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ORIGINAL INVESTIGATION

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Naltrexone decreases craving and alcohol self-administration in alcohol-dependent subjects and activates the hypothalamo–pituitary–adrenocortical axis

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Abstract *Background*: This laboratory study investigated the mechanisms by which the opioid antagonist, naltrexone, reduces the risk of relapse to heavy drinking in individuals with alcohol dependence. *Methods*: Eighteen alcohol-dependent, non-treatment-seeking volunteers were randomized to 50 mg naltrexone or placebo for 6 days and participated in an alcohol self-administration experiment on the sixth day. Following baseline assessments of craving and endocrine levels, subjects were first administered a priming drink designed to raise blood alcohol levels to 0.03 g/dl and then had the opportunity to drink up to eight additional drinks or to receive US $3 for each drink not consumed over a 2-h period. Each additional drink was designed to raise blood alcohol levels by 0.015 g/dl. *Results*: At baseline, naltrexone treatment resulted in higher cortisol levels and lower levels of craving than placebo treatment. Although there were no significant differences in response to the priming dose, naltrexone-treated subjects drank fewer drinks, consumed them more slowly, and reported lower levels of alcohol craving during the alcohol self-administration portion of the experiment. Naltrexone also resulted in higher levels of adrenocorticotropic hormone and cortisol than placebo treatment, and levels of cortisol were negatively correlated with intensity of alcohol craving. The number of drinks chosen was positively correlated with level of alcohol craving. Ratings of nausea were low and did not differ between the naltrexone and placebo groups at any point in the study. *Conclusions*: These results confirm the hypothesis that naltrexone reduces desire to drink and the amount of alcohol consumed in alcohol-dependent subjects. It is hypothesized that naltrexone may reduce drinking via suppressing craving for alcohol and that this effect may be related in part to naltrexone's ability to activate the hypothalamo–pituitary–adrenocortical axis.

Keywords Naltrexone · Opiate antagonist · Alcohol dependence · Self-administration · Craving · Hypothalamo–pituitary–adrenocortical (HPA) axis · ACTH · Cortisol · Laboratory paradigms · Neuroendocrine response · Drinking

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Introduction

A possible role for the endogenous opioid system in alcohol dependence has been supported by the discovery that the opiate antagonists naltrexone and nalmefene can help detoxified alcoholics drink less frequently and decrease the likelihood of heavy drinking (O'Malley et al. 1992, 1995; Volpicelli et al. 1992, 1997; Mason et al. 1994, 1999; Anton et al. 1999). One of the most interesting findings from these studies is that individuals who experience a lapse in abstinence are less likely to drink heavily if they are on naltrexone rather than placebo. Although suppression of craving in response to alcohol cues and following an initial drink has been hypothesized to mediate these beneficial effects, the reported findings regarding naltrexone's effects on craving have been equivocal, perhaps due to the retrospective collection of the assessments and the use of single-item analogue scales to measure craving in many clinical trials.

A number of human laboratory studies using alcohol administration have been conducted in an effort to understand the mechanism of naltrexone's efficacy in alcoholism (Swift et al. 1994; Doty and de Wit 1995; Davidson et al. 1996, 1999; Doty et al. 1997; King et al. 1997; McCaul et al. 2000). The majority have examined the effects of acute naltrexone administration on subjective and cognitive responses to fixed dosages of alcohol. Using social drinkers, Doty and colleagues (Doty and de Wit 1995; Doty et al. 1997) did not observe effects of acute administration of naltrexone on responses to a

range of alcohol doses (placebo, 0.25 g/kg, 0.5 g/kg, and 0.75 g/kg). However, other studies have noted that acute administration of naltrexone, compared with placebo, reduced the stimulating effects and increased the sedative effects of alcohol (Swift et al. 1994; King et al. 1997). More recently, McCaul and colleagues (McCaul et al. 2000) examined the effects of chronic dosing with three doses of naltrexone (placebo, 50 mg, 100 mg) in interaction with three doses of alcohol (0.0, 0.5, 1.0 g/kg) in heavy drinkers. Chronic naltrexone significantly increased subjective ratings of sedative effects and decreased ratings of liking, best effects, and desire to drink, particularly at the high doses of naltrexone and alcohol. High rates of nausea were also reported in these studies following naltrexone treatment alone or in interaction with alcohol. On the basis of these studies, it has been proposed that naltrexone may reduce the amount consumed through actions that make alcohol less reinforcing and perhaps even aversive.

The preceding studies employed administration of fixed doses of alcohol over a predetermined time period (e.g., 5 min per drink). Laboratory studies in which the subject is permitted to self-administer alcohol may provide a better parallel to the clinical situation in which patients typically control the rate and amount of alcohol that they consume. In a study of social drinkers allowed to drink in a naturalistic bar setting, Davidson et al. (1996) found that chronic pretreatment with naltrexone reduced the latency to drink alcohol but not the number of drinks or the latency to finish the drink. Using this same paradigm but with heavy drinkers (Davidson et al. 1999), naltrexone was shown to reduce the number of drinks consumed and the desire to drink.

To date, all of these studies have been conducted in social or heavy drinkers, thereby precluding an examination of naltrexone's effects on craving for alcohol and drinking in dependent subjects, the group for whom naltrexone is currently indicated. Thus, the current study was designed to evaluate the effects of chronic naltrexone on alcohol craving and drinking behavior in a sample of non-treatment-seeking, alcohol-dependent volunteers. Toward this end, we developed a laboratory paradigm in which subjects consumed a "priming" drink and were then given the opportunity to self-administer up to eight additional drinks at their own pace or to retain US $3 for each drink not consumed. In this way, the paradigm was designed to model the effects of an initial lapse in abstinence on continued drinking during the self-administration period, an effect that naltrexone has been shown to reduce in previous clinical trials.

