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The Delta$_2$-Opioid Receptor Antagonist Naltriben Selectively Attenuates Alcohol Intake in Rats Bred for Alcohol Preference

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KRISHNAN-SARIN, S., P. S. PORTOGHESE, T.-K. LI AND J. C. FROEHLICH. *The delta$_2$-opioid receptor antagonist naltriben selectively attenuates alcohol intake in rats bred for alcohol preference.* PHARMACOL BIOCHEM BEHAV 52(1) 153–159, 1995.—The relative importance of different opioid receptor types in mediating alcohol drinking behavior compared with the intake of other ingesta can be determined by characterizing the effects of selective opioid antagonists on the intake of various ingesta. Nonselective opioid receptor antagonists suppress the intake of many ingesta including alcohol, food, water, and sweets. Two distinct subtypes of delta-opioid receptors, delta$_1$ and delta$_2$, have recently been identified in rodent brain. We have previously reported that naltrindole (NTI), which blocks both delta$_1$ and delta$_2$ receptors, suppresses both alcohol and saccharin intake in rats selectively bred for high alcohol preference (P line). We now report that naltriben (NTB), an opioid antagonist that is selective for delta$_2$-opioid receptors, suppresses alcohol intake in rats of the P line and the effect appears to be both specific for alcohol and independent of alcohol palatability. NTB may reduce alcohol intake by attenuating the reinforcing pharmacological properties of alcohol.

Alcohol drinking Alcohol palatability Opioid receptor antagonists Naltriben Selectively bred rat lines

NONSELECTIVE opioid receptor antagonists, such as naloxone and naltrexone, reduce alcohol self-administration in both rodents and monkeys under a variety of experimental conditions (3,11,13,17,27,37,41,49,65). Evidence suggests that these opioid antagonists are not selective for alcohol as evidenced by the fact that they attenuate the intake of a wide variety of ingesta. For instance, both naloxone and naltrexone have been reported to decrease the intake of alcohol, sweets, fats, food, and water (1,9,13,17,26,28,36,38,50). Naloxone and naltrexone, which have been extensively studied, are "nonspecific" opioid receptor antagonists that bind to all three major opioid receptor types, mu, delta, and kappa, as a function of dose administered (5–8). The role of specific opioid receptor types in mediating the ingestion of alcohol compared with the ingestion of other substances is not known. Recent reports provide pharmacological evidence for the existence of two distinct subtypes of delta receptors, delta$_1$ and delta$_2$, in the rodent brain (29,42,54,60). The opioid antagonist naltrindole (NTI) blocks both delta$_1$- and delta$_2$-opioid receptor subtypes (58,60) as evidenced by the fact that NTI blocks the antinociceptive effect of the delta$_1$ agonist DPDPE and the delta$_2$ agonist DSLET in rats and mice (4,45). We have recently reported that NTI suppresses the intake of both a saccharin solution with alcohol and a saccharin solution without alcohol, suggesting that NTI is not specific for alcohol (31). It is possible that the delta$_1$ and delta$_2$ receptor subtypes contribute differentially to various physiological processes. Naltriben (or NTB), is a nonpeptide, highly potent receptor antagonist with high affinity and selectivity for delta$_2$-opioid receptors (39,48,54,57,58). The present study examines whether NTB decreases alcohol intake com-

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pared with the intake of sweet and bitter solutions presented alone and in combination with alcohol in rats selectively bred for alcohol preference.

METHOD

Subjects

Male rats of the selectively bred alcohol-preferring (P) line, from the 31st generation of selection for alcohol preference, weighing 500–700 g, served as subjects (33,35). The rats were housed individually in free hanging stainless steel cages in a room maintained on a 12L : 12D reverse cycle (lights off at 0900 h and on at 2100 h). Prior to initiation of the experiments all rats were given 8 weeks of free choice between a 10% (v/v) alcohol solution and water with food freely available. Fluids were presented in calibrated glass Richter tubes that were read to the nearest 0.5 ml. The positions of the Richter tubes containing alcohol and water were reversed daily to control for the effects of a possible positional preference. Rats were weighed daily for 4 days preceding and for 4 days following administration of each dose of each antagonist and were weighed twice weekly at all other times.

