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Opiate Delta-2-Receptor Antagonist Naltriben Does Not Alter Discriminative Stimulus Effects of Ethanol

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MHATRE, M. C., K. CARL, K. M. GARRETT AND F. A. HOLLOWAY. *Opiate delta-2-receptor antagonist naltriben does not alter discriminative stimulus effects of ethanol.* PHARMACOL BIOCHEM BEHAV **66**(4) 701–706, 2000.— The ability of a selective 2-opiate receptor antagonist, naltriben, to modulate ethanol discrimination was investigated in a rat model using a drug discrimination procedure. Rats were trained to discriminate ethanol (1.25 g/kg, IP) from saline on a fixed-ratio schedule, FR10. Once rats had acquired the ethanol-saline discrimination, ethanol dose–response tests were conducted with 15-min pretest injections. Following the characterization of the ethanol dose-response curve, the effect of naltriben on ethanol's discriminative stimulus was assessed by administering naltriben (0.032–5.6 mg/kg, IP) 15 min before the ethanol administration. In the present study, naltriben did not have any modulatory effect on ethanol discrimination, suggesting that either Δ_2-opiate receptors are not involved in the formation of ethanol's discriminative stimulus or the antagonism of Δ_2-opiate receptors is not sufficient to alter ethanol's compound discriminative stimulus. © 2000 Elsevier Science Inc.

Ethanol 2-Opiate receptors Drug discrimination Opiate antagonists

THE mechanisms through which ethanol exerts its discriminative effects are not well defined. Various behavioral studies have suggested that the anxiolytic, sedative, ataxic, and myorelaxant effects of ethanol, all play a critical role in the formation of ethanol's discriminative stimulus. Ethanol is suggested to function as a mixed or a compound discriminative stimulus, with various component stimuli that are mediated at least partially through the $GABA_A$/benzodiazepine receptor complex (11,38,41), *N*-methyl-D-aspartate (NMDA) receptors (10,17,19,40), L-type Ca^{2+} channels (8), as well as serotonin receptors (18,45). These studies have also shown that rats, which are trained to discriminate ethanol from water or saline, generalize asymmetrically to positive modulators of the $GABA_A$–benzodiazepine receptor complex [e.g., pentobarbital, chlordiazepoxide (11) or neurosteroids (3,16,20)], gamma-hydroxy-butyrate (9), NMDA receptor antagonists such as dizocilpine (MK-801) (10,40,41), and to some serotonin agonists such as trifluoromethylphenylpiperazine ($5\text{-}HT_{1B/2C}$) (18) and serotonin uptake inhibitors such as fluoxetin (29). At the same time, neither $GABA_A$–benzodiazepine receptor antagonists (3) nor NMDA receptor agonists (4) have been able to completely antagonize ethanol's discriminative stimulus, which suggests that ethanol's discriminative effects are not exclusively mediated by the sites or components targeted by these compounds. In fact, very few drugs have been able to even partially modulate the discriminative stimulus of ethanol, supporting the concept of ethanol cue being a compound stimulus composed of multiple components (38).

Besides GABAergic, NMDA, and serotonin neurotransmitter receptor systems, results from animal and human studies have indicated major involvement of the endogenous opiate system in ethanol's behavioral effects (2,12–15,21–23,25–27,33). Nonselective opioid antagonists, naloxone, and naltrexone have been shown to reduce the intake of alcohol in laboratory animals and humans (2,21,31–34,39,49). This suggests a possibility

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that opioid receptors may be involved in some of ethanol's behavioral effects that contribute to excessive ethanol drinking behavior. Consistent with this hypothesis, naltrexone has been reported to decrease positive reinforcing effects of alcohol in nonalcoholic drinkers (47). However, another study found that naltrexone pretreatment does not alter ethanol's subjective effects in social drinkers (12). Thus, the data from these clinical studies regarding any involvement of opiate receptors in ethanol's behavioral effects is not entirely conclusive.