A secondary aim of the study was to examine the effects of chronic naltrexone alone and in interaction with alcohol on measures of hypothalamo–pituitary–adrenocortical (HPA) axis activity, including adrenocorticotropic hormone (ACTH), cortisol, and prolactin, in order to glean preliminary information about some of the neurobiological effects of naltrexone. The actual neurobiological mechanism by which naltrexone has its effects on drinking is unknown. It has been hypothesized that naltrexone, by occupying brain opioid receptors, may prevent stimulation of these receptors by endogenous opioid peptides released after alcohol ingestion. Mu receptor-directed endogenous opioids have been shown to inhibit the tonic inhibitory regulation of dopaminergic neurons by γ-aminobutyric acid (GABA)-ergic afferents in the ventral tegmental area (Johnson and North 1992; Klitenick et al. 1992). This disinhibition of dopamine could presumably account for some of the reinforcing effects of alcohol (Widdowson and Holman 1992). By blocking opioid receptors, naltrexone may prevent the subsequent disinhibition of dopamine and thereby reduce the reinforcing effects of alcohol and the drive to continue drinking. Consistent with this hypothesis, alcohol-induced dopamine release is inhibited by perfusion of naloxone into the nucleus accumbens (Widdowson and Holman 1992).

Both acute and chronic opioid antagonist administration have also been found to increase peripheral blood levels of ACTH, beta-endorphin, and cortisol in healthy human volunteers as well as in former opiate-dependent persons and in alcohol-dependent individuals (Naber et al. 1981; Atkinson 1984; Kreek et al. 1984; Cohen and Cohen 1985; Kosten et al. 1986; Schluger et al. 1998). Chronic naltrexone blockade of opioid receptors has also been shown to stimulate proopiomelanocortin (POMC) peptide synthesis and release in rodent models (Jaffe et al. 1994). It also results in increased density and binding of mu opiate receptors but with no change in mu opioid receptor mRNA levels (Lahti and Collins 1978; Unterwald et al. 1995; Yoburn et al. 1995). These findings show that opioid antagonists activate the HPA axis, which results in a corresponding increase in circulating levels of ACTH, beta-endorphin, and cortisol. Interestingly, it has been shown previously that many alcoholics have suppressed basal HPA axis activity (Adinoff et al. 1990; Inder et al. 1995) and to have less HPA activation in response to a number of functional tests (Berman et al. 1990; Wand and Dobs 1991; Vescovi et al. 1997). Thus, it could also be hypothesized that naltrexone-induced opioid-receptor blockade and the subsequent increase in HPA activity with increased ACTH and cortisol levels may be partially responsible for naltrexone's effects on alcohol drinking and craving.

Methods and materials

Participants

Eighteen non-treatment-seeking volunteers who met DSM-III (Diagnostic and Statistical Manual of Mental Disorders, 3rd edn.)-R criteria for alcohol dependence participated in an alcohol self-administration experiment on the sixth day of study medication (naltrexone or placebo). These subjects were tested as inpatients prior to and after 3 days of the study medication using a different fixed-choice paradigm in which alcohol could be chosen at fixed 30-min intervals and consumed within 5 min. However, overall consumption was very low in both groups (2.2 drinks, SD=1.3, all F values <1), suggesting that the paradigm was insensitive for testing the effects of naltrexone on drinking. For simplicity of pre-

sentation, we will only present data from the self-administration experiment.

Subjects who drank between 20 and 40 drinks per week and were abstinent for no more than 3 days per week on average were eligible. The upper limit of 40 drinks per week was used in order to recruit a sample whose typical drinking quantities would be unlikely to exceed the amount of alcohol that would be available for possible administration during the laboratory sessions. Individuals were also excluded if they were currently using psychotropic medications, had medical contraindications to naltrexone or alcohol, had a history of significant withdrawal symptomatology, or if they had a history of abuse or dependence on substances other than alcohol or nicotine. Consistent with the National Institute on Alcohol Abuse and Alcoholism National Advisory Council recommended guidelines for the administration of ethyl alcohol (National Council on Alcohol 1988), we made a concerted effort to encourage participants to seek treatment at the end of the study (Sinha et al. 1999).

The eight subjects who received naltrexone did not differ significantly from the ten subjects who received placebo on demographic or baseline drinking or smoking characteristics (all *P* values >0.10). The mean age of the sample was 27.2±7.5 years (mean±SD) and was primarily male (13 of 18) and Caucasian (14 of 18). In the 90 days prior to the study, as assessed using the Timeline Follow-back Method (TLFB; Sobell and Sobell 1992), subjects reported drinking on 82±17% of the days and consumed an average of 5.8±2.1 drinks per drinking occasion. Of the 18 subjects, 5 (1 naltrexone, 4 placebo) were cigarette smokers and reported smoking 31±21.3 cigarettes per day on average. Measures of socioeconomic status, including occupational level, employment status, and educational level, were also comparable. Of the 18 subjects, 11 (61%) were employed either part or full-time, 4 (22.2%) were unemployed, and 3 (16.7%) were students. Over half (10) had completed college, five (27.8%) had completed partial college, and three (16.7%) had completed high school.

Procedures

Intake sessions

Written informed consent was obtained from all participants at the initial intake appointment. The *Structured Clinical Interview for DSM-III-R* (Spitzer and Williams 1985) was used to assess diagnostic criteria for alcohol and other substance use disorders. The TLFB (Sobell and Sobell 1992) was used to obtain information about drinking during the prior 90 days. A physical examination; laboratory assessments including urine toxicology, liver function tests, and a pregnancy test for women; and a psychiatric evaluation were completed in order to determine eligibility.

Medication conditions

Eligible subjects were randomly assigned to either 50 mg naltrexone daily or a matching placebo for 6 days. Both naltrexone and placebo capsules contained 50 mg riboflavin, and ultraviolet detection of riboflavin fluorescence in the urine was used to assess medication compliance on the sixth day. Both subjects and investigators were blind to the medication condition. Subjects were instructed to take their medication at 1000 hours each day. On the sixth and final day of taking study medication, subjects were admitted to the General Clinical Research Unit at Yale-New Haven Hospital at approximately 1230 hours for the laboratory session, during which they were tested individually.