Assignment of Animals to Drug or Saline Treatment Groups

Prior to administration of each dose of NTB, baseline alcohol and water consumption were each averaged over the 4 preceding consecutive days to even out minor daily fluctuations in alcohol and water intake. Rats were rank ordered and assigned to the NTB- or saline-treated group in a manner that ensured the two groups did not differ significantly in alcohol or water intake prior to the day of drug treatment. Specifically, the rats were ranked in descending order based on their average daily alcohol intake over a 4-day period. Each of the top two alcohol drinkers were randomly assigned to the drug or saline treatment group, followed by the next two highest drinkers, likewise randomly assigned, until both groups were complete. This assignment procedure produced two groups of rats that were matched on alcohol intake prior to administration of drug or saline. Alcohol and water intake are not mutually exclusive variables as evidenced by the fact that rats that chronically drink large amounts of alcohol drink small amounts of water. Therefore, by rank ordering and counterbalancing the treatment groups based on chronic alcohol intake, one effectively counterbalances the groups on water intake as well.

Drugs

Naltriben methanesulfonate (NTB, mol.wt. = 511.59), provided by Dr. P. S. Portoghese (University of Minnesota, Minneapolis, MN), was dissolved in saline containing enough NaOH to solubilize the compound and the pH of the solution was adjusted to 6.9–7.2 by titrated addition of 0.1 N HCl prior to IP injection. NTB was administered as a single injection in doses of 0.375 and 1.5 mg/kg b.wt. in a volume of 7.5 ml of saline and as two injections of 3.0 mg/3.75 ml saline/kg b.wt. each for a total dose of 6.0 mg/kg b.wt. The doses of NTB chosen are similar to those that, when administered peripherally, are effective in blocking the antinociceptive activity of ICV-administered opioid agonists in mice (54). The peak time and duration of action of NTB following peripheral administration in mice is 30 and 90 min, respectively (54).

Data Analysis

Within-line comparisons of the effects of NTB vs. saline on intake of alcohol, water, or flavored solutions were made using paired *t*-tests. The experimental protocol involved rank ordering and assigning rats to the drug or saline treatment groups in a manner that produced groups that did not differ in alcohol or water intake prior to drug or saline administration. Given that the groups were not formed by random assignment of animals, but rather by assignment of pairs of animals, a basic assumption required for use of an unpaired *t*-test was not met. This counterbalanced design eliminated group differences in the variables of interest, namely alcohol and water intake, prior to drug treatment and reduced the degree of potential variance between groups that dictated the use of a paired *t*-test for comparison of group means (66).

Experimental Design and Procedure

Experiment 1. Following 8 weeks of 24-h free choice between a 10% (v/v) alcohol solution and water, P rats were given daily scheduled access to the alcohol solution for 8 h during the dark portion of the light/dark cycle (0900–1700 h), with food and water available ad lib for 3 weeks. Alcohol intake was recorded at the end of the daily 8-h alcohol access period and water intake was recorded every 24 h. Alcohol intake stabilized following 3 weeks of scheduled access to alcohol and then rats were assigned to the drug or saline treatment groups as previously described. Average daily alcohol and water intake was calculated for each rat over 4 consecutive days prior to the day of NTB administration. On the day of drug treatment one of two doses of NTB (0.375 or 1.5 mg/kg b.wt.) or an equal volume of saline was administered IP 30 min prior to the first daily alcohol access period. Intake of alcohol (8-h access) and water (24-h access) was recorded on the day of drug administration and on days 1, 2, and 3 following drug treatment. The administration of each dose of NTB was separated by 3 weeks to ensure that stable baseline alcohol and water intake was achieved for at least 2 weeks prior to drug treatment.

Experiment 2. Following completion of Experiment 1, the P rats from Experiment 1 continued to receive scheduled access to an alcohol solution (10% v/v) for 8 h per day with food and water available ad lib for 3 weeks. Alcohol and water intake was recorded daily and average intake was calculated for each rat over 4 consecutive days prior to NTB administration. Rats were assigned to the drug or saline treatment groups as previously described. On the day of drug treatment, rats received a 6.0-mg/kg dose of NTB as two separate IP injections of 3.0 mg/3.75 ml/kg b.wt. each. One injection was given prior to the onset of the 8-h alcohol access period (at 0900 h) and the other was given at the midpoint of the 8-h alcohol access period (at 1300 h). Intake of alcohol was recorded at the midpoint of the 8-h alcohol access period (at 1300 h) and at the end of the alcohol access period (at 1700 h) on the day of drug administration and on days 1, 2, and 3 following drug treatment.

