Pharmacology Biochemistry & Behavior, Vol. 21, pp. 423–429, 1984. © Ankho International Inc. Printed in the U.S.A. 0091-3057/84 $3.00 + .00

Effects of Ethanol and Naltrexone on Free-Operant Avoidance Behavior in Rats[1]

MARK GALIZIO, STACY C. SMALTZ AND BARBARA A. SPENCER

Department of Psychology, University of North Carolina at Wilmington, Wilmington, NC 28406

Received 7 November 1983

GALIZIO, M., S. C. SMALTZ AND B. A. SPENCER. *Effects of ethanol and naltrexone on free-operant avoidance behavior in rats.* PHARMACOL BIOCHEM BEHAV 21(3) 423–429, 1984.—Several recent studies have suggested that some effects of ethanol may be mediated by the opioid receptor systems. The present study examined the possibility of a common link between ethanol and opiates by determining whether the effects of ethanol on rat's free operant avoidance behavior could be reversed by the opiate antagonist naltrexone. In Experiment 1 ethanol produced a dose-dependent impairment of avoidance performance (characterized by a decrease in response rate and/or an increase in shock rate) in all three subjects. Naltrexone (3 mg/kg) alone suppressed avoidance rates, but failed to reverse or reduce the effects of ethanol. In contrast to the expectations of the "common-link" hypothesis, the greatest impairment of performance was observed after high doses of ethanol in combination with naltrexone. In Experiment 2 the effects of chronic naltrexone administration were examined. Since previous research has suggested that chronic treatment with opiate antagonists produces a heightened sensitivity to opiate agonists and antagonists, Experiment 2 addressed the issue of whether sensitization to naltrexone would transfer to ethanol. Although increased sensitivity to the rate-decreasing effects of naltrexone was observed, there was no evidence of heightened sensitivity to ethanol. Taken together the results provided little support for the hypothesis that the effects of ethanol on avoidance performance are mediated by the opiate receptor system.

Ethanol Naltrexone Avoidance Opiate antagonists Supersensitivity

THE idea of a common biochemical link between alcoholism and opiate addiction originated in papers by Davis and Walsh [11] and Cohen and Collins [9] who suggested the possibility that condensation products of ethanol metabolization might possess opioid properties. The analysis of this common-link hypothesis was given impetus a few years later with the discovery of opiate receptors and the endorphins. Several recent reviews have suggested that ethanol effects might be mediated by the endorphin system, and that this might provide a common neural substrate important to opiate addiction and alcoholism [2, 6, 18, 27]. As these reviewers noted, there is now strong support for the notion that at least some of the effects of ethanol are mediated by the opioid system, but it is also apparent that not all effects of ethanol are so mediated. The growing literature has yet to clearly delineate which effects of ethanol are opioid-mediated and which are produced through actions on other systems.

The strategy of research most widely used to determine which effects of ethanol are mediated by the opiate receptor system has been to examine reversal of selected ethanol effects by opiate antagonists like naloxone and naltrexone. Several studies have reported naloxone-reversal of ethanol effects. For example, Ho and Ho [19] noted that naloxone increased the LD 50 for ethanol in mice, and shortened ethanol-induced sleep duration. Another physiological effect of ethanol, induction of hippocampal discharge, has been shown to be a naloxone-reversible effect [4], and there have been a number of studies indicating that ethanol self-administration can be reversed by opiate antagonists [1, 2, 10, 25].

Several studies have failed to confirm the reversal of ethanol effects by opiate antagonists. For example, Harris and Erickson [15] did not obtain naloxone-reversal of ethanol-induced motor impairment in rats or mice, and Harris and Snell [16] found that ethanol-induced suppression of food-reinforced bar-pressing in rats was actually potentiated by naloxone. Studies with humans have also had mixed results. While Jeffcoate [21] found that naloxone blocked the effects of ethanol on reaction time and perceived intoxication in humans, Catley *et al.* [8] reported that naloxone did not reverse such effects. Bird *et al.* [5] varied the order of administration of naloxone and ethanol, but found no evidence of naloxone prevention or reversal of ethanol effects in humans.

