Neuropsychopharmacology (2006) 31, 1793–1800

www.neuropsychopharmacology.org

Potentiation of Low Dose Ketamine Effects by Naltrexone: Potential Implications for the Pharmacotherapy of Alcoholism

John H Krystal*[,1,2,3], Steven Madonick[1,2,3,4], Edward Perry[1,2,3], Ralitza Gueorguieva[3,5], Laura Brush[1,2], Yola Wray[1,2], Aysenil Belger[1,2,6] and Deepak Cyril D'Souza[1,2,3]

[1]Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA; [2]Alcohol Research Center (116-A), VA Connecticut Healthcare System, West Haven, CT, USA; [3]Clinical Neuroscience Research Unit, Abraham Ribicoff Research Facilities, Connecticut Mental Health Center, New Haven, CT, USA; [4]Institute of Living, Hartford Hospital, Hartford, CT, USA; [5]Section of Biostatistics, School of Epidemiology and Public Health, Yale University School of Medicine, New Haven, CT, USA; [6]Department of Psychiatry, University of North Carolina Medical School, Chapel Hill, NC, USA

The interplay of opiate and NMDA glutamate receptors may contribute to psychosis, cognitive function, alcoholism, and substance dependence. Ketamine and ethanol block the NMDA glutamate receptor. The purpose of this randomized double-blind, placebo-controlled human laboratory study was to evaluate whether the interactive effects of drugs acting at opiate and NMDA glutamate receptors might partially explain the efficacy of naltrexone for the treatment of alcoholism, that is, whether naltrexone 25 mg pretreatment would modulate ketamine effects in healthy human subjects. Two groups of healthy subjects were studied. An initial group ($n = 31$) received a perception-altering subanesthetic dose of ketamine (bolus of 0.23 mg/kg over 1 min followed by a 60-min infusion of 0.58 mg/kg or saline bolus and infusion). A second group ($n = 24$) completed the same testing procedures, but received a subperceptual ketamine dose (bolus 0.081 mg/kg over 10 min followed by an infusion of 0.4 mg/kg/h). Ketamine produced positive symptoms, negative symptoms, emotional discomfort, and cognitive effects as measured by the Positive and Negative Syndrome Scale (PANSS) in a dose-related fashion. The lower ketamine dose produced subjective effects similar to two standard ethanol drinks, whereas the higher ketamine dose produced effects similar to five standard drinks. Although naltrexone produced no significant behavioral effects, it significantly magnified the increase in the total PANSS score produced by the lower subperceptual dose of ketamine, but not the higher perception-altering dose of ketamine. These data suggest that the interplay of opiate receptor antagonism and NMDA receptor antagonism may be relevant to the protective effects of naltrexone on alcohol consumption via potentiation of dysphoric effects associated with the NMDA receptor antagonist effects of ethanol. However, these data suggest that at levels of NMDA receptor antagonism associated with heavy drinking, this protective effect of naltrexone on drinking is no longer present.
Neuropsychopharmacology (2006) **31,** 1793–1800. doi:10.1038/sj.npp.1300994; published online 4 January 2006

Keywords: NMDA receptor; psychosis; alcoholism; opiate receptor; naltrexone

INTRODUCTION

N-methyl-D-aspartate (NMDA) glutamate receptors and μ-opiate receptors may play opposing roles in the regulation of reward, mood, and cognition. However, little is known about psychopharmacologic aspects of the interplay of drugs acting at these receptors in humans. Binding studies describe colocalization of NMDA and μ-opiate receptors in the nucleus accumbens (Gracy *et al*, 1997) and nucleus tractus solitarius (Huang *et al*, 2000). In the raphe nucleus, nucleus accumbens, and prefrontal cortex, the excitatory effects of NMDA receptor stimulation are opposed by the inhibitory effects of μ-opiate receptor stimulation. Also, NMDA receptor antagonist effects are reduced by opiate receptor antagonists (Jolas and Aghajanian, 1997; Marek and Aghajanian, 1998; Martin *et al*, 1997). In contrast, in *Xenopus* oocytes, there is evidence that opiates administered at very high doses may inhibit NMDA receptor function at a site within the cation channel (Yamakura *et al*, 1999).

