and effects of three within factors ETOH, Ro 15-1788, CGS 8216 were analyzed in a 2×2×2 ANOVA design. The effects of Ro 15-4513 were separately analyzed, using multivariate ANOVA with the conditions including Ro 15-4513 + Control consituting one within factor, followed by paired comparisons with univariate F-tests to determine differences between conditions.

In the VI 40″-FR10 schedule total number of responses was measured and the effect of the different doses of Ro 15-4513 were analyzed by means of multivariate ANOVA with the doses of Ro 15-4513 + Control constituting one within factor. One-factor ANOVA with repeated measures, followed by the Newman-Keuls test was performed to make paired comparisons.

For all effects a significance level of 5% was chosen.

RESULTS

In the DRL 5″ schedule the percentage of responses resulting in reinforcement ranged from 21% to 73% for the 14 animals, with a mean of 51%.

For the total number of reinforcements a significant overall effect, $F(5,9)=4.0$, $p<0.05$, was found (Fig. 1). ETOH decreased, $F(1,13)=9.1$, $p<0.05$, the total number of reinforcements, while CGS 8216 and Ro 15-1788 were without effect. The effect of ETOH was not blocked by Ro 15-1788, shown by a nonsignificant difference between the ETOH and the Ro 15-1788/ETOH condition, nor by CGS 8216, shown by the nonsignificant difference between the ETOH and CGS 8216/ETOH condition.

Similar results were obtained for the number of responses between 1 and 5 seconds. There was a significant overall effect, $F(5,9)=26.6$, $p<0.05$. ETOH, $F(1,13)=30.4$, $p<0.05$, decreased the number of responses. Ro 15-1788 was without effect. Neither Ro 15-1788 (the difference between the ETOH and the Ro 15-1788/ETOH condition was nonsignificant) nor CGS 8216 (the difference between the ETOH and the CGS 8216/ETOH condition was nonsignificant) influenced the effect of ETOH. In contrast to the results for the total number of reinforcements, CGS 8216 decreased response rate, $F(1,13)=9.9$, $p<0.05$.

No significant treatment effect for the number of burst responses was found.

In the FR10 schedule ETOH, $F(1,13)=70.4$, $p<0.05$, and CGS 8216, $F(1,13)=80.7$, $p<0.05$, significantly depressed responding (Fig. 2). Ro 15-1788 showed no effect. A post hoc comparison showed that the observed difference between the Ro 15-1788 and the vehicle condition was significant, $F(1,13)=4.9$, $p<0.05$. Of the primary interactions only the ETOH × CGS 8216 interaction was significant, $F(1,13)=8.9$, $p<0.05$. Subsequent paired comparisons showed that the difference between the ETOH and the CGS 8216/ETOH condition was not significant, while the difference between the CGS 8216 and the CGS 8216/ETOH condition did show significance, $F(1,13)=10.8$, $p<0.05$. The ETOH × Ro 15-1788 × CGS 8216 interaction was not significant.

For the conditions including Ro 15-4513 a significant overall effect, $F(4,10)=40.0$, $p<0.05$, was obtained (Fig. 2). Ro 15-4513 decreased the number of responses as compared to vehicle, $F(1,13)=142.7$, $p<0.05$. The value for the Ro 15-4513/ETOH condition was smaller than the value for the Ro 15-4513 condition, $F(1,13)=10.7$, $p<0.05$. CGS 8216 further depressed responding, as shown by the small number of responses in the CGS 8216/Ro 15-4513/ETOH condition (21.1 ± 15.2), being smaller than the value for the Ro 15-4513/ETOH condition, $F(1,13)=8.1$, $p<0.05$.

A significant overall effect of Ro 15-4513, $F(5,6)=11.2$, $p<0.05$, was obtained in the VI 40″-FR10 schedule (Fig. 3). Response rates orderly declined with higher doses. Ro 15-1788 in doses of 15, 30 and 60 mg/kg was not able to antagonize the response suppressing effect of 5 mg/kg of Ro 15-4513.

DISCUSSION

The response decreasing effects of ETOH in the DRL 5″ and the FR10 schedule were not anatagonized by prior administration of Ro 15-1788. Although the DRL 5″ schedule generated low rates of responding in all animals, no response increasing effect of Ro 15-1788 was observed. Ro 15-1788 had a small response stimulating effect in the FR10 schedule. These results are consistent with previous findings, in which response increasing effects of Ro 15-1788 are not observed or tend to be small (23). The stimulating effect of Ro 15-1788 was completely overshadowed by the response depressing effects of ETOH and therefore the results were not in line with the findings in our pilot experiments, in which a response increasing effect of Ro 15-1788 compensated for the ETOH-induced depression. It must be concluded that Ro 15-1788 at the dose of 10 mg/kg has, if any, minimal response increasing effects and cannot antagonize the response suppression caused by ETOH.