The inconsistent results reviewed above suggest a need for more systematic research to determine which effects of ethanol are mediated by the opiate system. One gap in the ethanol-opiate antagonist literature involves the effects of ethanol on aversively-motivated behavior, and the present study evaluated the effects of ethanol and naltrexone on the performance of free-operant avoidance behavior in rats. Previous research on the effects of ethanol on free-operant avoidance has not been consistent. Reynolds and van Sommers [28] reported a biphasic response to ethanol in rats performing on a Sidman avoidance schedule. Low doses of ethanol increased avoidance responding, while higher doses

[1]The research was supported in part by Grants No. 8110 and No. 8300 from the North Carolina Alcholism Research Authority and Grant No. RII-8308469 from the National Science Foundation.

depressed response rates. However, other studies using different types of avoidance schedules obtained suppression of responding throughout the effective dose range in rats [17] and squirrel monkeys [22]. Thus, Experiment 1 reexamined the effects of a range of ethanol doses on Sidman avoidance in rats, and further determined whether the effects were reversible by naltrexone.

EXPERIMENT 1

METHOD

Subjects

Three male, albino Sprague-Dawley rats served as subjects. Rats were individually housed with ad lib food and water in a room with 24 hr illumination. Animals were between 90 and 100 days old (350–400 g) and were experimentally naive at the onset of the experiment.

Apparatus

A standard single-lever rodent chamber (Lafayette model 8422) was enclosed in a styrofoam sound-attenuating chest. The chest was equipped with a fan which provided masking noise (c 75 dBA), and ventilation. The chamber had stainless steel and panels and Plexiglas sidewalls (dimensions 29×22×23 cm). The lever was mounted about 7 cm above the grid floor in the center of the apparatus, and a 24-V signal lamp was situated 5 cm above the it. A Lafayette Master Shocker (model 82404) delivered scrambled shock of 0.8 mA intensity and 0.3 sec duration through 0.5 cm-diameter stainless steel floor grids spaced 1.6 cm apart. Programming and recording operations were performed by a microcomputer located in an adjacent room.

Procedure

Lever pressing to avoid shock was shaped by the method of successive approximations. Within 30 min control of shock presentation was transferred to an avoidance schedule where each response postponed shock for 20 sec and in the absence of responding shocks were programmed every 5 sec (Sidman avoidance schedule with response-shock interval=20 sec and shock-shock interval=5 sec). In addition to resetting the response-shock interval, each response terminated the house light for 0.5 sec. Activation of the fan and house light signalled the beginning of the session, and offset of both stimuli signalled the end of the sessions which were normally 2 hr in duration. Sessions were terminated early if the animal was unable to respond (50 consecutive shocks automatically aborted the session).

Subjects were tested five days per week on the Sidman schedule (weekends off), for a minimum of 30 sessions, and until they attained a split-half stability criterion where the difference between the most recent 3 sessions and the immediately preceding three had to be less than 10% of the six day average for both response rate and shocks received. Once stability had been reached, the drug regimen was initiated. Drug sessions were scheduled twice per week (Wednesday and Friday), and baseline sessions were conducted three days per week (Monday, Tuesday and Thursday). On drug days, animals received two injections (IP with 26 ga., 3/8 in. needles) prior to the avoidance session. Thirty min prior to the onset of the session one of three ethanol doses (0.5, 1.0, or 1.5 g/kg) or a volume of isotonic saline equivalent to that of the highest ethanol dose was administered. Ethanol was delivered in 10% (w/v) saline solution. Then, 10 min before the onset of the session (20 min following ethanol administration) either naltrexone (3 mg/kg in saline vehicle) or an equivalent volume of saline was administered. This rather high dose of naltrexone was chosen as comparable to the naloxone dose of 10 mg/kg which Ho and Ho [19] found to antagonize ethanol effects in mice.