Naloxone and naltrexone are nonselective opiate antagonists, known to bind differentially to all three major opioid receptor types, mu, delta and kappa, depending on the dose administered (5–7,28,35). In animal studies, naloxone is most effective in reducing alcohol consumption when given at a dose of 1–12 mg/kg, a range at which it occupies both μ and δ-opiate receptors (13). Results from various studies have suggested that alcohol-induced activation of the endogenous enkephalinergic system and occupation of δ-opiate receptors may be partly involved in ethanol's behavioral effects that may contribute to excessive alcohol drinking behavior (13,14,25–27). Naltriben, a δ_2-opiate antagonist and a benzofuran analogue of naltrindole hydrochloride (26,37), suppressed alcohol drinking in genetically selected, alcohol-preferring rats irrespective of alcohol's palatability (25). This suggests that δ_2-opiate antagonists may also be involved in modulating some of ethanol's behavioral effects partly responsible for excessive ethanol drinking behavior.

There is a difference in opinion as to whether the discriminative stimulus properties of the drug contribute to the development and maintenance of addictive behavior. By studying discriminative effects of self-administered ethanol in rats, Shelton and Macenski (42) have suggested that ethanol at the same dose is able to exhibit both reinforcing and discriminative functions. The present study was designed to evaluate the possibility that some of the discriminative stimulus properties of ethanol are mediated via δ_2-opiate receptors.

METHOD

Animals

Fifteen male Sprague–Dawley rats (Harlan–Sprague–Dawley, Inidanapolis, IN) were housed individually in suspended cages, and were given ad lib access to food and water during the first week after their arrival. Before the beginning of the study, rats were reduced to approximately 85% of their free-feeding body weights, and during the study they were allowed to gain 10 g per month to allow for normal growth and development. The animal colony room was maintained on a 12 L:12 D cycle (lights on at 0600 h), temperature at 20 to 22°C, and relative humidity of 60%.

Drugs

Ethanol and saline injections were administered intraperitoneally (IP). Each rat was tested with five doses of ethanol (ranging between 0.25–1.25 g/kg). The ethanol solution was a 10% (w/v) mixture of ethanol and normal saline.

Naltriben was purchased from Research Biochemicals Inc., Natic, MA. Naltriben was dissolved in 50:50 dimethyl sulfoxide (DMSO)/alkamuls (1mg in 20 μl), and was subsequently diluted as 1:50 in saline (further diluted for lower doses) and administered intraperitoneally 15 min before ethanol administration.

Apparatus

Experimental sessions were conducted in standard rat operant chambers (Lafayette Instruments, Lafayette, IN) equipped with two response levers, one stimulus lamp on the top of each lever, a house lamp, and a pellet dispenser, housed within a sound attenuating cubicle. Experimental contingencies and data collection were controlled by a Commodore 64C microcomputer system interfaced with the operant chambers (American Neuroscience Research Foundation, Yukon, OK).

Drug Discrimination Training

Subjects were initially trained to the location and operation of the pellet dispenser and operation of both levers by the method of a successive approximation. The illumination of stimulus and house lamps signaled the beginning of experimental sessions. Initially, each response on either lever was reinforced with a food pellet (P.J. Noyes Inc., Lancaster, NH). Once rats were trained to press the lever for food, they received either saline or 1.25 g/kg ethanol intraperitoneally 15 min prior to the session. The appropriate lever to obtain food was then determined according to the drug (ethanol or saline) administered before the session. The number of responses required for reinforcement for food delivery was raised in successive training sessions to 10 consecutive responses. For drug discrimination training, exposure to ethanol and saline was kept comparable by alternating ethanol and saline sessions throughout training. Training was conducted 5 days per week, and continued until each rat gave (a) fewer than 20 responses before the delivery of the first food pellet, (b) greater than 90% of the total responses, within a trial on the correct injection-appropriate lever, and earned (c) at least 50 reinforcers within each trial. Responding was considered to be under stimulus control when 90% of the total responses emitted during the session occurred on the appropriate lever and the number of responses required for the first reinforcement was less than 20 for each session.

