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The Effects of Ro 15-4513 on Ethanol-Induced Taste Aversions

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JEFFREYS, R. D., S. POURNAGHASH, J. R. GLOWA AND A. L. RILEY. *The effects of Ro 15-4513 on ethanol-induced taste aversions*. PHARMACOL BIOCHEM BEHAV **35**(4) 803–806, 1990.—Ro 15-4513 is an imidazobenzodiazepine that has been reported to block a range of behavioral effects of ethanol. In the present experiments, the effects of Ro 15-4513 were assessed on the acquisition of an ethanol-induced conditioned taste aversion. Specifically, rats were given a novel saccharin solution to drink followed by an injection of one of a range of doses of Ro 15-4513 (0.5 and 1.0 mg/kg, Experiment 1A, and 2.0 and 3.0 mg/kg, Experiment 1B) and an injection of ethanol (1.75 g/kg). Ro 15-4513 failed to block the acquisition of the ethanol-induced taste aversion. Possible reasons for this failure were discussed.

Ro 15-4513 Ethanol Conditioned taste aversions

THE imidazobenzodiazepine Ro 15-4513, a benzodiazepine receptor photoaffinity label with a high affinity for central benzodiazepine receptors (33,45), has been reported to be effective in blocking GABA-mediated effects through its actions at the GABA-benzodiazepine receptor complex (30, 31, 46). Ro 15-4513 has also been reported to block some of the effects of ethanol. For example, Ro 15-4513 blocks ethanol's stimulatory effect on GABA-mediated Cl^- flux in synaptoneurosomal preparations (46). In addition, Ro 15-4513 reverses the ethanol-induced depressant effects on motor neurons and Renshaw cells (6). Ro 15-4513 has also been reported to reverse ethanol-induced suppression of exploratory activity on the holeboard test (25,26), ethanol-induced deficits in motor performance (4–6, 17, 22), ethanol-induced soporific (22, 34, 47), ataxic (46), anticonvulsive (20, 34, 36) and anticonflict effects (19,46), ethanol-produced discriminative stimulus properties (39), ethanol-induced increases in reaction time (19) and ethanol-induced lethality (8).

The present study further examined the interaction of ethanol with Ro 15-4513, specifically within the conditioned taste aversion (CTA) procedure (18, 37, 40–42). In the CTA design (41), an animal is given a novel solution to drink, e.g., saccharin, and is then injected with a toxin, e.g., LiCl (9). On a subsequent exposure to the taste, thirsty rats will avoid consuming the solution presumably because of a learned association between the taste and the effects of the toxin. Under such a procedure, ethanol has been shown to induce dose-dependent taste aversions (1, 3, 7, 21, 23, 24, 29).

The CTA procedure can also be used to study the pharmacology of an agent used as the toxic stimulus. For example, Romano and King (43) demonstrated that neuroanticholinergic compounds such as atropine and benactyzine blocked aversions induced by the anticholinesterases, physostigmine and pyridostigmine. Further, Van Der Kooy and Phillips (48) demonstrated that aversions to morphine could be blocked by the opiate antagonist naloxone. Similarly, Grupp (11) demonstrated that aversions to amphetamine were blocked by the dopaminergic antagonist, pimozide. Accordingly, it would be expected that ethanol-induced aversions would be weakened (or possibly blocked) by the administration of Ro 15-4513. The present study assessed this possibility. Specifically, animals were given saccharin to drink followed by one of a range of doses of Ro 15-4513 (0.5 and 1.0 mg/kg, Experiment 1A, and 2.0 and 3.0 mg/kg, Experiment 1B) and ethanol (1.75 g/kg).

EXPERIMENT 1A

METHOD

Subjects

The subjects were 60 experimentally naive female rats of Long-Evans descent, approximately 120 days of age at the beginning of the experiment. The rats were maintained on a 12:12 L:D cycle (lights on 0800 hr) and were given ad lib access to Purina Rat Chow throughout the experiment.