The response depressing effects of ETOH on the number of reinforced responses and the number of responses with an interresponse-time between 1 and 5 seconds in the DRL 5″ were neither antagonized nor potentiated by CGS 8216. CGS 8216 had no effect on the number of reinforced responses,

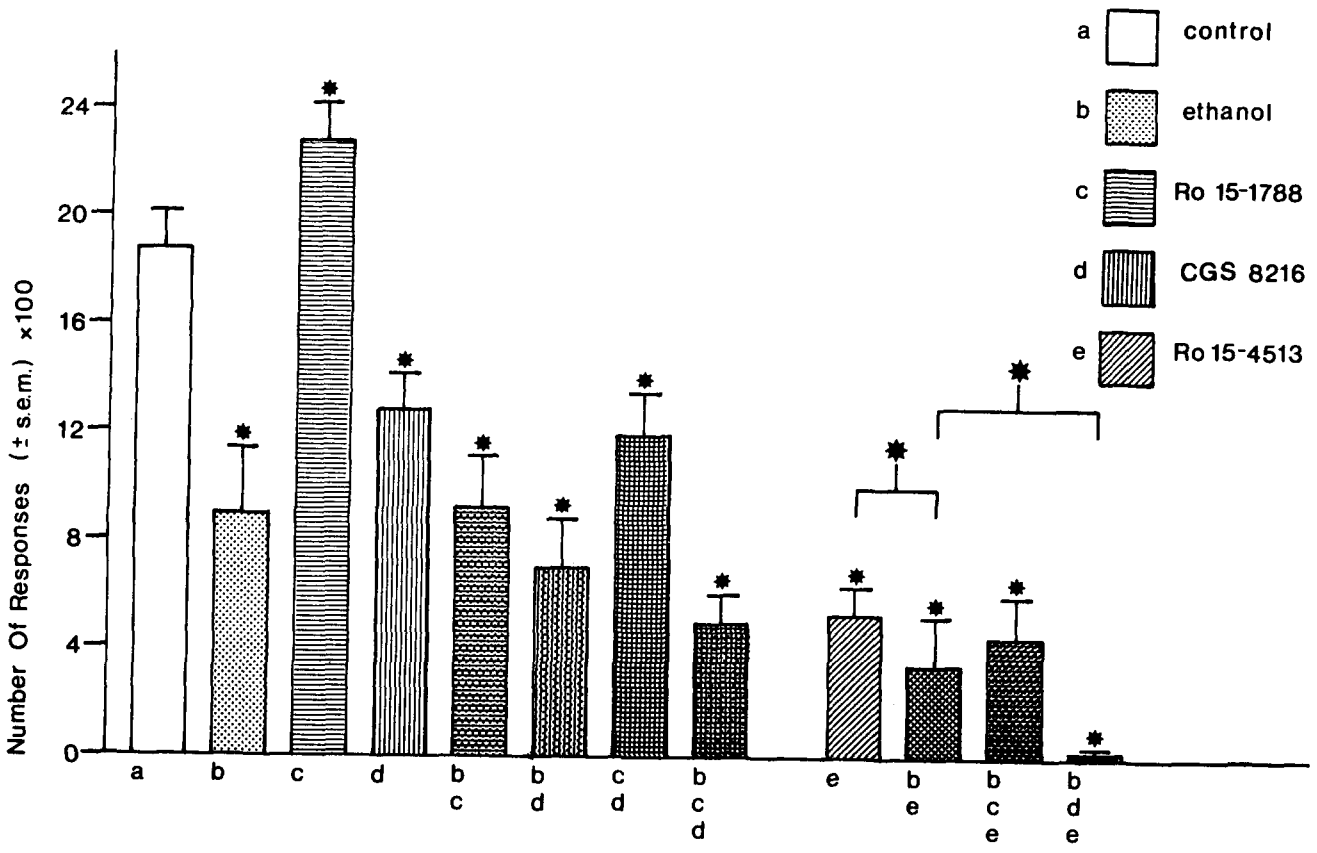

FIG. 2. Effects of Tween-vehicle, ethanol (1250 mg/kg), Ro 15-1788 (10 mg/kg), CGS 8216 (5 mg/kg), Ro 15-4513 (5 mg/kg), the effects of ethanol after pretreatment with Ro 15-1788, CGS 8216, Ro 15-4513, Ro 15-1788 + CGS 8216, Ro 15-1788 + Ro 15-4513, CGS 8216 + Ro 15-4513 and the effects of CGS 8216 after pretreatment with Ro 15-1788 on the number of responses under the FR10 schedule of food presentation. Asterisks indicate the significance of differences from control or differences between marked pairs (*$p<0.05$).