Discrimination Test Sessions

The test sessions were conducted in similar manner as the training sessions. In the test sessions, 10 consecutive responses on either lever resulted in food. Test sessions were conducted following two consecutive training sessions in which the training criteria were met. Conditioning and test trials were carried out between 0900 and 1200 h daily.

Ethanol Discrimination Test Sessions

Once stimulus control was established in the discrimination task, dose–effect curves for ethanol were generated for every animal using four doses of ethanol ranging from 0.125 to 2.5 g/kg. During a test session, saline or ethanol (0.125–2.5 g/kg) was administered 15 min prior to the beginning of the session. During each week, training and test sessions were alternated. Ethanol dose–response test sessions were conducted following two consecutive training sessions. To ensure the stability of the dose–response functions for ethanol, ethanol discrimination tests were also conducted at regular intervals between naltriben test sessions. From the data collected using dose–response test sessions, effective dose values ED_{33} and ED_{66} were calculated for each rat using regression analysis.

Ethanol Discrimination Test Sessions Following Naltriben Pretreatment

Following the characterization of the initial ethanol dose–response curve, naltriben was administered, and the crossgeneralization and antagonism tests were conducted. Naltriben (0.032–5.6 mg/kg, IP) was administered 15 min prior to etha-

nol or saline treatment and 30 min prior to the beginning of these discrimination test sessions.

Blood Ethanol Levels

Blood samples were drawn from the brachial vein following pretreatment with naltriben (1.8 and 3.2 mg/kg) and ethanol (0.75 g/kg and 1.0 g/kg) administration. These blood samples were drawn using the same time course used in the discrimination test sessions, and were analyzed for ethanol levels by gas chromatography as previously described (36).

Data Analysis

The percentage of responses made on the ethanol-appropriate lever was calculated by dividing the number of responses made on the ethanol-appropriate lever by the total number of responses made on either lever during that session. Response rates were expressed as total number of responses made on either lever divided by session length (in seconds). Group average was calculated and expressed as the mean ± SEM. When greater than 80% of the total responses were made on the saline-appropriate lever following pretreatment with the drug and (ED_{100}) dose of ethanol, it was classified as antagonism of ethanol discrimination by the drug. Differences in the response rate following pretreatment with vehicle and drug were tested for significance using Student's *t*-test.

RESULTS

The number of training sessions required to reach the criteria for demonstrating discriminative stimulus control over responding ranged from 50 to 70 sessions (mean = 63.2 ± 5). Control rates of responding during training sessions following ethanol administration were not different from control rates following saline administration: (ethanol: 1.08 ± 0.06 responses per second; saline: 1.06 ± 0.06 responses per second).

During the test sessions in which saline or 0.25 g/kg ethanol was administered, rats (n = 15) responded almost exclusively on the saline-appropriate lever. Higher doses of ethanol beginning at 0.5 g/kg resulted in a shift in responding from the saline to the ethanol lever. The mean ED_{100} value for ethanol-lever selection (n = 15) was 0.85 ± 0.05 g/kg,and the mean ED_{66} value was 0.74 ± 0.06 g/kg. Administration of 1.5 g/kg and higher doses of ethanol had a rate-decreasing effect with an ED_{50} of 1.46 g/kg on total responding (Fig. 1).

Effect of Naltriben Pretreatment on the Discriminative Effect Produced by the ED_{100} Dose of Ethanol

The results of naltriben pretreatment, given in combination with the ED_{100} dose of ethanol (for each rat), are shown in Fig. 2A. Pretreatment with naltriben (0.01–3.2 mg/kg) did not have any effect on ethanol-appropriate responding, as shown in Fig. 2A. The rats responded exclusively on the ethanol-appropriate lever following pretreatment with naltriben (0.01–3.2 mg/kg). The combination of 3.2 mg/kg naltriben and the ED_{100} dose of ethanol resulted in a significant decrease in the response rate ($p < 0.005$), whereas the treatment with 5.6 mg/kg naltriben completely suppressed responding. Pretreatment with the vehicle did not have any effect on the saline-appropriate or on the ethanol-appropriate responding following administration of each.