The interplay of NMDA glutamate receptors and μ-opiate receptors may be particularly important to the field of addiction research. With respect to opiate addiction, NMDA receptor antagonists block the development of opiate dependence (Sepulveda *et al*, 2002; Trujillo and Akil, 1995). A growing body of alcoholism research has emphasized the interplay of opiate antagonists and ethanol,

*Correspondence: Dr JH Krystal, Alcohol Research Center (116-A), Yale University School of Medicine, VA Connecticut Healthcare System, 950 Campbell Avenue, Park Street, West Haven CT 06516, USA, Tel: +203 937 4790, Fax: +203 937 3468;
E-mail: john.krystal@yale.edu
Received 1 June 2005; revised 5 August 2005; accepted 7 September 2005
Online publication: 28 October 2005 at http://www.acnp.org/citations/Npp102805050360/default.pdf

itself an NMDA receptor antagonist (Krystal *et al*, 2003b). Opiate receptor antagonists reduce the rewarding effects of ethanol(O'Malley *et al*, 1996; Volpicelli *et al*, 1995) and the consumption of ethanol (O'Malley *et al*, 1992; Volpicelli *et al*, 1992). Further, the combination of NMDA and opiate receptor antagonists may have greater beneficial effects for recovering alcohol-dependent patients than either drug administered by itself (Kiefer *et al*, 2003).

The NMDA receptor antagonist, ketamine, is the principal drug used to probe the role of NMDA glutamate receptors in human cognition and behavior (Krystal *et al*, 1999). However, the interpretation of ketamine effects generated by the racemic formulation that is most commonly used in psychopharmacology research may be complicated by the modest affinity that the R-isomer of ketamine possesses for the μ-opiate receptor (Hustveit *et al*, 1995; Smith *et al*, 1980). Other preclinical studies suggest that opiate receptor-mediated effects are not relevant to the cognitive and behavioral effects of ketamine (Byrd *et al*, 1987; Fidecka, 1987; France and Woods, 1989; Fratta *et al*, 1980; Shannon and Holtzman, 1977), but this finding has yet to be demonstrated in humans outside of the context of anesthesia (Stella *et al*, 1984).

The purpose of the current study was to evaluate glutamate–opiate receptor interactions in humans by studying the impact of pretreatment with naltrexone, 25 mg, p.o., upon the dose-related cognitive and behavioral effects of ketamine in a double-blind, randomized, double placebo-controlled design.

METHODS

This study was approved by the Yale Department of Psychiatry Research Committee, New Haven, CT, the Yale University Human Investigations Committee, New Haven, CT, and the Human Subjects Subcommittee of the VA Connecticut Healthcare System, West Haven, CT. The study was conducted at the Neurobiological Studies Unit (VA Connecticut Healthcare System, West Haven, CT). Healthy subjects were recruited by public advertisement and compensated for their research participation. After giving written informed consent, subjects underwent a rigorous evaluation that determined that they (1) were medically healthy by history, physical examination, and laboratory testing, (2) did not meet a DSM-IV axis I diagnosis by structured diagnostic interview (Spitzer *et al*, 1990), and (3) did not give evidence of substance abuse or dependence by history, physical examination, or urine toxicology (performed at screening and on each test day). Subjects were instructed to refrain from caffeine intake for 2 weeks prior to testing and throughout the study.

Subjects

A total of 55 healthy human subjects completed testing: 31 completed the four test days involving a higher perception-altering ketamine dose and 24 subjects completed the four test days involving the subperceptual ketamine dose. The mean age of the sample was 28.1 ± 7.6 year (SD). In all, 26 subjects were female (47.3%) and 29 subjects were male (52.7%). The majority of subjects were nonsmokers ($n = 42$, 76.4%), four subjects smoked (7.3%); one subject had smoked in the past (1.8%), and smoking data were not available for eight subjects (14.5%).

Procedures

This study was conducted in two phases. In the initial phase, the higher dose of ketamine (i.v. bolus of 0.23 mg/kg over 1 min followed by 0.58 mg/kg/h) was tested. Subjects completed four test days in randomized order under double-blind conditions: placebo naltrexone and saline (placebo ketamine), naltrexone 25 mg, p.o. and saline, placebo naltrexone and ketamine, and naltrexone and ketamine. The drugs were administered in a fixed order with naltrexone 25 mg or a matched placebo given 90 min prior to the initiation of ketamine or saline infusion. In the second phase, identical procedures were followed, except that a lower ketamine dose (bolus 0.081 mg/kg over 10 min followed by an infusion of 0.4 mg/kg/h) was administered.