Experiment 3. Following completion of Experiment 2, 16 P rats with the highest alcohol intake from Experiment 2 continued to receive daily access to the alcohol solution (10% v/v) for an 8-h period (0900–1700 h) with food and water freely available for 3 additional weeks. The rats were then given a two-bottle concurrent free choice between a sweet solution without alcohol (saccharin, 0.45 g/l of water) and a sweet solution containing alcohol (10% alcohol v/v in water containing 0.45 g saccharin per liter) for 8 h per day (0900–1700 h) with water available for the remaining 16 hours per day (1700–0900 h) and food available ad lib. Consumption of food, water, sweetened solution without alcohol, and sweetened solu-

tion with alcohol was recorded daily. The rats were maintained on this schedule for 1 month until the daily intake of the two sweetened solutions (with and without alcohol) was stable and relatively equal. Average daily intake of the sweet solutions (with and without alcohol) was calculated for each rat over 4 consecutive days prior to the day of NTB administration. Rats were assigned to the NTB or saline treatment groups based on their average daily intake of the sweet solution containing alcohol, as previously described.

NTB, in a dose of 6.0 mg/7.5 ml/kg b.wt., was divided in half and administered as two separate IP injections of 3.0 mg/3.75 ml/kg b.wt. each. The first injection was administered prior to the 8-h alcohol access period (at 0900 h) and the second injection was given at the midpoint of the access period (at 1300 h). Intake of each of the two sweetened solutions (with and without alcohol) was recorded at the end of the 8-h access period (1700 h) on the day of drug administration and on days 1, 2, and 3 following drug treatment. Water intake was recorded daily.

Experiment 4. Following completion of Experiment 3, the rats from Experiment 3 were given scheduled access to a 10% (v/v) alcohol solution (unflavored) for 8 h daily (0900–1700 h) with food and water freely available for 3 weeks until alcohol intake stabilized. The rats were then given a two-bottle concurrent free choice between a bitter solution without alcohol (quinine, 0.05 g/l of water) and a bitter solution containing alcohol (10% alcohol v/v in water containing 0.05 g quinine per liter) for 8 h per day (0900–1700 h) with water available for the remaining 16 hours per day (1700–0900 h) and food available ad lib. Consumption of food, water, bitter solution without alcohol, and bitter solution with alcohol was recorded daily. After 3 weeks of concurrent presentation of the two solutions, rats were consuming much more of the bitter solution containing alcohol than the bitter solution without alcohol. Average daily intake of water was approximately 17.4 ml, average daily intake of the bitter solution containing alcohol was 28.0 ml, but the average daily intake of the bitter solution without alcohol was only 0.5 ml. To be able to detect a suppressive effect of NTB on intake of the bitter solution it was necessary to induce rats to drink more of the bitter solution without alcohol. Therefore, the following changes in the fluid access paradigm were introduced sequentially.

Phase 2. Access to water for 16 h per day was eliminated and rats were given access to the bitter solution without alcohol (quinine, 0.05 g/l of water) and the bitter solution containing alcohol (10% alcohol v/v in water containing 0.05 g quinine per liter) presented concurrently for 8 h per day with food freely available for 7 days. Total fluid consumption averaged 33.4 ml per day, which was accounted for, almost exclusively, by intake of the bitter solution containing alcohol (32.4 ml).

Phase 3. The concentration of quinine was reduced by half from 0.05 g/l to 0.025 g/l. Rats continued to receive a daily 8-h free choice between the bitter solution containing alcohol and the bitter solution without alcohol with food freely available for 28 days. Reducing the concentration of quinine by half did not increase the intake of the bitter solution without alcohol. Average daily intake of the bitter solution containing alcohol was 33.0 ml per day whereas the average daily intake of the bitter solution without alcohol was only 2.3 ml per day.