The design thus formed was a 2×4 factorial with naltrexone (placebo, 3 mg/kg) and ethanol (placebo, 0.5, 1.0, 1.5 g/kg) as the main factors. Each animal was exposed to the 8 dose combinations three times. Order of administration was random with the constraint the same combination of doses was not administered on consecutive drug days, and each cycle of 8 conditions was completed before beginning the next cycle. Finally, preliminary research in our laboratory has indicated that the first exposure to IP ethanol produced uncharacteristically strong effects, so in order to eliminate such non-representative effects each animal was exposed to one ethanol (1.0 g/kg) session before the above drug regimen began. Since the first naltrexone administration may also be non-representative [32], another preliminary session was conducted where animals received the 3 mg/kg naltrexone dose. These two preliminary sessions did not count toward completing the cells of the factorial design.

RESULTS

Figure 1 presents response and shock rates as a function of drug dose for all three subjects. The upper panels show the results for subject S1, and results for S3 and S4 are shown in the middle and bottom panels, respectively. For each rat, the mean responses per min (left panel) and mean shocks received per min (right panel) are presented on the ordinates, with ethanol dose on the abscissas. Vertical lines indicate the ranges of measures. The conditions in which saline placebo was administered instead of ethanol are indicated "PL." Filled circles represent performances observed when naltrexone was given in addition to the ethanol condition, while open circles represent performances when saline vehicle was administered instead of naltrexone. Each data point plotted in Fig. 1 is thus the mean of the three replications of the condition depicted except for the mean values of the Drug Baseline Condition performances which are represented by triangles and labeled "DBL" on the abscissa. The DBL values were determined by considering only data obtained during the Tuesday and Thursday sessions immediately preceding a injection session (response rates were elevated somewhat on Monday sessions which followed two days without training). No injections were administered on DBL sessions. Because of the large number of replications, vertical lines represent standard deviations for the DBL response and shock data.

Ethanol Alone

Consider first the effects of ethanol alone (open circles). Effects of ethanol were similar in each subject, a generalized impairment of avoidance, but the impairment was manifested in somewhat different ways depending on the subject. For S1 (top panels) there was a trend toward a linear decline in response rate with increasing doses of ethanol. Only at the high dose (1.5 g/kg), however, was this effect reliable when contrasted with the Placebo or DBL conditions. Ethanol-induced impairment is more clearly shown when the shocks received are considered for S1. In accordance with the reduction of response rates, there was a trend toward a linear