Effect of Naltriben Pretreatment on the Discriminative Effects of the ED_{66} dose of Ethanol

The results of naltriben pretreatment, given in combination with the ED_{66} dose of ethanol, are shown in Fig. 2B. Naltriben

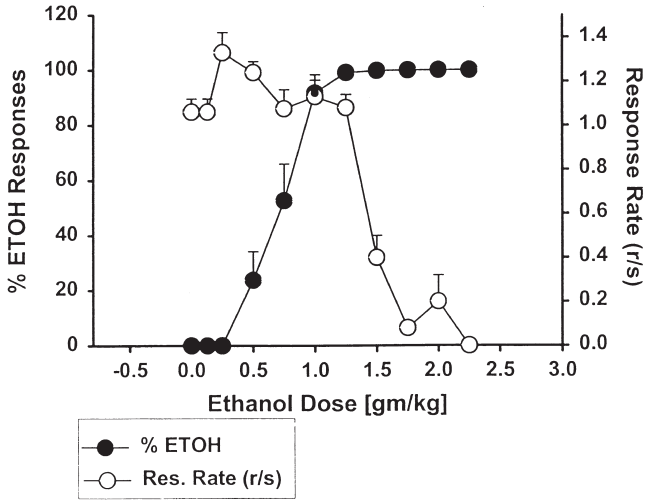

FIG. 1. Effect of ethanol (0.125–2.25 g/kg) on the percentage of ethanol lever responses (●) and the response rate (○).

(0.032–3.2 mg/kg), in combination with the ED_{66} dose of ethanol, did not have any significant effect on the percentage of responses made on the ethanol lever (Fig. 2B). One out of nine rats showed generalization with ethanol following pretreatment with naltriben (1.8 mg/kg) followed by ED_{66} dose of ethanol in comparison to that following pretreatment with vehicle and ED_{66} dose of ethanol. However, the group difference between percentage responses on the ethanol-appropriate lever with or without naltriben was not statistically significant ($p > 0.05$).

Treatment with the combination of 3.2 mg/kg naltriben and the ED_{66} dose of ethanol resulted in a significant decrease in the response rate ($p < 0.005$). This decrease in the response rate following pretreatment with 3.2 and 5.6 mg/kg doses of naltriben suggests a nonspecific effect of naltriben on the motor performance (Fig. 2A and B, 3). Naltriben (3.2 mg/kg) administered alone did not have a rate-suppressant effect. However, naltriben (3.2 mg/kg) in combination with ethanol exhibited significant motor suppressant effects [$p < 0.05$ between naltriben (3.2 mg/kg)-saline and naltriben (3.2 mg/kg)-ethanol (ED_{66} and ED_{100}) treatment groups]. Naltriben, at the dose of 5.6 mg/kg, by itself showed significant rate-suppressant effects ($p < 0.005$).

To determine whether naltriben and ethanol have any pharmacokinetic interaction, blood ethanol levels following naltriben vs. vehicle pretreatment were compared. Blood ethanol concentrations were not different between rats treated with vehicle and ethanol (0.75 and 1 g/kg) and a combination of naltriben (1.8 or 3.2 mg/kg) and ethanol (0.75 and 1 g/kg) (Table 1).

DISCUSSION

Drugs antagonizing the opiate system such as naloxone and naltrexone have repeatedly been shown to reduce alcohol intake both in animals and in humans. However, the precise mechanism underlying this effect of opiate antagonists on ethanol consumption is unknown. Naltrexone has been reported to reduce ethanol-induced euphoria in humans (47). However, drug discrimination studies in laboratory animals have provided inconsistent data regarding the role of opiates and opiate antagonists in ethanol discrimination (1,24,43,44,46,48,50).