Phase 4. The concentration of alcohol in the bitter solution was increased from 10% to 20% (v/v) and rats were given access to the bitter solution without alcohol (quinine, 0.025 g/l of water) and the bitter solution containing alcohol (20% alcohol v/v in water containing 0.025 g quinine per liter) presented concurrently for 8 h per day with food freely available for 21 days. Doubling the concentration of alcohol in the bitter solution served to enhance consumption of the bitter solution without alcohol. Average daily intake of the bitter solution containing alcohol (20% v/v) remained relatively constant at 33.7 ml/day and intake of the bitter solution without alcohol rose to 7.5 ml/day. Even though intake of the bitter solution with and without alcohol was not equal, rats of the P line were now consuming enough of the bitter solution without alcohol to detect a potential suppressive effect of NTB treatment.

Baseline intake of the two concurrently presented bitter solutions (with and without 20% alcohol v/v) was calculated over 4 consecutive days and the rats were counterbalanced and assigned to the NTB or saline groups based on their average intake of the bitter solution containing alcohol as described in Experiment 1. NTB, in a dose of 6 mg/kg b.wt., was divided in half and was administered as two separate IP injections of 3.0 mg/3.75 ml/kg b.wt. each, with one injection given prior to onset of the 8-h access to the two bitter solutions (at 0900 h), and the second injection given at the midpoint of the 8-h access period (at 1300 h). Consumption of the two bitter solutions (with and without alcohol) was recorded at the end of the 8-h access period (1700 h) on the day of NTB administration and on days 1, 2, and 3 following drug treatment.

RESULTS

Experiment 1

NTB, when administered as a single injection in doses of 0.375 and 1.5 mg/kg, did not alter alcohol or water intake on the day of NTB administration (Fig. 1A,B) or on days 1–3 following NTB treatment (data not shown). When drug vs. saline groups were compared, all two-sided significance levels were greater than 0.57.

Experiment 2

Administering a 6.0-mg/kg dose of NTB in two injections, of 3.0 mg/kg each, reduced alcohol intake by 40% during the entire 8-h alcohol access period on the day of NTB administration ($t = -4.85$ with a two-sided significance level of 0.0007). Alcohol intake was reduced by 21.6% from 0900–1300 h, and by 55.4% from 1300–1700 h. NTB did not significantly alter water intake (Fig. 1C; $t = -0.66$ with a two-sided significance level of 0.52). NTB did not alter alcohol or water intake on days 1–3 following NTB treatment (data not shown). Although food intake was not directly measured, it appears that NTB did not alter food intake as evidenced by the fact that no significant differences in body weight were evident when individual weights on the day preceding NTB treatment were compared with weights on the day of drug or with weights on the day after drug. Additionally, the weight of animals in the drug-injected group did not differ from the those in the saline-injected group prior to, during, or following drug treatment.

Experiment 3

Rats of the P line consumed roughly equivalent amounts of the saccharin solution with and without alcohol. NTB significantly reduced intake of the saccharin solution containing alcohol by 33% ($t = -4.25$ with a two-sided significance level of 0.004) without altering intake of the saccharin solution without alcohol ($t = -0.83$ with a two-sided significance level of 0.44) on the day of NTB administration (Fig. 2). No suppression of intake of either solution was seen on days 1–3