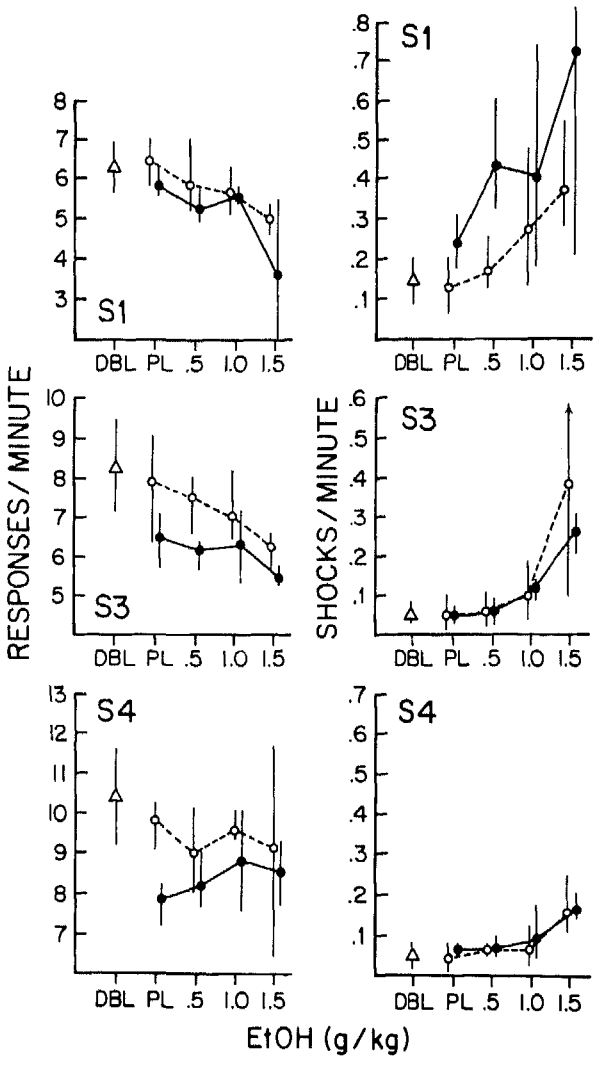

FIG. 1. Mean response and shock rates for subjects exposed to ethanol (open circles), and ethanol with 3 mg/kg naltrexone (filled circles). Responses per minute for each animal are shown in the left-hand panels, and shocks per minute are on the right. Vertical lines passing through the circles represent the range of values observed in that condition, while the vertical lines passing through the triangles (which represent mean values for drug baseline sessions abbreviated "DBL") indicate standard deviations. The various doses of ethanol are indicated on the abscissa, and "PL" indicates conditions where saline placebo was administered instead of ethanol.

increase in the number of shocks received by S1 as a function of increasing ethanol dose. Again, range overlap exists except at the 1.5 g/kg condition, where the number of shocks received was greater than under the DBL or Placebo conditions.

Effects of ethanol on Subject S3 (middle panels of Fig. 1) were generally comparable to those of S1. As the left panel reveals, response rates declined as a function of ethanol dose in the absence of naltrexone. Again there was a considerable range overlap, except at the 1.5 g/kg dose level. At this dose the response rate was reliably lower than rates observed in the Placebo, DBL and 0.5 g/kg conditions. Shock rate data were comparable with very few shocks received in the DBL, Placebo, or 0.5 g/kg dose conditions. Reliable increases in shocks received were apparent at the 1.5 g/kg dose and the effects of the 1.0 g/kg level were intermediate. It should be noted that the first exposure to the 1.5 g/kg dose produced such severe impairment that the session was terminated following 50 consecutive shocks. Data points were computed for this session on the basis of the time actually spent in the apparatus. Subsequent 1.5 g/kg sessions produced measureable, but less dramatic impairment. Unlike the previous animals, ethanol produced virtually no effect on response rates of S4 (bottom, left-hand panel). Ethanol-induced impairment was apparent, however, as an increase in shocks received at the 1.5 g/kg dose level in S4 (bottom, right-hand panel).

Naltrexone Effects and Naltrexone-Ethanol Combinations

Naltrexone administration also interfered with avoidance performance in all three animals. First consider the effect of naltrexone for S1. It is clear from the top panel of Fig. 1 that naltrexone did not reverse or reduce the ethanol-induced impairment whether defined in terms of response or shock rates. There was a tendency for naltrexone alone to produce some avoidance impairment (note the increased shocks and slightly depressed rates when naltrexone was given in combination with saline placebo). When combined, naltrexone and ethanol tended to produce additive effects. Thus the greatest amount of impairment of avoidance was observed when naltrexone and high doses of ethanol were combined. It should be noted though that the extreme impairment seen in the Naltrexone-1.5 g/kg Ethanol condition was largely due to S1's first session under these conditions, where the extreme reaction caused premature termination of the session.

Naltrexone appeared to suppress response rates across the various conditions for S3 (middle panel). Without ethanol, naltrexone suppressed rates by comparison with DBL sessions and, although there was range overlap, perhaps with the Placebo conditions as well. Clearly the rate-decreasing effects of naltrexone added to the rate-decreasing effects of ethanol. Rates were lower when naltrexone was combined with each ethanol dose and these differences were virtually without range overlap at the 0.5 and 1.5 g/kg conditions. The effects of naltrexone were largely confined to response rate with shock rates affected only by ethanol. Naltrexone also reduced response rates across all conditions for S4. The naltrexone-induced suppression was particularly apparent in S4 without ethanol, but additive effects were apparent when naltrexone was combined with ethanol. As with S3, naltrexone's effect on response rate was not paralleled by an increase in shocks received, but neither was there any evidence of naltrexone-reversal of ethanol's effect on shocks received.