Baseline assessment period

Upon admission, urine toxicology and breath alcohol levels were obtained to confirm that subjects were abstinent. Presence of riboflavin in the urine was verified using a hand-held ultraviolet light by the research coordinator (Dr. Krishnan-Sarin) and subjects whose urine did not fluoresce were not allowed to participate in the drinking paradigm. No subject was excluded for noncompliance as measured using riboflavin. Time of dosing that day was confirmed by self-report. Information about drinking during the 5-day pretreatment period was also obtained. No smoking was permitted from this time forward. An i.v. cannula was inserted at 1430 hours. At 1530 hours, baseline reports of alcohol craving were obtained using the Alcohol Urge Questionnaire (AUQ) (Bohn et al. 1995). Blood was drawn at 1555 hours (6 h after oral naltrexone administration) for baseline assays of cortisol, ACTH, and prolactin.

Priming dose period

The alcohol administration procedures began at 1600 hours (6 h after the last oral dose of naltrexone or placebo). Subjects were provided with a priming drink designed to raise blood alcohol levels (BALs) to 0.03 g/dl and were instructed to consume it within 5 min. This drink was mixed using their preferred liquor (80 proof) and fruit juice in a 1:3 ratio. The volume of alcohol was determined using a formula based on the sex, age, and body weight of the subject (Watson 1989). The AUQ was administered 10, 20, and 30 min following the onset of the priming drink. Plasma samples were obtained for assays of ACTH, cortisol, and prolactin, and for measurement of BALs at each of these time points and at 40 min.

This priming drink was included in order to measure responses to a fixed dose of alcohol, to normalize drinking in the laboratory environment, and to model the influence of a first drink on subsequent drinking in the self-administration paradigm. The 40-min observation period for the priming dose was selected to determine whether naltrexone modified responses to the priming drink, while not being so long as to have BALs drop significantly prior to additional opportunities to consume alcohol.

Alcohol self-administration period

Following the priming drink, participants were exposed to two consecutive 1-h alcohol self-administration periods (choice blocks 1 and 2). In each hour, participants were provided with a tray of four drinks (each designed to raise BALs 0.015 g/dl) and a “tab” in which each drink was worth US $3, approximating the cost of a drink purchased in a neighborhood bar. Subjects were instructed that they could choose to drink as many of the drinks as they desired over the next 60 min or to receive the corresponding dollar amount the next morning for drinks that they did not consume. At the end of the first hour, the remaining drinks were removed; the second tray of four drinks was then brought in and the instructions repeated. Thus, subjects could drink up to eight drinks or earn up to US $24 depending on how many drinks they declined. Money was provided as an alternative reinforcer in order to provide some incentive for not drinking and to enhance the likelihood that the effects of naltrexone on the reinforcing value of alcohol would be detected. The inclusion of this alternative reinforcer was felt to be important because subjects in the laboratory study were not treatment seeking, whereas those in the clinical trials of naltrexone were treatment seeking and presumably motivated to abstain. In addition, the availability of alternative reinforcers can provide a sensitive test of the relative reinforcing value of alcohol or other drugs and of the effects of medications on the reinforcing value of the abused substance (Epstein et al. 1991; Carroll 1993; Higgins 1997; Rodefer et al. 1997).

The AUQ and blood samples for measurement of BALs and endocrine levels were obtained every 30 min during the alcohol self-administration period. The subject was left undisturbed between assessments and the sessions were videotaped for later analysis of drinking behavior. At the end of the second hour, any remaining drinks were removed. After the i.v. was removed, the subject was brought dinner and remained in the hospital overnight.

Smokers were provided with access to nicotine gum if they so desired for the rest of the evening. On the following morning, the participant met with one of the investigators who provided feedback and information about the participant's heavy drinking patterns in an effort to motivate participants to seek treatment (Sinha et al. 1999).

Subjects were paid US $50 for completing the intake and outpatient phases and US $150 for completing the inpatient alcohol self-administration experiment on day 6, during which they could earn an additional US $24 depending on the number of drinks declined.

Dependent measures

Timeline follow-back method

The TLFB method (Sobell and Sobell 1992) was used to obtain information about the number of drinking days and the number of drinks consumed per drinking occasion during the 5 days of treatment with either naltrexone or placebo prior to the laboratory session, which occurred on the sixth day of medication.

Number of drinks consumed during each hour of the ad lib drinking period was the primary dependent measure. In addition, videotapes were reviewed later in order to determine behavioral measures of drinking. Raters recorded the time from the presentation of the drinks to the first sip and the time between sips within each tray. Number of sips per drink was computed as the total number of sips taken divided by the number of drinks consumed during the 2-h ad lib period. Inter-sip interval was an average of the time until the first sip following presentation of the tray of drinks and the times between each subsequent sip up until the last sip within a tray. These times were averaged across trays to obtain an inter-sip interval score. Time to the first sip was not examined separately, since the ad lib drinking occurred in the context of having already consumed the priming dose.

Alcohol urge questionnaire

This 8-item self-report measure, the AUQ (Bohn et al. 1995), was designed to assess an individual's desire to drink alcohol right now. Items are rated on a seven-point Likert scale with responses ranging from "strongly disagree" to "strongly agree", and a total score is derived from the sum of these items following reverse scoring of two items. The AUQ was inadvertently omitted from the assessments administered to two subjects, one in each medication condition.

Nausea during the experimental session was rated on a visual analogue scale from "0=not at all" to "100=extremely".

Blood alcohol levels

Samples for BALs taken during the laboratory session were refrigerated (40°C) in air-tight vials and analyzed within 1–2 weeks of collection. BALs were analyzed using gas chromotographic techniques [Smith Kline Beecham Clinical Laboratories, Philadelphia, Pa.; reportable limit of 0.005 g/dl (%)].