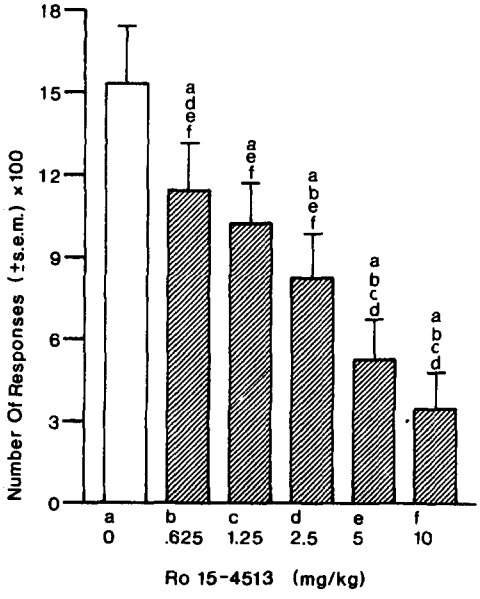

FIG. 3. Effects of different doses of Ro 15-4513 on the number of responses under the VI 40"-FR10 schedule of food presentation. Literals indicate 5% significance of difference (a=different from control, b=different from 0.625 mg/kg, c=different from 1.25 mg/kg, d=different from 2.5 mg/kg, e=different from 5 mg/kg, f=different from 10 mg/kg).

but a small response decreasing effect on the number of responses with an interresponse-time between 1 and 5 seconds. The lack of influence of CGS 8216 on the number of reinforced responses in the present experiment was also found in a study of Nakamura and Carney (19). In that study CGS 8216 in doses up to 10 mg/kg did not influence both reinforced and nonreinforced responses, while higher doses decreased both to an equal extent. In the FR10 schedule CGS 8216 decreased response rate substantially, but it did not block or potentiate ETOH-induced response suppression. The significant ETOH × CGS 8216 interaction in any case does not suggest that CGS 8216 antagonizes ETOH-induced response suppression. For this to be true the interaction would have to be in the opposite direction, including a higher value for the CGS 8216/ETOH condition as compared to the ETOH condition. Together with the failure of Ro 15-1788 to antagonize ETOH-induced response suppression, this leads to the conclusion that the response decreasing effects of ETOH are not modulated by BDZ antagonists.

The finding that CGS 8216 only slightly decreased nonreinforced response rate and did not decrease the number of responses with an interresponse-time between 1 and 5 seconds in the DRL 5" schedule, while it decreased responding substantially in the FR10 schedule, suggests that the response decreasing effects of CGS 8216 may be schedule and rate dependent.

Ro 15-1788 failed to antagonize the response depressing effect of CGS 8216 in the FR10 schedule. This is consistent

with other reports (25) and adds support to the suggestion that the response depressing effects of CGS 8216 are not mediated by the BDZ receptor and are therefore not a part of the partial agonistic profile of CGS 8216 at the BDZ receptor (7,25). Lack of antagonism by Ro 15-1788 of effects of CGS 8216 has furthermore only been reported for the anxiogenic activity of CGS 8216 in the social interaction test (13).

Completely contrary to expectation, 5 mg/kg of Ro 15-4513 did not antagonize the response suppression caused by ETOH. Furthermore, Ro 15-4513 itself had a strong response suppressing effect. It cannot be excluded that doses of Ro 15-4513 without intrinsic effects are able to antagonize the response suppression induced by 1500 mg/kg of ETOH. This is unlikely however. In the rat ETOH antagonizing effects of Ro 15-4513 below 2.5 mg/kg have not been reported. In the present experiment a response suppressing effect of Ro 15-4513 was observed at a dose as small as 0.625 mg/kg. Therefore the results in the present experiment suggest that ETOH-induced suppression of schedule-controlled responding cannot be antagonized by doses of Ro 15-4513 that are not response suppressing themselves. Lack of antagonism by Ro 15-4513 has previously only been found for the hypothermia caused by 1500 mg/kg of ETOH (16), the lethal effects of ETOH (15) and the stimulation of locomotor activity by a dose of ETOH of 1000 mg/kg (18). With respect to the intrinsic behavioral activity of Ro 15-4513, a pentylenetetrazol proconvulsive effect (4) and an exploration decreasing effect (18) have been established. These effects can all be ascribed to the inverse agonistic action of Ro 15-4513 at the BDZ receptor. The failure to antagonize the effect of 5 mg/kg of Ro 15-4513 by doses of Ro 15-1788 up to 60 mg/kg in the present experiment suggests that the strong response suppression caused by Ro 15-4513 is not mediated by the BDZ receptor. Substantiation of this suggestion awaits further investigation.

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