DISCUSSION

Although the results of Experiment 1 were complex, a number of consistent effects were observed. First, contrary to the findings of Reynolds and van Sommers [28] ethanol did not produce an increase in response rate or a reduction in shock rate for any of the animals tested at any dose. Instead, an impairment of avoidance performance was observed in all three animals at all doses where any effect was observed. Decreased response rates were seen in 2 out of 3 subjects, and increased shock rates were seen in all 3 subjects as a

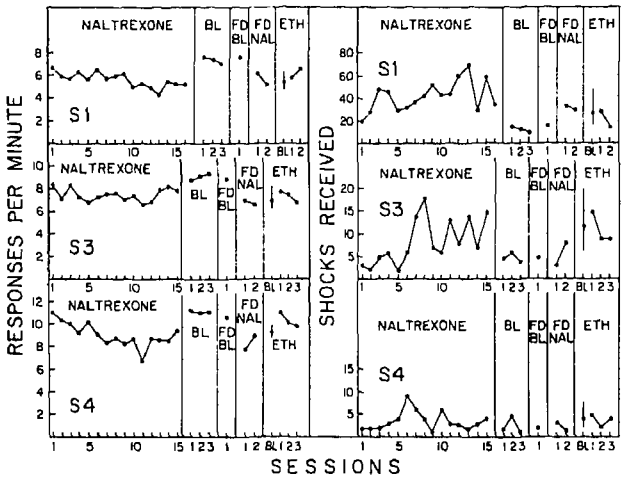

FIG. 2. Responses per minute and total shocks received during the sessions of Experiment 2. Panels labeled "Naltrexone" represent data collected during the chronic naltrexone (6 mg/kg) regimen with responses per minute in the left panels and shocks received in the right-hand panels. Data for S1 are presented in the top panels, S3 in the middle, and S4 in the lower panels. Panels labeled "ETH" indicate the results of the ethanol (1 g/kg) test sessions, and also include the mean and range of responses and shocks obtained in response to 1 g/kg ethanol in Experiment 1 (label "BL" on the abscissa). The panel labeled BL indicates the outcomes of the drug free sessions run following the chronic procedure, and the panels labeled "FD NAL" and "FD BL" represent the results of the sessions obtained while animals were food deprived with and without naltrexone administrations, respectively.

dose-dependent function of ethanol. Naltrexone alone also produced an impairment of avoidance performance in all three subjects. Of particular interest, the present findings did not show any naltrexone reversal or reduction of any ethanol effect. Indeed, the ethanol-naltrexone combination generally produced additive effects. In conditions where ethanol produced a performance decrement, impairment became even more pronounced when naltrexone was also administered.

The failure to obtain stimulatory effects of ethanol on Sidman avoidance performance is actually consistent with other studies of free-operant avoidance which reported depressed rates of avoidance across the effective range of ethanol doses [17,22]. In fact in the one study which found stimulatory effects on free-operant avoidance [28], the effects were modest, and occurred in only 2 of the 3 rats tested. However, in other procedures involving aversively-motivated behavior, ethanol doses comparable to those administered in the present study produce reliable stimulation of responding (i.e., shuttle-avoidance [13] jump-up avoidance extinction [3,14]). It would be of considerable interest to determine why these different types of shock-motivated behavior are affected so differently by the same dose of ethanol.

The present results provided no support for the common-link hypothesis. The absence of a naltrexone-ethanol interaction runs counter to what would be expected if the effects of ethanol on avoidance behavior were mediated by the opiate receptor system. The fact that in most cases naltrexone effects appeared to add to the effects of ethanol argues even more strongly against the notion that ethanol and naltrexone stand in an agonist/antagonist relationship, at least with regard to the effects of ethanol studied here.