Apparatus

Subjects were individually housed in stainless-steel, wire-mesh

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cages. In the front of each cage were openings into which graduated 50 ml Nalgene tubes were placed for the presentation of tap water or 0.1% w/v saccharin (sodium saccharin, Fisher Purified).

Drugs

Ro 15-4513 (Hoffmann-La Roche) was prepared as an emulsion in a vehicle of 4% Tween-80 in distilled water. Ethanol was administered as a 20% (v/v) solution, prepared by diluting 95% ethanol with distilled water.

Procedure

Initially, all rats were deprived of water for 24 hours. On the next day, all rats were given 20-min access to water. This procedure was repeated for 14 consecutive days at which point all rats were approaching and drinking from the tube within two sec of its presentation. On Day 15, all subjects were given 20-min access to a novel saccharin solution. On this day, subjects were divided into six groups matched for saccharin consumption ($n = 6$ per group) and 15 min following saccharin access were given two consecutive intraperitoneal injections, separated by no more than 15 sec. Groups V/E, R0.5/E and R1.0/E were injected with 4% Tween-80 (the Ro 15-4513 vehicle), 0.5 mg/kg and 1.0 mg/kg of Ro 15-4513, respectively, followed by an injection of 1.75 g/kg of ethanol. Subjects in Groups V/V, R0.5/V and R1.0/V were injected with vehicle, 0.5 mg/kg and 1.0 mg/kg of Ro 15-4513, respectively, followed by an injection of distilled water (the ethanol vehicle). On the three days following conditioning, all subjects were given 20-min access to water. This alternating procedure of conditioning/water recovery was continued until subjects received four complete cycles. On the day following the last water-recovery session, all rats were given 20-min access to saccharin in a final aversion test.

EXPERIMENT 1B

METHOD

Subjects and Apparatus

The subjects were 24 rats of the same age, sex and strain and maintained under the same conditions as in Experiment 1A.

Procedure

The procedure was the same as in Experiment 1A with the following exceptions. On conditioning trials, Groups R2.0/E and R3.0/E were injected with 2.0 mg/kg and 3.0 mg/kg of Ro 15-4513, respectively, followed by an injection of 1.75 g/kg ethanol. Groups R2.0/V ($n = 5$) and R3.0/V were injected with 2.0 mg/kg and 3.0 mg/kg of Ro 15-4513, respectively, followed by an injection of distilled water.

RESULTS

All determinations of statistical significance are based on Wilcoxon signed rank tests and Kruskal-Wallis one-way analysis of variance with significance set at $p<0.05$.

EXPERIMENT 1A

Figure 1 presents the percent shift in saccharin consumption from baseline for all groups over repeated conditioning trials and on the final aversion test. On the first exposure to saccharin, there were no significant differences among groups ($H = 6.590$), with