Endocrine measures

Blood samples for ACTH, cortisol, and prolactin were split into three heparinized tubes (0.15 µl heparin) and placed on ice immediately after blood drawing. Within 15 min of collection, blood was centrifuged at 4°C and the serum transferred to a microtube and stored at –20°C. The ACTH, cortisol, and prolactin assays were performed at Dr. Kreek's laboratory at Rockefeller University using standard radioimmunoassay procedures within 2 months of collection. The sensitivity of the ACTH and cortisol assays, respectively, are 1 pg/ml and 0.22 µg/dl. The intra-assay coefficient of variation is 9.4% for ACTH and 2.9% for cortisol. The inter-assay coefficient of variation is 15.1% for ACTH and 6.0% for cortisol.

Statistical analyses

The two medication groups were compared on demographic and drinking characteristics using one-way analyses of variance for continuous variables and Chi-Square Fisher's Exact Test for categorical variables. These methods were also used to compare the two groups on pre-alcohol baseline measures of the AUQ, ACTH, cortisol, and prolactin. Analyses of data obtained following alcohol consumption were completed separately for the priming dose period and for the ad lib drinking period. After testing for homogeneity of regression slopes (Tabachnick and Fidell 1993), repeated-measures analyses of covariance were performed using the pre-alcohol baseline value of the dependent measure as a covariate. The assumption of homogeneity of regression slopes between the covariate and the dependent variable within treatment groups was met for AUQ, ACTH, and cortisol. It was not met for prolactin. Since the two medication groups did not differ significantly on prolactin at the pre-alcohol baseline, repeated-measures analysis of variance was used for prolactin with the baseline entered as a time point rather than as a covariate. BALs were analyzed using repeated-measures analysis of variance. In order to examine the relationship between the variables that distinguished the naltrexone- and placebo-treated groups, measures of area under the curve (AUC) were computed. The associations between these variables were explored using Pearson correlation coefficients. Analyses of individual peak levels were not possible because of the limited ob-

Table 1 Significant results from analyses of craving, drinking behavior, blood alcohol level (BAL) and endocrine measures, as well as mean±SEM for medication main effects. *ACTH* adrenocorticotropic hormone, *AUQ* Alcohol Urge Questionnaire

Time period	Dependent variable	Naltrexone mean±SEM	Placebo mean±SEM	Significant effect	*F* value	df	*P* value
Baseline	AUQ[a]	13.9±1.2	22.7±3.3	Medication	5.17	1, 16	0.039
	Cortisol[a]	11.5±2.0	6.5±0.8	Medication	6.29	1, 16	0.023
Ad lib	Drinks per hour[b]	1.9±0.7	4.6±0.9	Medication	5.66	1, 16	0.030
	Inter-sip interval[a]	4.91±0.59	2.7±0.27	Medication	15.30	1, 13	0.002
	BAL[b]	0.018±0.004	0.045±0.005	Medication	5.11	1, 16	0.038
				Medication × time	3.91	3, 48	0.014
	AUQ[c]	12.69±1.66	20.60±1.43	Medication	4.72	1, 13	0.049
	ACTH[c]	13.27±1.11	8.46±0.99	Medication	5.02	1, 15	0.041
				Baseline ACTH[d]	38.62	1, 15	0.000
	Cortisol[c]	11.80±0.91	5.63±0.80	Medication	9.04	1, 15	0.009

[a] One-way analysis of variance
[b] Repeated-measures analysis of variance
[c] Repeated-measures analysis of covariance; least squares means are presented
[d] Baseline ACTH was significant as a covariate in this analysis

servation period for the priming dose and because the assessments during the ad lib period were too infrequent to permit an accurate determination of peak levels. The results of the statistical tests for significant effects and the means for significant medication main effects are provided in Table 1.

Results

Drinking behavior during naltrexone/placebo pretreatment period

As described earlier, subjects were outpatient for 4 days of the 5 days prior to the self-administration study, which took place on the sixth day of taking study medication. Indices of drinking during this pretreatment period were compared between groups using TLFB reports of drinking for the four outpatient days. The number of days on which alcohol was consumed during this period did not differ between the two medication conditions (F<1). On average, subjects drank alcohol on 2.56± 1.29 days (mean±SEM). With regard to the number of drinks consumed per drinking occasion during this period, placebo-treated subjects drank 6.14±1.50 drinks, whereas naltrexone-treated subjects consumed 3.27±1.29 drinks. This difference did not reach statistical significance ($F_{1,16}$=2.78, P=0.12).

Baseline pre-alcohol measures

The significant results of the one-way analyses of variance comparing the naltrexone and placebo groups on the pre-alcohol assessments of the primary dependent measures are presented in Table 1. As can be seen, the naltrexone-treated group had significantly lower levels of craving at baseline (P<0.05) than the placebo group as measured using the AUQ 30 min prior to administration of the priming drink. With respect to the neuroendocrine measures taken 5 min prior to the priming drink, the groups were comparable on ACTH. However, naltrexone-treated subjects had higher levels of cortisol than placebo-treated subjects (P<0.05). Although there was a trend for prolactin levels to be lower for the naltrexone group (5.66±0.98) than the placebo group (8.10±0.62), this difference was not significant ($F_{1,16}$=3.92, P=0.07). No differences were found on self-reports of nausea.

Priming dose period

The BALs (Fig. 1A) achieved as a result of the priming dose did not differ between the naltrexone and placebo groups in the repeated-measures analysis of variance. There was a significant effect of time in which BALs increased over time (P<0.0001). The average BALs (±SEM) at 10, 20, 30, and 40 min were 0.008±0.002, 0.026±0.002, 0.025±0.001, and 0.022±0.001 g/dl, respectively. The average BAL over the priming dose period was 0.02±0.001 g/dl.