There are, however, a number of alternative explanations of the present failure to find ethanol effects to be naltrexone-reversible. One possible account which suggested an empirical test is the finding of several investigators that genetic sensitivity to morphine and ethanol are related [20,30]. It is possible that Sprague-Dawley rats in general, or perhaps the particular rats used in the present study were relatively insensitive to opioids. In Experiment 2 we exposed these animals to a procedure designed to enhance sensitivity to opioids in order to determine whether such sensitivity would transfer to ethanol. Recent studies of the effects of chronic administration of opiate antagonists have suggested that animals become more sensitive to opioid agonists and antagonists after a chronic opiate receptor blockade, and that this "supersensitivity" may relate to an increase in the number of opiate receptors [23, 24, 35]. Thus, in Experiment 2, the subjects were exposed to chronic administration of naltrexone and their ethanol-sensitivity was then tested. If the effects of ethanol on avoidance are indeed mediated by the opioid system, then chronic administration of naltrexone should make animals more sensitive to morphine and opiate antagonists. Finally, Snell *et al.* [32] in a recent study, found that supersensitivity to the impairment of avoidance performance induced by naloxone was eliminated by food deprivation. In order to further examine the role of the feeding state of the organism in determining the effects of opiate antagonists, we tested subjects under ad lib feeding conditions (as in Experiment 1), and then later after food deprivation.

EXPERIMENT 2

METHOD

The same animals used in Experiment 1 served in the second experiment. The procedures of Experiment 2 began on the first scheduled drug day (Wednesday or Friday) after the last drug day of Experiment 1. As in Experiment 1, rats were tested five days per week on a Sidman avoidance schedule with a response-shock interval of 20 sec and a shock-shock interval of 5 sec. All parameters of the schedule were identical to those used in Experiment 1. However, in Experiment 2 the rats were exposed to a chronic opiate receptor blockade. This was accomplished by daily IP injections of 6 mg/kg of naltrexone. Higher doses of naltrexone were used in Experiment 2 to prolong the receptor blockade. During the week the naltrexone injection always preceded the beginning of the avoidance session by 10 min, and injections were also given at approximately the same time of day on weekends. Thus, during the initial phase of Experiment 2, each animal received 6 mg/kg naltrexone every 24 hr. At several points during the chronic naltrexone procedure, ethanol test probes were administered. Ethanol probes consisted of a two-day suspension of the chronic naltrexone procedure. First, a baseline session (no injections at all) was conducted to permit the naltrexone to be eliminated from the animal's system. The next session was preceded by injection of 1 g/kg of ethanol 30 min prior to the onset of the avoidance schedule. Following the ethanol session animals were returned to the chronic naltrexone regimen. For subjects S3 and S4, three Ethanol probes were conducted: one,

after 13 chronic naltrexone days, a second, after the 25th chronic naltrexone day, and the third after the 30th chronic naltrexone day. Subject S1 received only 2 ethanol probes: the first following 20 chronic naltrexone days, and the second after the 30th chronic naltrexone day.

After the final ethanol probe session, naltrexone administration was discontinued, and all three rats were exposed to three baseline sessions. Following the recovery of baseline, the rats were food-deprived and brought to 90% of their ad lib body weights. Avoidance sessions continued during the food deprivation period but three test sessions were conducted after animals had come within 1% of the target weight. The first and last test sessions were preceded by an injection of 6 mg/kg naltrexone 10 min prior to the onset of the session, and the second test session was preceded by an injection of saline vehicle to provide a control data point for the food-deprivation conditions.