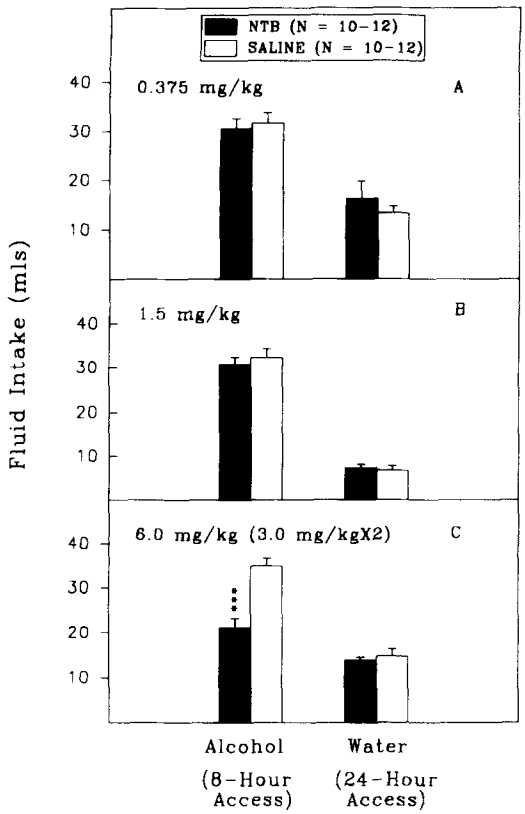

FIG. 1. Effect of NTB, administered either as a single injection or as two injections, on alcohol and water intake in rats of the P line on the day of NTB administration. Rats were given ad lib access to food and water and scheduled access to alcohol (10% v/v) for 8 h daily. Each bar represents the mean ± SE and *N* indicates the number of rats per group. Asterisks indicate significant differences between the NTB- and saline-treated groups (***$p < 0.001$; paired *t*-test).

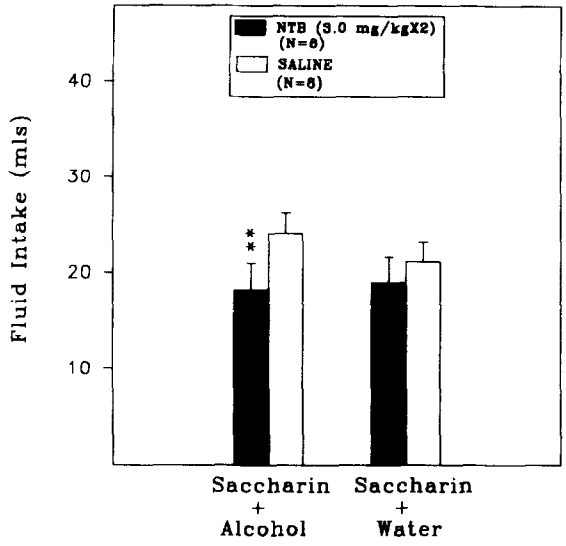

FIG. 2. Effect of NTB, administered in two doses of 3.0 mg/kg b.wt. each, on intake of a saccharin solution containing alcohol and a saccharin solution without alcohol, in rats of the P line on the day of NTB administration. Rats were given ad lib access to food and water and scheduled access to a free choice between saccharin solutions (0.45 g/l) with and without alcohol (10% v/v) for 8 h (0900–1700 h) daily. Each bar represents the mean ± SE and *N* indicates the number of rats per group. Asterisks indicate significant differences between the NTB- and saline-treated groups (**$p < 0.01$; paired *t*-test).

following NTB administration (data not shown). NTB did not alter water intake on the day of NTB administration or on days 1-3 following NTB treatment (data not shown). Individual body weights prior to and following drug treatment within and between the NTB- and saline-treated groups were compared as in Experiment 2. No change in body weight was seen as a function of drug treatment, which suggests that NTB did not alter food intake (data not shown).

Experiment 4

NTB significantly reduced intake of the quinine solution containing alcohol by 31% ($t = -2.76$ with a two-sided significance level of 0.04) without altering the intake of the quinine solution without alcohol ($t = 1.07$ with a two-sided significance level of 0.34) on the day of NTB treatment (Fig. 3). NTB did not significantly suppress intake of either solution on days 1-3 following NTB administration (data not shown). Individual body weights prior to and following drug treatment within and between the NTB- and saline-treated groups were compared as in Experiments 2 and 3. No change in body weight was seen as a function of drug treatment, which suggests that NTB did not alter food intake (data not shown).

DISCUSSION

Rats of the P line represent an animal model of alcoholism that is particularly well suited for testing the efficacy of pharmacological agents that have the potential to reduce alcohol intake (14,15). It has previously been demonstrated that rats of the P line consume alcohol for its pharmacological effect rather than for its caloric value, taste, or smell, as evidenced by the fact that they self-administer alcohol intragastrically in amounts sufficient to produce intoxication when food and water are available (63). In the present study, decreasing the palatability of alcohol did not alter the amount of alcohol consumed by rats of the P line. When given a free choice between a bitter solution containing alcohol and a similar solution without alcohol P rats consumed as much of the bitter alcohol solution (34.0 ± 1.7) as they did of unflavored alcohol presented concurrently with water (35.0 ± 1.8). Procedural manipulations such as eliminating access to water, doubling the concentration of alcohol (from 10% to 20% v/v), and diluting the concentration of quinine (from 0.05 to 0.025) did not alter alcohol drinking behavior in rats of the P line. The results agree well with a previous report that P rats consume significant quantities of alcohol when presented with a free choice between water mixed with a preferred flavor and alcohol mixed with a nonpreferred flavor (40). The results provide further evidence that alcohol consumption by P rats is not dependent on alcohol palatability and that alcohol is a potent reinforcer for rats of the P line.