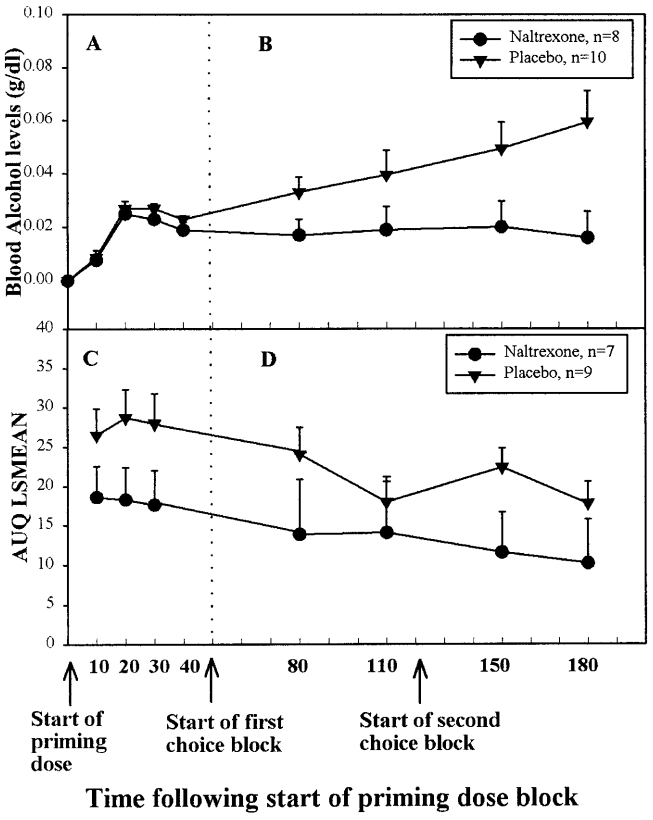

Fig. 1 Blood alcohol levels and craving (Alcohol Urge Questionnaire; AUQ) scores measured before and after a priming drink of 0.3 g/dl (*left panels*) and during an alcohol self-administration period during which subjects had the opportunity to drink up to four drinks (0.15 g/dl) in each of 2 h (*right panels*). Analyses of the priming dose period and of the self-administration period were completed independently. The naltrexone-treated (50 mg) group is represented by *circles*; the placebo-treated group by *triangles*. **A**, **B** Blood alcohol levels during the priming dose and the alcohol self-administration period. **C**, **D** AUQ least squares (mean±SEM) during the priming dose period and the alcohol self-administration period covaried with the –30-min pre-alcohol baseline. Naltrexone n=7, placebo n=9

There were no significant main effects of medication group or significant interactions of medication and time for any of the other dependent variables measured during the priming dose period. Specifically, the two medication groups had comparable levels of nausea, ACTH, cortisol, and prolactin. Craving during the priming dose was somewhat lower for the naltrexone group, but this was not statistically significant ($F_{1,13}$=2.83, P=0.12; Fig. 1C).

Alcohol self-administration period

Drinking behavior

During the 2-h alcohol self-administration period that followed the priming drink, subjects could elect to consume up to four additional drinks during each hour, for a possible total of eight drinks. The number of drinks consumed was analyzed with medication as a between-subjects factor and choice block (first, second) as a within-

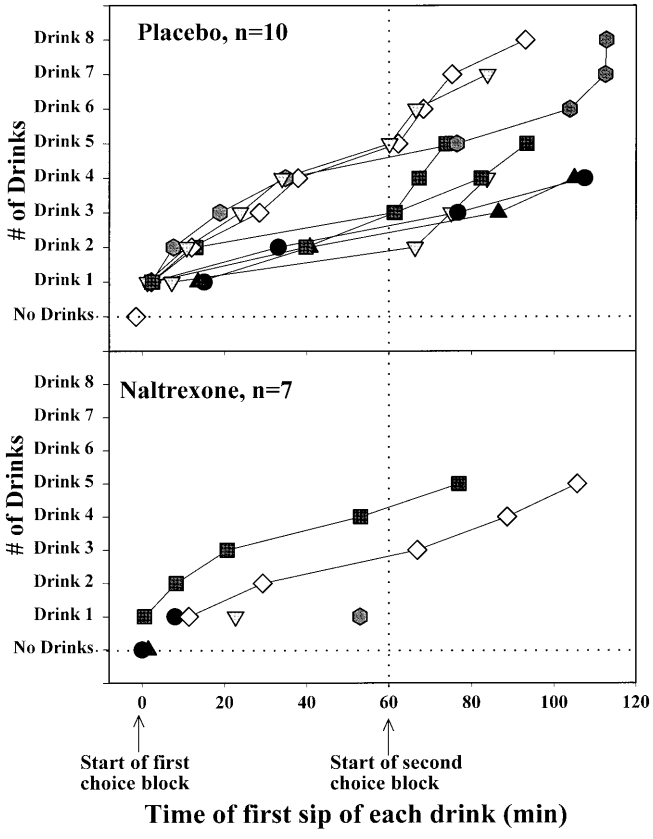

Fig. 2 Cumulative number of drinks consumed over time during the self-administration period by individual subjects within the placebo-treated group (*top graph*) and the naltrexone-treated group (*bottom graph*). Subjects could choose to drink up to four drinks (0.15 g/dl) from each of two trays of drinks for a total of eight possible drinks. Tray 1 was available for 1 h and then was replaced with tray 2 for the second hour. Time is graphed continuously in minutes from the presentation of the first tray of drinks, and the *symbols* indicate the time of the first sip of each drink. Because of a tape failure, one subject in the naltrexone-treated group, who consumed one drink from tray 1 and one drink from tray 2, is not included in this graph

subjects factor. A significant (P<0.05) main effect of medication condition was found in which placebo-treated subjects chose to drink 4.6±0.85 drinks compared with only 1.9±0.72 drinks for the naltrexone-treated subjects over the course of the 2-h period. The interaction of medication condition and choice block approached the level of a trend ($F_{1,16}$=2.77, P=0.12). Although the number of drinks consumed by the naltrexone-treated subjects (1.25±0.48) was somewhat lower than that of the placebo-treated subjects (2.20±0.043) during the first hour, differences in drinking were more pronounced during the second hour (naltrexone 0.65±0.45; placebo 2.40±0.41). The main effect of choice block was not significant (P=0.40).

In order to illustrate the drinking behavior of subjects during the self-administration session, Fig. 2 graphically presents the time of the first sip of each drink consumed during the 2-h self-administration period for individual subjects within the naltrexone and placebo groups. One naltrexone-treated participant who consumed a total of two drinks, one during each choice block, is not included in the graph because the tape recording failed. As can be seen, most subjects in the placebo group continued to drink into the second hour of the experiment, while only a minority of the naltrexone group did.