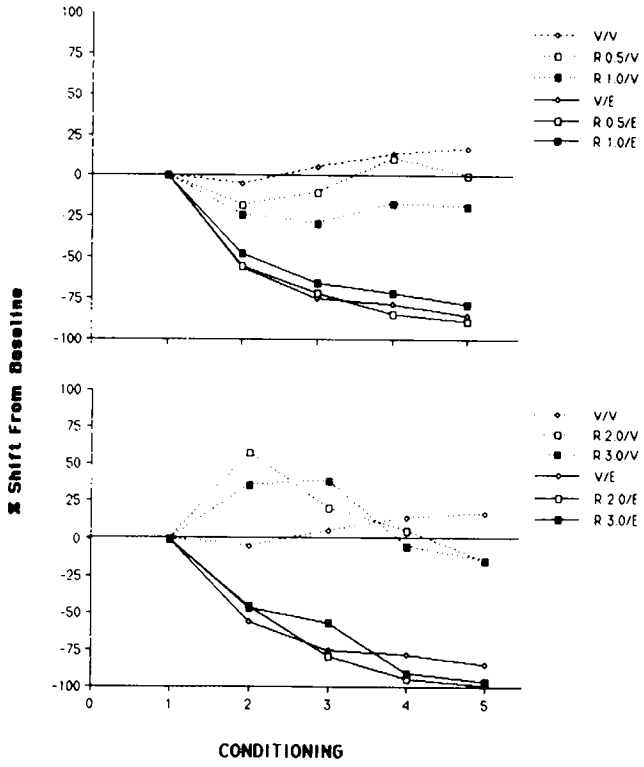

FIG. 1. The percent shift in saccharin consumption from baseline for Groups V/V, V/E, R0.5/V, R1.0/V, R0.5/E and R1.0/E (upper panel) and Groups R2.0/V, R3.0/V, R2.0/E and R3.0/E (bottom panel). Data for subjects in Groups V/V and V/E are also included on the bottom panel for comparison.

subjects in all groups drinking a mean of approximately 11 to 12 ml. On the next exposure to saccharin (the first exposure following conditioning), subjects in Groups V/V and R1.0/V displayed no significant changes in saccharin consumption relative to consumption on the initial conditioning trial (both T's ≥ 3.00). Subjects in the remaining groups displayed significant decreases in saccharin consumption on this exposure (all T's ≤ 1.00). On the first aversion test, there was a significant difference in the percent shift in saccharin consumption among groups ($H = 18.095$). Subjects in Groups V/V, R0.5/V and R1.0/V differed from subjects in Groups V/E, R0.5/E and R1.0/E. No other comparisons were significant (see Fig. 1, top panel).

Over repeated conditioning trials, subjects in Group V/V increased saccharin consumption slightly, consuming on the final aversion test 16% above the amount consumed on the initial conditioning trial. Subjects in Group R0.5/V displayed no systematic changes in saccharin consumption, while subjects in Group R1.0/V decreased significantly below their initial conditioning level (all T's ≤ 2.00). On the final conditioning trial, subjects in Groups R0.5/V and R1.0/V drank 3% and 19% below the amount consumed on the initial conditioning trial, respectively. Subjects in Groups V/E, R0.5/E and R1.0/E continued to decrease saccharin consumption, drinking 84%, 88% and 78% below the initial trial. On the final aversion test, there was a significant difference in the percent shift in saccharin consumption among groups ($H = 28.256$). Subjects in Group V/V differed from subjects in Groups V/E, R1.0/V, R0.5/E and R1.0/E. There were also significant differences in the percent shift between subjects in Group R0.5/V and R1.0/V and subjects in Groups V/E, R0.5/E and R1.0/E. No other comparisons were significant.

EXPERIMENT 1B

On the first exposure to saccharin, there were no significant differences among groups ($H = 0.025$), with all groups drinking approximately 8 to 9 ml. On the next exposure to saccharin (the first exposure following conditioning), subjects in Group R2.0/V displayed no significant changes in consumption ($T = 1.00$), while subjects in Group R3.0/V displayed a significant increase relative to consumption on the initial conditioning trial ($T = 1.00$). Subjects in Groups R2.0/E and R3.0/E displayed significant decreases in saccharin consumption on this exposure (both T's ≤ 1.00; see Fig. 1, bottom panel). On this first aversion test, there was a significant difference in the percent shift in saccharin consumption among groups ($H = 13.188$). Subjects in Groups R2.0/V and R3.0/V differed from subjects in Groups R2.0/E and R3.0/E. No other comparisons were significant.

Over repeated conditioning trials, subjects in Groups R2.0/V and R3.0/V decreased saccharin consumption and by the final conditioning trial were drinking 4% and 10% below the amount consumed on the initial conditioning trial, respectively. Neither of these percent shifts was significant (both T's ≥ 4.50). Subjects in Groups R2.0/E and R3.0/E continued to decrease saccharin consumption, drinking on the final aversion test, 99% and 97% below the initial trial, respectively. On the final aversion test, there was a significant difference in the percent shift in saccharin consumption among groups ($H = 17.751$). Groups R2.0/V and R3.0/V differed from subjects in Groups R2.0/E and R3.0/E. No other comparisons were significant.