RESULTS

The main results are presented in Fig. 2 which shows responses per minute (left-hand panels) and shocks per 2-hr session (right-hand panels) for the conditions for Experiment 2. The effects of the chronic naltrexone regimen on avoidance behavior are shown in the panels labeled "Naltrexone" for each subject. Plotted are the data from sessions which took place Tuesdays through Fridays (Monday sessions and sessions which followed probe days were excluded from analysis—thus, only 15–16 Naltrexone sessions are presented). The effects of naltrexone can be contrasted with data obtained after the chronic naltrexone conditions: the baseline recovery period, labeled "BL" in Fig. 2. Naltrexone depressed response rates in all three subjects compared to baseline conditions (left-hand panels), and there was a tendency for an increased sensitivity to the rate decreasing effects of naltrexone to develop with repeated administration of naltrexone in S1 and S4. Enhanced sensitivity to naltrexone was even more marked when the shock data is also considered (right-hand panels). Consider number of shocks received for S1 across the repeated naltrexone sessions. Initially, S1 received more than his usual number of shocks per session (as compared to the BL period), but note the gradual deterioration of performance which becomes quite pronounced beyond Naltrexone session 10. This increased sensitivity to naltrexone is also seen as a slight, but progressive decline in response rates over the 16 plotted sessions. A comparable effect was seen in subject S3. For S3 the rate-decreasing properties of naltrexone were slight to begin with, and did not decline much during the course of the chronic naltrexone regimen (middle-left panel). Rather, the effects of naltrexone were most apparent in terms of shocks received which showed progressive increases with repeated naltrexone administration (middle-right panel). Finally, subject S4 showed only an occasional increase in number of shocks received, and the effect of chronic naltrexone was primarily detected as a decrease in response rate (bottom panels). These effects cannot be attributed to non-specific performance factors (although all three rats lost between 5 and 30 g during the 30 day naltrexone regimen) because of the clear recovery of normal baseline performance on sessions when no naltrexone was administered (BL) for all three subjects.

The results of the ethanol probe sessions (1.0 g/kg) are labeled ETH in Fig. 2. In addition to the probe sessions (numbered according to the sequence given), the mean and range of the Ethanol 1.0 g/kg conditions of Experiment 1 are presented for each subject for comparison purposes in the same panel. The two ethanol probes for S1 failed to reveal any enhanced sensitivity to ethanol due to chronic naltrexone treatment. The results of the first probe session (which followed 20 days of naltrexone administration) were well within the range of the previous ethanol data both for response rate (left panel) and shocks (right panel). The second probe session, which followed 30 days of naltrexone, seemed to reveal even less sensitivity to ethanol than that seen in Experiment 1, with shock and response rates intermediate between the Experiment 1 data and the no drug sessions of Experiment 2. Similar results were apparent for subjects S3 and S4. S3 was within the range of the Experiment 1 results for response rate and shocks on all three probes (which followed 13, 25, and 30 days of chronic naltrexone, respectively), and S4, if anything, was slightly less sensitive to ethanol than was apparent in Experiment 1.

The final phase of Experiment 2 involved an examination of the modulation of naltrexone sensitivity by the feeding state of the rats. The results of this phase are also shown in Fig. 2. Plotted under the label: "FD NAL" are the outcomes of the two sessions where 6 mg/kg naltrexone was administered to the animals while deprived of food, while under the label: "FD BL" is shown the outcome of the session where saline vehicle was administered to the food-deprived rats. As Fig. 2 shows, naltrexone effects were essentially unchanged by the food-deprivation procedure. All three subjects showed rate-decreases comparable to those produced in the undeprived state, and shock-rate increases were apparent in S1 and S3. Thus, food-deprivation did not abolish the ability of naltrexone to impair avoidance performance in the present study. Note also that food-deprivation itself did not affect avoidance performance (FD BL).

DISCUSSION

The main finding of Experiment 2 was that sensitization to naltrexone produced by daily administration of 6 mg/kg did not lead to increased sensitivity to the effects of ethanol. Although no direct measure of brain opiate receptors was taken in the present study, previous research has shown that chronic administration of naltrexone results in increased numbers of opiate receptors [24,35], and increased sensitivity to morphine as well as to opiate antagonists [23,34]. Thus, the failure of chronic naltrexone to enhance ethanol sensitivity may be taken as lack of support for the hypothesis that ethanol effects on avoidance are mediated by the opioid receptor system. It would be of interest to examine other ethanol effects in animals whose sensitivity to opiates has been enhanced by chronic naltrexone treatment, and perhaps to study a broader range of ethanol doses in this regard.