Ratings of the number of sips per drink and the inter-sip interval were also analyzed for the subjects who consumed at least one drink during the self-administration period and had tape recordings available (n=14). The analyses revealed that, although both groups took an average of 6.4±0.67 sips to complete each drink, the inter-sip interval was significantly longer (Table 1, P<0.001) for subjects on naltrexone than subjects on placebo.

Blood alcohol levels

Consistent with the observed reduction in the number of drinks consumed and slower drinking rate, the BALs achieved by the naltrexone group during the alcohol self-administration period were significantly lower than in the placebo group (Table 1, Fig. 1B). Repeated-measures multiple comparison procedures indicated that, over time, BALs increased across the four time points for the placebo group ($F_{3,39}$=6.49, P<0.01) but not for the naltrexone group ($F_{3,39}$<1, *NS*). At the end of the study, the mean BAL of the naltrexone group was 0.016± 0.010 g/dl, whereas that of the placebo group was 0.060±0.012 g/dl. Of interest, the total amount of alcohol consumed over the course of the experiment for the placebo-treated subjects (the priming drink + 4.6 additional drinks on average during the ad lib period) was similar to the amount they typically drank per occasion during the 90-day baseline (5.8 drinks).

Subjective craving

During the ad lib drinking period, a main effect of medication was found for the AUQ (Table 1, Fig. 1D, P<0.05) in the analysis of covariance. Specifically, placebo subjects reported significantly higher craving for alcohol than naltrexone subjects.

Nausea

The analysis of variance for nausea ratings during the ad lib drinking period indicated that nausea did not differ significantly as a function of medication condition, time, or their interaction.

Endocrine measures

ACTH levels were significantly higher during the self-administration period for naltrexone than for placebo-treated subjects (P<0.05; Table 1, Fig. 3B). No other effects were significant for ACTH. A significant effect of

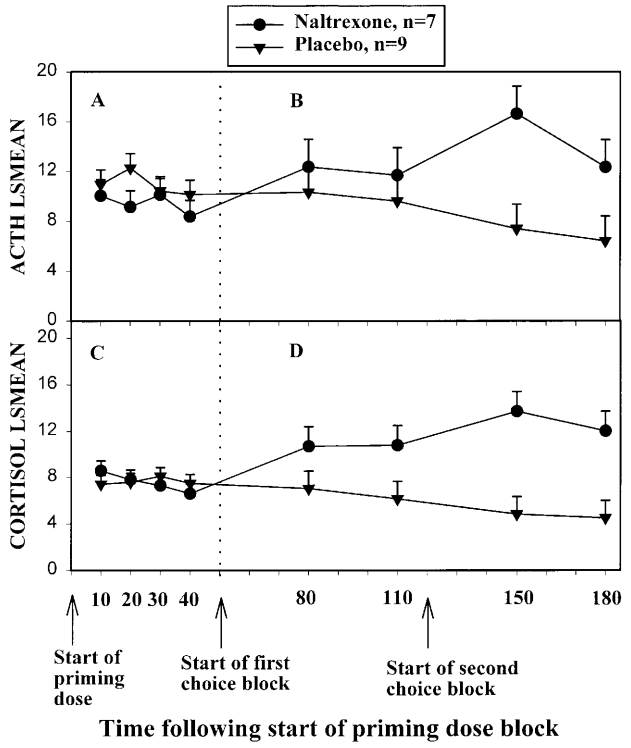

Fig. 3 Adrenocorticotropic hormone (ACTH) and cortisol levels after a priming drink of 0.3 g/dl (*left panels*) and during an alcohol self-administration period in which subjects had the opportunity to drink up to four drinks (0.15 g/dl) in each of 2 h (*right panels*). **A**, **B** ACTH least squares (mean±SEM) during the priming drink period and the alcohol self-administration period covaried for the –5 pre-alcohol baseline. Naltrexone *n*=8, placebo *n*=10. **C**, **D** Cortisol least squares (mean±SEM) during the priming dose period and the alcohol self-administration period covaried for the –5 pre-alcohol baseline. Naltrexone *n*=8, placebo *n*=10

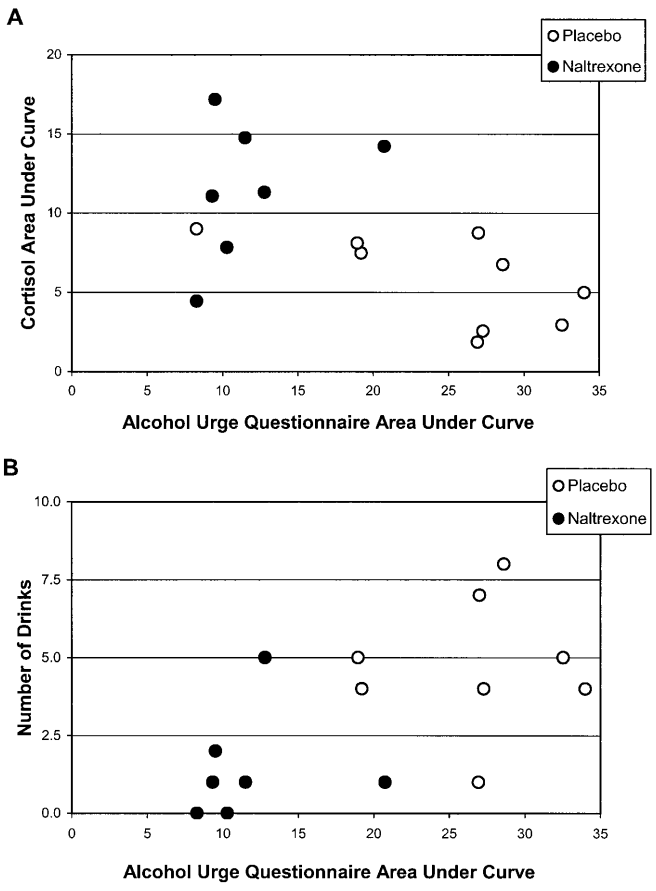

Fig. 4 **A** Scatterplot of the correlation between Alcohol Urge Questionnaire (AUQ) AUC scores and cortisol AUQ levels measured during the ad lib drinking period. **B** Scatterplot of the correlation between AUQ AUC scores and number of drinks chosen during the ad lib drinking period. The naltrexone-treated (50 mg) group is represented by the *closed circles* and the placebo-treated group is represented by the *open circles*