GENERAL DISCUSSION

At doses ranging from 0.5 to 3.0 mg/kg, Ro 15-4513 failed to block ethanol-induced taste aversions (1.75 g/kg). The basis for this failure is unknown, although several possibilities exist.

This failure to antagonize ethanol-induced taste aversions may be related to the temporal parameters of Ro 15-4513. That is, although the temporal parameters used in Experiments 1A and 1B were similar to other studies reporting the blocking of ethanol's effects by Ro 15-4513 (36,46), it is possible that the effects of Ro 15-4513 did not completely overlap the toxic effects of ethanol that induce an aversion. Even though Ro 15-4513 may have overlapped and blocked some of these effects of ethanol, the remaining toxicity may still have been sufficient for an aversion to be acquired. Although possible, the fact that ethanol produces graded, dose-dependent aversions [see (1, 3, 7, 21, 23, 26, 29)] suggests that if some of the toxic effect of ethanol had been blocked by Ro 15-4513, aversions, though still evident, would have been weakened. It is also possible that the dose of ethanol was too high to be antagonized by Ro 15-4513. Others, however, have reported that Ro 15-4513 (at doses similar to those used in the present experiments) completely antagonized the effects of ethanol at doses as high as 2.0 g/kg (36,46). Thus, the failure to block ethanol-induced taste aversions by Ro 15-4513 is not likely due to the specific temporal or dosage parameters utilized in the present study.

It is possible that the reported blocking of ethanol by Ro 15-4513 depends upon an interaction of the intrinsic effects of the two compounds. That is, instead of being due to a receptor interaction the effects of ethanol and Ro 15-4513 in combination may reflect an interaction of the behavioral and physiological effects of the compounds. Lister and Nutt (28) have offered this explanation for the blocking by Ro 15-4513 of ethanol's effects on seizure thresholds. Following the demonstration that ethanol increased seizure threshold, Lister and Nutt reported that Ro 15-4513 reversed the effect. They also noted, however, that Ro 15-4513 alone produced a proconvulsant effect, indicating that the blocking of ethanol's effect on seizure threshold by Ro 15-4513 may be due to an interaction of their intrinsic effects. Similarly, Belzung, Misslin and Vogel (2) reported that in a light/dark choice procedure and in a staircase test, Ro 15-4513 completely blocked the disinhibitory effects of ethanol. When Ro 15-4513 was given alone, however, it was found to have anxiogenic properties, again indicating that the blocking of ethanol by Ro 15-4513 might be due to a functional opposition of their behavioral effects.

Response additivity, thus, may be necessary to evidence blocking. In this context, the absence in the present studies of any intrinsic effects of Ro 15-4513 opposite in direction to those of ethanol is consistent with the failure of Ro 15-4513 to block the acquisition of ethanol-induced taste aversions. (The significant increase in percent saccharin consumption by subjects in Group R3.0/V on the second conditioning trial was likely due to the relatively low levels of consumption by this group on the first conditioning trial prior to the Ro 15-4513 injection.) Although the present data [and those of others; see (2, 27, 28, 49)] are consistent with a response additivity interpretation, it should be noted that there are reported instances of blocking of ethanol by Ro 15-4513 in the absence of any intrinsic effects of Ro 15-4513 [see (10, 32, 44)]. Thus, the absence of an interaction of any intrinsic effects of Ro 15-4513 and ethanol in the present studies remains only a possible account of the failure of blocking within the aversion design.

Ro 15-4513 generally blocks the effects of ethanol (see introduction). The present data, thus, appear inconsistent with what is typically reported. Although blocking is the general finding when the two drugs are combined, recently a number of instances of the failure of Ro 15-4513 to block ethanol's effects have been reported [see (12–16, 32, 35, 38, 47)]. The present data on the failure of Ro 15-4513 to block the toxic effects of ethanol [as indexed by the conditioned taste aversion procedure; see (41)] extend the range of ethanol's effects that are resistant to such blocking. The basis for the failure remains unknown.

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