A large body of evidence suggests that nonselective opioid antagonists decrease consumption of a wide variety of ingesta including alcohol, sweets, fats, food, and water (1,9,13,17,26, 28,36,38). We have recently reported that the opioid antagonist naltrindole (NTI), which blocks both the delta$_1$- and

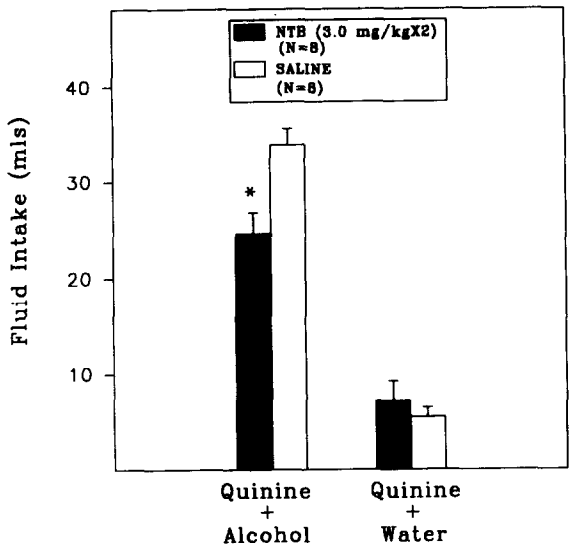

FIG. 3. Effect of NTB, administered in two doses of 3.0 mg/kg b.wt. each, on intake of a quinine solution containing alcohol and a quinine solution without alcohol, in rats of the P line on the day of NTB administration. Rats were given ad lib access to food and scheduled access to a free choice between quinine solutions (0.025 g/l) with and without alcohol (20% v/v) for 8 h (0900–1700 h) daily. Each bar represents the mean ± SE and N indicates the number of rats per group. Asterisks indicate significant differences between the NTB- and saline-treated groups (*$p < 0.05$; paired t-test).

delta$_2$-opioid receptor subtypes (58,60), suppresses the intake of both alcohol and a sweet solution in rats of the alcohol preferring (P) line (31). NTI, in doses of 5.0–20.0 mg/kg b.wt. IP, attenuated alcohol intake in a dose-dependent manner, without altering water intake. Administering the maximally effective dose of NTI (15 mg/kg b.wt, IP) in two parts, separated by 4 h, served to prolong the duration of action of NTI and produced an attenuation of alcohol intake that lasted for at least 28 h. This same dose of NTI (15 mg/kg b.wt, IP), administered in two parts, also suppressed the intake of a saccharin solution with and without alcohol, which indicates that the effect of NTI is not specific for alcohol.