Table 2 Correlations among measures that were significantly different between naltrexone- and placebo-treated subjects. *ACTH* adrenocorticotropic hormone, *AUQ* Alcohol Urge Questionnaire, *AUC* area under curve

Time period	Dependent measures	Baseline		Ad lib period			
		AUQ	Cortisol	AUQ AUC	ACTH AUC	Cortisol AUC	Number of drinks
Baseline	AUQ	1.00					
	Cortisol	–0.35	1.00				
Ad lib period	AUQ AUC	0.68**	–0.50	1,00			
	ACTH AUC	–0.03	0.12	–0.17	1.00		
	Cortisol AUC	–0.53*	0.58*	–0.58*	0.32	1.00	
	No. of drinks	0.15	–0.05	0.65**	–0.16	–0.20	1.00

*P<0.05; **P<0.01; ***P<0.001

medication condition (P<0.01) was found for cortisol levels. Naltrexone subjects had higher levels of cortisol during the self-administration period than placebo-treated subjects (Table 1, Fig. 3D). The higher level of cortisol in the naltrexone group during ad lib drinking was remarkable given that the placebo group consumed significantly more alcohol, which would be expected to stimulate cortisol. Prolactin levels did not differ as a function of medication condition, time, or their interaction.

Correlations among measures discriminating naltrexone and placebo

Correlational analyses were used to explore the relationships between the variables that significantly discriminated between the naltrexone- and placebo-treated subjects in the preceding analyses. These included baseline cortisol and AUQ scores, and measures from the self-administration period including ACTH, cortisol, AUQ, and

the number of drinks chosen. (BAL was not included in the analyses because it highly correlated with the number of drinks chosen.) AUC (area under the curve) was computed for ACTH, cortisol, and AUQ during the alcohol self-administration period and was used as a summary measure in these correlational analyses. The resulting correlation coefficients are presented in Table 2. These analyses revealed that baseline AUQ scores were negatively correlated with cortisol levels during the ad lib drinking period (r=–0.53). Similarly, AUQ AUC during the ad lib period was negatively related to cortisol AUC (r=–0.58) during the same period such that lower levels of cortisol were associated with greater craving (AUQ) as presented in the scatterplot in Fig. 4A. Although subgroup analyses were not possible given the small sample size, visual inspection of the scatterplot suggests that this relationship between low cortisol and high craving is due principally to the placebo group. Finally, AUQ AUC during the self-administration period was significantly related to the number of drinks chosen (r=0.65) such that higher levels of craving were associated with greater alcohol consumption (Fig. 4B).

Discussion

The results of this laboratory study confirmed the hypothesis that naltrexone treatment reduces the amount of alcohol consumed and the urge to drink in alcohol-dependent individuals given a choice between alcohol and money. As such, these data support the finding of reduced alcohol consumption following a lapse in abstinence reported retrospectively among patients receiving naltrexone compared with placebo in the original naltrexone efficacy studies (O'Malley et al. 1992, 1995; Volpicelli et al. 1992). In the current study, subjects treated with naltrexone chronically for 6 days consumed fewer drinks following a priming drink and achieved lower BALs as a result of drinking less than subjects treated with placebo during the self-administration portion of the experiment. These results suggest that naltrexone may alter the relative reinforcing value of alcohol in alcohol-dependent subjects.

Naltrexone-treated subjects also consumed their drinks more slowly. Of interest, speed of drinking has been proposed as a behavioral measure of craving, and alcoholic subjects have been found to drink more quickly than non-alcoholics (Sobell et al. 1972; Rankin et al. 1979). While we cannot rule out the possible influence of baseline differences in speed of drinking, these data provide indirect evidence of naltrexone's attenuation of craving. On subjective reports of craving, naltrexone-treated subjects reported significantly lower levels of urge to drink than placebo-treated subjects at baseline prior to drinking. This suggests that naltrexone may have an effect on craving that does not depend directly on consumption of alcohol and that it may reduce craving in situations involving alcohol-related cues. This finding is consistent with that reported by McCaul et al. (2000) in which desire to drink measured immediately before alcohol administration was lower when subjects were on 50 mg naltrexone. However, participants in our study were permitted to drink during the 5 days prior to the laboratory session while they were taking the study medication, so it is conceivable that this previous experience may have contributed to the differences in baseline craving and subsequent drinking during the self-administration period.

Naltrexone also suppressed craving during the 2-h self-administration period when measured every 30 min relative to placebo. This was noteworthy given that alcohol was readily available during this period, and subjects knew alcohol would no longer be available that evening due to the overnight inpatient stay. The striking suppression of craving in the naltrexone group during the self-administration period and the observed correlation between craving during this period with the number of drinks consumed suggests that the effect of naltrexone on craving may be one factor that mediates the observed reduction in drinking. Whereas documentation of the hypothesized effects of opiate antagonists on craving has been elusive in prior clinical trials, the results of this study together with the findings of other laboratory studies (Davidson et al. 1999; McCaul et al. 2000) begin to provide convincing evidence that naltrexone can reduce craving or desire to drink. Confirmation of the hypothesized effect of naltrexone on craving is likely to be useful to clinicians in describing the potential benefits of naltrexone to alcohol-dependent patients seeking treatment.