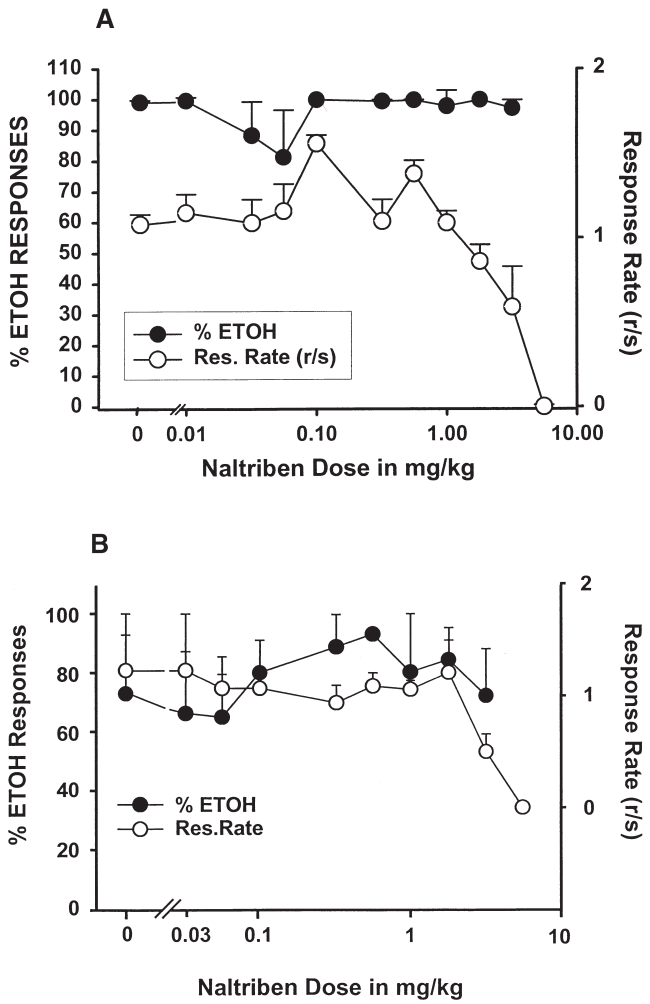

FIG. 2. (A) Effect of naltriben (0.01–5.6 mg/kg) on the percentage of ethanol lever responses (●) and the response rate (○) following ethanol (the ED_{100} dose) administration. (B) Effect of naltriben (0.032–5.6 mg/kg) on the percentage of ethanol lever responses (●) and the response rate (○) following ethanol (the ED_{66} dose) administration.

Although both morphine (μ-opiate agonist) and ethanol are classified as depressants of the central nervous system, they are found to be nonequivalent in terms of their stimulus properties. Morphine and ethanol did not share any stimulus properties in tests in which ethanol was administered to morphine-trained rats and vice versa (48). Also, in another study, morphine sulphate failed to elicit ethanol-appropriate responding in squirrel monkeys trained to discriminate ethanol from saline (50). The reports about the role of nonselective opiate antagonists, naloxone and naltrexone, in the formation of ethanol stimulus are also quite conflicting (1,24,43,44,46,50). The administration of naloxone at a dose (0.4 mg/kg) that antagonized morphine's interoceptive stimulus, had no effect upon discriminative stimulus effects of ethanol (50). Consistent with these studies, Altshuler and coworkers (1) did not find any modulation of ethanol's discriminative stimulus properties by either naloxone and naltrexone, even at high doses. However, the same researchers in a subsequent study reported that naltrexone modulates the discriminative effects of ethanol in the 6-min postdose excitatory phase (43,44). In another study, naltrexone (10 mg/kg) partially antagonized (15-min post injection) ethanol discrimination suggesting that ethanol discriminative behavior is partly mediated by activation of the opiate system (24). However, this partial antagonism by naltrexone was also accompanied by a small but significant disruption in the response rate (24). Naloxone and naltrexone are nonselective opiate antagonists (28,35), and therefore, the data regarding these compounds does not clearly differentiate between the roles of different opioid receptor subtypes in the formation of ethanol's compound discriminative stimulus.

