Pharmacology Biochemistry & Behavior, Vol 27, pp 517–519 © Pergamon Journals Ltd , 1987 Printed in the U S A 0091-3057/87 $3 00 + 00

RAPID COMMUNICATION

Oral Ethanol Reinforcement in the Rat: Effect of the Partial Inverse Benzodiazepine Agonist RO15-4513[1]

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Received 13 March 1987

SAMSON, H H , G A TOLLIVER, A O PFEFFER, K G SADEGHI AND F G MILLS *Oral ethanol reinforcement in the rat Effects of the partial inverse benzodiazepine agonist RO15-4513* PHARMACOL BIOCHEM BEHAV 27(3) 517–519, 1987 —The partial inverse benzodiazepine agonist RO15-4513 has been found to reverse the sedating and anti-conflict effects of acute ethanol administration In non-food or fluid-deprived rats, orally self-administering 10% ethanol in an operant situation, RO15-4513 resulted in a dose-dependent suppression on ethanol intake Doses of 0 3, 1 0 and 3 0 mg/kg suppressed responding from approximately 25% to 60% respectively A dose of 0 1 mg/kg had no significant effect upon responding These findings were discussed in terms of the potential independence of brain mechanisms related to ethanol reinforcement and sedation

Ethanol RO15-4513 Self-administration Rats

THE imidazobenzodiazepine RO15-4513, a partial inverse benzodiazepine agonist, has been shown to reverse some of the effects of higher doses of ethanol [1, 2, 8, 15] However, its actions on ethanol oral self-administration have not been examined In the last several years, we have developed a methodology for maintaining oral ethanol self-administration in the rat without using food or fluid restriction [12] We report here the results of an initial study to determine the dose-effect curve of RO15-4513 on oral ethanol self-administration in the non-food or fluid-deprived rat

METHOD

Animals

Three adult male rats (Long Evans) obtained from the University of Washington's Department of Psychology breeding colony were used for this study The animals weighed 349 g, 243 g and 229 g at the start of the experiment They were housed in individual stainless steel hanging rodent cages Artificial illumination was on from 08 00 to 20 00 daily

Apparatus

Daily sessions were conducted in operant chambers which have been previously described [10] The chambers contained a single lever and a dipper fluid dispenser which when activated presented 0 1 ml of fluid (Gebrand Corp , model GS-RH) All experimental control was with Apple microcomputers The computer was set to control session length, schedule requirements, and reinforcement delivery Time of each response and reinforcement delivery were recorded by the computer for later analysis

Drugs

RO15-4513 was suspended in 2 to 3 drops of Tween 80 and diluted with sterile water to a given concentration All solutions were made immediately prior to injection and were shaken on a mechanical shaker for 30 seconds prior to each injection Doses of 0 1, 0 3, 1 0 and 3 0 mg/kg were tested

Procedure

The animals were initiated to self-administer ethanol

[1]This research was supported in part by a grant to H H S from the National Institute on Alcohol Abuse and Alcoholism (AA 06845) and by the Alcoholism and Drug Abuse Institute of the University of Washington The RO15-4513 was most graciously supplied by Drs Da Prada and Eigenmann, Hoffmann-La Roche Co , Basel, Switzerland

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using the sucrose-fading procedure previously reported [11] Following this initiation, the animals were given one week of baseline self-administration with 10% ethanol on a fixed ratio 4 reinforcement schedule prior to the start of the drug testing procedure Each animal received a single 30-minute session in the operant chamber each day, with sessions conducted Monday through Friday At no time during the experiment were the animals either food or fluid restricted

After the baseline procedure, the animals were then tested each week using the following injection procedure On Mondays, Tuesdays and Fridays, the animals received no treatment prior to their 30-minute session of ethanol self-administration On Wednesdays, the animals were given an injection of vehicle, while on Thursdays they received drug All injections were given intraperitoneally, 15 minutes prior to the session Each dose was tested twice, in a descending order of drug concentration

The number of responses, reinforcers, and cumulative records of responding in time were used to analyse the effects of drug administration on ethanol intake