The present study examined whether NTB, an opioid antagonist that is highly selective for the delta$_2$ receptor subtype (39,48,54,57,58), suppresses alcohol intake compared with the intake of sweet and bitter solutions in rats selectively bred for alcohol preference (P line). NTB is a benzofuran analogue of the delta-opioid receptor antagonist NTI, which was developed using the message-address concept that recognizes that the Phe^4 residue of the enkephalins is a part of both the address and message sequence required for recognition of, and interaction with, delta receptors (34,46,47). The selectivity of NTB for delta$_2$ receptors has been demonstrated in antinociceptive assays where NTB produces a larger magnitude of change in the ED_{50} for delta$_2$ agonists (fourfold) when compared to the ED_{50} for delta$_1$ agonists (1.4-fold) (54). The doses of NTB used in the present study are similar to those used to antagonize the antinociceptive activity of delta$_2$ receptor-selective agonists (54). NTB, in a dose of 6.0 mg/kg b.wt, significantly suppressed alcohol intake without altering water intake or body weight in rats given a free choice between alcohol and water for 8 h daily. The absence of alterations in body weight following drug administration suggests that NTB did not alter food intake. The 6.0-mg/kg dose of NTB suppressed alcohol intake during the entire 8-h alcohol access period. The prolonged duration of action of NTB may be due to the fact that NTB exhibits high affinity for the delta$_2$-opioid receptor subtype and NTB is a nonpeptide antagonist and hence is resistant to enzymatic degradation by peptidases (46,54). When alcohol was mixed with saccharin and rats were presented with a free choice between alcohol + saccharin vs. saccharin alone, NTB significantly suppressed intake of the saccharin solution containing alcohol without altering intake of saccharin without alcohol. Similarly, when alcohol was mixed with quinine and rats were presented with a free choice between alcohol + quinine vs. quinine alone, NTB significantly attenuated intake of the quinine solution containing alcohol without altering intake of the quinine solution without alcohol. These results suggest that the suppressive effects of NTB may be specific for alcohol.

We have previously postulated that the endogenous opioid system is activated by consumption of alcohol and that activation of this system may be a neurobiological mechanism that contributes to the hedonic value of, development of preference for, and continued ingestion of, alcohol (14,16,18,19). This hypothesis is supported by a number of divergent findings. First, nonspecific opioid receptor antagonists, such as naloxone and naltrexone, reduce alcohol self-administration under a variety of experimental conditions, in rodents and monkeys (3,11,13,27,37,41,49,61,65) as well as in humans (43, 62). Second, alcohol increases release of beta-endorphin in vivo in both rats and humans (21,23,44,59) and in vitro in preparations of rat hypothalamus and pituitary (10,21,24,30). Alcohol also increases genetic message for opioid peptide synthesis in rat brain and pituitary (19,20,22,51,64). Third, opioid peptides function as positive reinforcers as indexed by peripheral and central self-administration that is attenuated by opioid antagonists, by opioid peptide-induced alterations in pattern of responding for electrical brain stimulation that is blocked by opioid antagonists, and by preference for environmental stimuli associated with opioid peptide administration that is also attenuated by opioid antagonists [for review see (12,52,53,56,67)]. Taken together, these findings suggest that activation of the opioid system in response to alcohol ingestion might serve to enhance the hedonic value of, and reinforcing effect of, alcohol. An enhancement of alcohol's reinforcing action might serve to support continued drinking during a single drinking bout and to increase the probability of redrinking or the initiation of subsequent drinking bouts.

Opioid antagonists, such as NTB, may reduce the intake of alcohol by attenuating the reinforcing effect of alcohol. However, it has also been suggested that opioid antagonists may suppress alcohol intake by attenuating alcohol palatability rather than by attenuating its reinforcing effect. This hypothesis is based, in part, on studies of the effects of opioid antagonists on the intake of highly palatable substances. Naltrexone has been found to be more effective in reducing the intake of sweetened solutions compared with tap water (32,56) and in reducing the intake of highly palatable foods compared with lab chow (2,25). One approach to determining whether opioid antagonist-induced suppression of alcohol intake is dependent on palatability is to examine the effects of opioid antagonists on alcohol solutions that differ in palatability. In the present study, altering palatability of alcohol did not alter the magnitude of suppression of alcohol intake produced by NTB. This suggests that NTB-induced attenuation of alcohol

drinking is not dependent on alcohol palatability and instead may be due to an attenuation of the reinforcing properties of alcohol. This hypothesis is supported by the results of two recent clinical trials that examined the effects of naltrexone on alcohol drinking in outpatient alcoholics (43,62). Both studies independently demonstrated that a naltrexone-induced decrease in alcohol consumption was accompanied by a decrease in alcohol craving and alcohol-induced subjective "high."

Recent advances in our understanding of the basic biochemical mechanisms underlying alcohol drinking behavior have resulted in an increased effort to identify and characterize agents that may be used to decrease alcohol drinking. The results of the present study indicate that the delta$_2$-opioid receptor antagonist, NTB, selectively attenuates alcohol intake and suggest that NTB may be potentially useful as a pharmacotherapeutic agent in the treatment of alcoholism and alcohol abuse.

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