The increased sensitivity to the avoidance-impairment effects of naltrexone after chronic treatment provides a replication of other studies showing sensitization to the effects of opiate antagonists [23,32]. In the present study 6 mg/kg per day was sufficient to produce the sensitization effect, and it was apparent that the effect is progressive, since animals seemed to become increasingly sensitive to the effects throughout the 30-day chronic naltrexone procedure. Finally, the present study was not consistent with the that of Snell *et al.* [32] with regard to the interaction of naltrexone sensitization and food deprivation. Unlike Snell *et al.*, food-deprivation did not block naltrexone sensitization in the

present study. A possible explanation for the discrepancy between the two studies is that we took our subjects to 90% of their normal body weight, while Snell *et al.* brought their animals down to 80%. Perhaps a more extreme level of food deprivation is necessary to obtain the effects noted in the Snell *et al.* study.

GENERAL DISCUSSION

Taken together, the two experiments reported here did not support the notion that ethanol-induced impairment of free operant avoidance behavior is mediated by an opioid substrate. In Experiment 1 naltrexone failed to reverse or reduce ethanol induced impairment at any dose of ethanol, and seemed to add to the ethanol-induced impairment under some conditions. Experiment 2 showed that sensitization to naltrexone produced by chronic administration does not result in any transfer of heightened sensitivity to ethanol.

Although the present findings did not support the notion of a "common link" between ethanol and opioids, there were a number of limitations which should be considered. We did not observe ethanol stimulation of behavior at any dose level in the present study, and it may be that the motor stimulation effect of ethanol is more sensitive to reversal by opiate antagonists [31]. It would be of interest to develop an operant paradigm which permits analysis of the biphasic effects of ethanol in order to examine this possibility. Naltrexone was always administered after ethanol in the present study and it may be that the other order is more likely to reveal an interaction, but, in at least one study designed to test this hypothesis, order of administration did not matter [5].

An interesting aspect of the present results was the impairment of avoidance produced by naltrexone (3 or 6 mg/kg). Snell *et al.* [32] noted a similar disruption of avoidance following naloxone administration, but only after previous exposure to high doses of naloxone and only when animals were receiving ad lib food. The present studies, however, observed impairment of avoidance by naltrexone without any pretreatment and independently of the animal's feeding schedule. Consistent with Snell *et al.* though, Experiment 2 did reveal a sensitization to naltrexone's disruptive action with chronic administration. The mechanism of naltrexone disruption of avoidance remains unclear. Kelleher and Goldberg [23] showed that naloxone depressed bar-press rates maintained by food reinforcement in monkeys, and also noted that sensitivity to this effect was enhanced by chronic administration. They considered the effect to involve a nonspecific depression of response rate, and such an account may be appropriate here (see also [26]). However, naltrexone did not suppress response rates in recent studies of appetitive operant behavior in rats [29,33], and studies involving aversive control have shown that opiate antagonists may enhance performance on such tasks, presumably because opioid-mediated analgesia is reversed by the antagonist ([7]). The impaired avoidance produced by naltrexone in the present study is not necessarily incompatible with an account in terms of an opiate-specific hyperalgesia. For example, Fanselow and Bolles [12] found that naloxone enhanced post-shock freezing tendencies in the rat. Since freezing is incompatible with bar-pressing, such an effect in the context of a free-operant avoidance schedule could have produced the impaired avoidance which we observed.

ACKNOWLEDGEMENTS

The authors thank Michael Perone for advice on software development and comments on the manuscript. The assistance of Julian Keith and Frank Stanley is gratefully acknowledged.

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