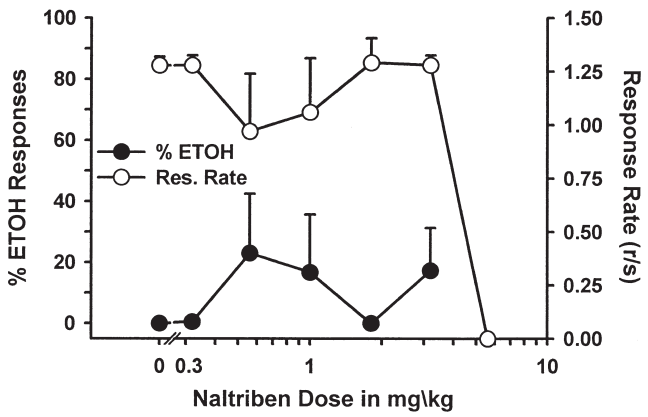

FIG. 3. Effect of naltriben (0.032–5.6 mg/kg) on the percentage of ethanol lever responses (●) and the response rate (○) following saline administration.

In this study, naltriben, a specific antagonist of the δ_2-opiate receptors did not alter the discriminative stimulus of ethanol. Because the discriminative stimulus of ethanol is complex and mediated by several neurotransmitter receptor systems, drugs or drug mixtures interacting at individual receptor systems have shown the ability to substitute for ethanol cue. On the other hand, as ethanol stimulus is composed of several components, antagonizing only one component of that stimulus may not be sufficient to block the complete stimulus. Therefore, only a small number of drugs have been able to partially antagonize the discriminative stimulus of ethanol. Considering these facts, the results from the present study suggest that either δ_2-opiate receptors are not involved in the formation of ethanol's compound discriminative stimulus, or blocking δ_2-opiate receptors is not sufficient to modulate ethanol's discriminative stimulus properties. This data is consistent with a recent report in which another δ-opiate antagonist, naltrindole hydrochloride, is not shown to have any effect on ethanol discrimination in Sprague–Dawley rats as well as in C57BL/6 mice (30). Previously, high concentrations of naltrexone have been shown to partially antagonize ethanol's

TABLE 1

BLOOD ETHANOL LEVELS FOLLOWING NALTRIBEN VERSUS VEHICLE PRETREATMENT

Pretreatment	Ethanol (0.75 gm/kg)	Ethanol (1 gm/kg)
vehicle	60.82 ± 3.7 mg/dl	102 ± 11 mg/dl
naltriben (1.8 mg/kg)	63.27 ± 4.0 mg/dl	99 ± 18 mg/dl
naltriben (3.2 mg/kg)	65.20 ± 3.2 mg/dl	100.2 ± 16 mg/dl

No. of animals = 15.

compound discriminative stimulus (24,46). The δ_2-opiate receptors do not appear to be involved in this effect of naltrexone. Also, contrary to these findings (24,46), in the same strain of rats used to assess effects of naltriben, naltrexone (0.56–10 mg/kg) was not found to have any effect on ethanol discrimination (Mhatre et al., data not shown).

Previously, naltriben (3 mg/kg) was shown to selectively suppress the alcohol intake in rats bred for alcohol preference, irrespective of alcohol's palatability, in the study done by Krishnan-Sarin and coworkers (25). The results from the present study suggest that this suppression of alcohol drinking is not associated with the modulation of ethanol discrimination. It also appears from the previous studies that the reduction in ethanol intake produced by drugs is not always due to a change in the ethanol's interoceptive stimulus. The present study also indicates that naltriben is not a promising candidate for the pharmacotherapy of alcoholism because naltriben has significant effects on the motor performance at the dose found to be effective in reducing alcohol intake.

In summary, the results of the present study suggest that naltriben, a δ_2-antagonist, does not solely modify ethanol discrimination in rats.

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