RESULTS

At the end of the experiment the animals weighed 580 g, 554 g and 549 g respectively During baseline, their average ethanol intakes were 0 63 g/kg, 0 67 g/kg and 0 45 g/kg These intakes are comparable to our previous findings using this initiation procedure [11,12] A dose-related suppression of ethanol responding was found with RO15-4513 (Fig 1) A two-way analysis of variance with repeated measures was significant for both drug dosage, $F(3,16)=9\ 0282$, $p<0\ 01$, and for drug vs vehicle administration, $F(1,16)=22\ 7314$, $p<0\ 01$ Using Bonferonni t-tests [3] for each dose compared to vehicle control, significant reductions in responding were found for all doses except 0 1 mg/kg

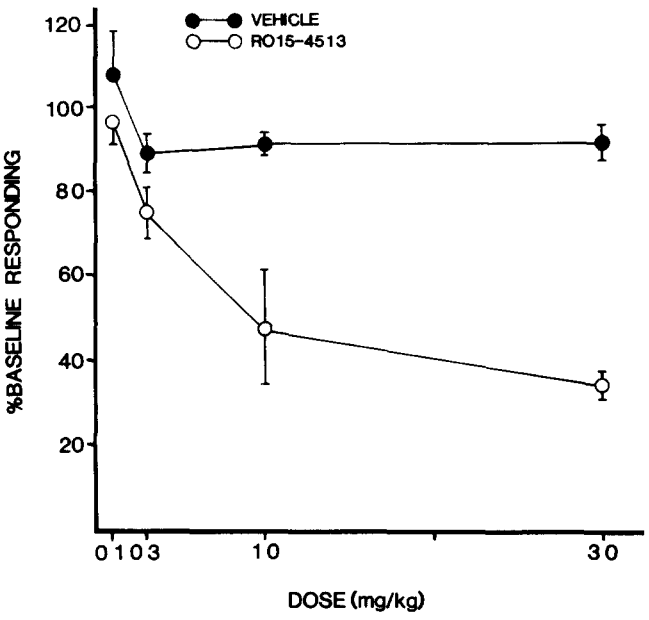

FIG 1 Effects of vehicle and RO15-4513 on responding reinforced with 10% ethanol (Error bars are Standard Error of the Means)

DISCUSSION

Since RO15-4513 reverses the sedating and anti-conflict effects of ethanol [2, 8, 15], it could be hypothesized that the drug might produce increased drinking However, at doses equal to and below those reported to reverse sedating and anti-conflict actions, a significant reduction in ethanol self-administration was observed

There are several possible explanations for this result First and perhaps most plausible, is that the brain mechanisms which are involved with ethanol self-administration (i e , reinforcement) are not directly related to the processes which result in sedation during ethanol intoxication In order to observe sedation effects higher doses of ethanol are required, and there are data which indicate that these higher ethanol doses are not reinforcing [9,14] Thus, while the sedation effects of higher ethanol doses may be antagonized by RO15-4513, the drug's action on reinforcement mechanisms in the CNS could at the same time act to decrease ethanol's function as a reinforcer

The reduction in ethanol self-administration, particularly the change in the pattern of responding seen under RO15-4513, suggests that its effects are very similar to the dopamine agonists we have previously studied [5–7] With both dopamine agonists and RO15-4513, a dose-related increase in pausing between reinforcements and a reduction in response rate accounts for the decrease in the number of reinforcements received per session If the dopamine and GABA system, as outlined by Scheel-Kruger [13], function in a complex reciprocal fashion, then the effects found with a dopamine agonist should be similar to those produced by an inverse benzodiazepine agonist This result was found However, before this hypothesis can be substantiated, several additional controls are required and other inverse agonists must be tested

Another possible explanation for the reduction in ethanol-maintained behavior is that RO15-4513 produced pro-convulsive motor effects which interfered with responding Examination of the cumulative response patterns suggests that this did not occur, as the animals responded at the same rate in each set of four responses to obtain a reinforcement, but, as stated above, increased the pausing between sets of responding

It is known that some of the inverse benzodiazepine agonists are anxiogenic One hypothesis concerning alcohol consumption suggests that it functions to reduce anxiety In this study, no evidence could be found for any increase in ethanol self-administration at any dose tested While we have made no assessment of the anxiogenic potential of the doses tested, the doses of 1 mg/kg and 3 mg/kg would possibly have anxiogenic activity [4] However, both doses suppressed intake Only further understanding of both the anxiogenic potential of these doses and the capability of this self-administration procedure to show anxiety-induced drinking can determine if increased alcohol intake might result from administration of inverse benzodiazepine partial agonists

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