Altered subjective responses and aversive interactions with alcohol are two additional mechanisms that have been proposed to account for the ability of opioid antagonists to reduce alcohol drinking. The effect of naltrexone on subjective responses to alcohol was not tested in this study because of the focus on craving and drinking behavior that led to the decision to limit the scope of the assessments. However, potential aversive interactions were assessed in a limited fashion by inclusion of a question regarding nausea. No differences were observed in nausea ratings between the naltrexone and placebo conditions at baseline or following alcohol consumption, whereas previous studies of social drinkers have reported increased nausea on days on which naltrexone was administered (Swift et al. 1994; Doty and de Wit 1995; Davidson et al. 1996, 1999; King et al. 1997). The discrepancy in rates of nausea between studies may be related to testing chronic, rather than acute, administration of naltrexone, differences in the drinking histories and ages of the subjects studied, and differences in the alcohol doses used. We have previously shown that among alcohol-dependent drinkers, younger age and lower levels of alcohol consumption are associated with increased risk of nausea from naltrexone (O'Malley et al. 2001). The choice of younger social drinkers in previous studies, rather than alcohol-dependent subjects as in the present study, may have contributed to the high rates of nausea reported. In addition, our study used a self-adminis-

tration paradigm in which the subject controlled the pace and amount of alcohol consumed; thus, subjects may have regulated their alcohol consumption to lower levels that would not cause nausea in interaction with naltrexone. Indeed, the BALs achieved by the naltrexone-treated subjects in this study were lower and rose more slowly than those achieved in the previous fixed-dose studies. Consistent with the hypothesis that aversive interactions with naltrexone may be alcohol dose dependent, McCaul et al. (2000) observed that ratings of nausea while on naltrexone, compared with placebo, were greatest following the high alcohol dose and were less pronounced following a moderate dose. Although our results suggest that naltrexone can suppress drinking without making alcohol-dependent patients feel ill (i.e., most patients will limit their drinking before these adverse interactions with alcohol occur), they do not preclude the possibility that alcohol may become aversive when consumed rapidly and in large quantities or that aversive effects other than nausea may limit drinking.

BALs were comparable for naltrexone- and placebo-treated subjects following the fixed-dose priming drink suggesting that naltrexone did not significantly alter alcohol pharmacokinetics. Although a careful pharmacokinetic study has not been completed to date, this observation is consistent with other laboratory studies in which effects of naltrexone on pharmacokinetic parameters have not been found (Swift et al. 1994; King et al. 1997; McCaul et al. 2000).

Analyses of the endocrine measures revealed that after 6 days of treatment, predrinking levels of cortisol were significantly higher for naltrexone-treated subjects than placebo-treated subjects. In addition, the ACTH and cortisol levels of naltrexone-treated subjects during alcohol self-administration were significantly higher than seen in the placebo-treated subjects in analyses that controlled for baseline differences. These data are consistent with previous findings of similar augmentation of naltrexone-induced cortisol levels following exposure to an acute alcohol dose in non-alcohol-dependent subjects (Teoh et al. 1988). The relative increases in ACTH and cortisol during the alcohol self-administration period for the naltrexone group, relative to the placebo group, were particularly striking given that subjects treated with naltrexone consumed significantly fewer drinks. Furthermore, cortisol levels were inversely related to urge to drink, suggesting that naltrexone-induced augmentation of baseline (unstimulated) or alcohol-induced (stimulated) HPA axis activity may be a potential mediator or possible marker of its ability to reduce alcohol craving. This hypothesis receives support from the extensive literature documenting a relationship between the HPA axis and alcohol drinking (Wand 1999; Wand et al. 1999). In addition, preclinical investigations have found decreased alcohol drinking following exposure to ACTH (Krishnan et al. 1991) and corticotrophin releasing factor (CRF; Bell et al. 1998) molecules, both of which are known to activate the pituitary–adrenal axis and release cortisol. The present study, however, cannot establish a direct cause and effect, and future experiments are needed to further evaluate the hypothetical link between craving, alcohol drinking, and HPA axis activation with regard to opiate antagonist drugs. Further experimentation is also needed to determine whether the observed effects would be present after several days of abstinence. The potential moderating influence of family history of alcoholism and of smoking status should also be examined, given that these variables are known to influence neuroendocrine responses to opiate antagonists (Krishnan-Sarin et al. 1999; Wand et al. 1999).

The results of this study validate the utility of self-administration paradigms for studying the effects of pharmacotherapies on alcohol craving and alcohol drinking. Although fixed-dose paradigms are useful for carefully examining interactions between pharmacological agents and alcohol on parameters such as self-reports of intoxication, mood, behavioral impairment, and hormonal responses, these controlled access designs are probably less sensitive in evaluating the potential of a medication to reduce drinking behavior. In this respect, the paradigm used in this study provides an opportunity to model an initial lapse in abstinence on subsequent drinking by administration of a priming drink and the evaluation of continued drinking during the self-administration portion of the experiment. The provision of multiple opportunities to choose alcohol when desired, the availability of an alternative reinforcer, and the selection of subjects whose typical drinking patterns fall within the amount of alcohol available during the course of the experiment probably contributed to the sensitivity of the paradigm. At the same time, the findings may not generalize to alcohol-dependent subjects outside of the laboratory who may be exposed to more alcohol-related cues, and who have the option of consuming alcohol at a higher concentration and quantity. Nonetheless, the results of this study are consistent with the findings of clinical trials of naltrexone in alcohol-dependent subjects. In addition, Davidson et al. (1999) who tested the effects of chronic naltrexone in heavy beer drinkers using an ad lib paradigm in a naturalistic bar setting found that naltrexone reduced the urge to drink, speed of drinking, and number of drinks consumed.

In summary, this study directly demonstrates that the opioid antagonist naltrexone reduces craving, alcohol drinking, and, thus, drinking-induced BALs in alcohol-dependent subjects using a laboratory paradigm designed to model an initial lapse in abstinence on subsequent drinking. In addition, naltrexone treatment was associated with higher levels of cortisol prior to drinking and higher levels of ACTH and cortisol during alcohol self-administration. Exploratory analyses suggested that this activation of the HPA axis was associated with a less intense urge to drink. Although the results of this study must be considered preliminary given the small sample, the findings have important implications for understanding the effectiveness of opioid antagonists in the management of alcoholism and in extending our knowledge concerning the neurobiology of this disease.

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