A timeline for test days is presented in Figure 1. Subjects fasted after midnight prior to test days. They appeared for testing at approximately 0830 hours on test days. This study employed cognitive and clinical assessments that we have used previously to study ketamine effects in healthy subjects and alcohol dependent patients (Krystal *et al*, 1994, 1998, 2003a). The Positive and Negative Syndrome Scale (PANSS (Kay *et al*, 1989)) was employed to assess several dimensions of behavior. In this report, empirically derived factors are reported excluding those items that could not be assessed during the test sessions (Bell *et al*, 1994): positive symptom factor (delusions, unusual thoughts, somatic concern, grandiosity, suspiciousness, and hallucinations), negative symptom factor (emotional withdrawal, blunted affect, poor rapport, disturbance of volition, preoccupation, and motor retardation), cognitive factor (difficulty in abstract thinking, stereotyped thinking, cognitive disorganization, lack of judgement and insight, poor attention, tension, mannerisms, and posturing), hostility (excitement, hostility, impulse control, and uncooperativeness), emotional discomfort (depression, anxiety, and guilt). In addition, subjects completed visual analog scales (VAS) measuring high, drowsiness, nervousness, and the number of standard alcohol drinks that would be anticipated to produce the subjective effects experienced at a given timepoint (the 'number of drinks' scale) (Krystal *et al*, 1998). The Biphasic Alcohol Effects scale (BAES) contains seven items measuring stimulatory effects associated with ethanol and seven items that assess sedative effects associated with ethanol (Martin *et al*, 1993). The Hopkins Verbal Learning Test (HVLT) (Brandt, 1991) also was administered on each test day.

Data Analysis

Data were checked for normality before analysis. Since most outcome variables exhibited floor effects and positive skewness, we used the nonparametric approach for repeated measures data (Brunner *et al*, 2002). In the overall model for BAES ascending, BAES descending, PANSS total score, the five PANSS subscales (positive, negative, cognitive, emotional, and hostility), the four VAS subscales (high, tired, drowsy, and nervous), and the similarity to alcohol

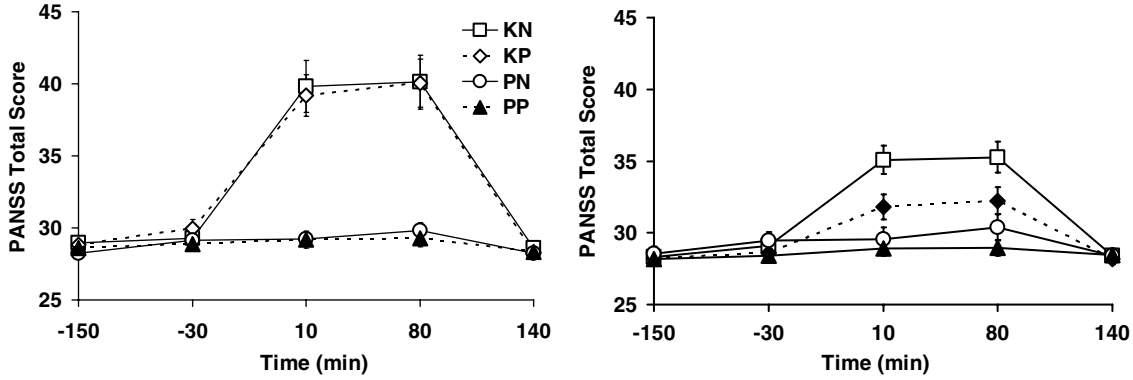

Figure 1 This figure depicts the PANSS total score results. Data are presented as mean values ± SEM. Results of the data analyses are presented in Table 2. The left figure presents the results of the higher perception-altering dose of ketamine and the right figure shows the results from the lower subperceptual dose of ketamine. K = ketamine, N = naltrexone, P = placebo.

Table 1 The Timing of Procedures for Test Days

Time (min)	Procedure
−150:	IV placed. ETOH Battery (Biphasic Alcohol Effects Scale; Visual Analog Scales for mood, similarity to ethanol, side effects; Number of Drinks Scale)
−120:	Positive and Negative Symptoms Scale (PANSS), Clinician-Administered Dissociative States Scale (CADSS),
−90	*Administration of naltrexone 25 mg or matched placebo, p.o.*
0:	Infusion of *ketamine or saline placebo*
5:	ETOH Battery
15:	Continuous performance test of distractibility
	Hopkins Verbal Learning Test
30:	ETOH battery, PANSS, CADSS, vital signs
60:	ETOH battery; *ketamine infusion terminated*
70:	PANSS, CADSS
100:	ETOH battery, PANSS, CADSS, Ribicoff Abstinence Rating Scale
180:	PANSS, CADSS, Test Day Debriefing and Discharge

effect, ketamine dose (low dose *vs* high dose) was used as a between-subject factor, whereas ketamine (Active, Placebo), naltrexone (Active, Placebo), and time (study timepoints, see Table 1) were used as within-subject factors. Subject was used as the clustering factor. The analysis of HVLT data was similar, except instead of time there was an effect of repetition for immediate recall to assess learning effects. The analysis was performed via the use of PROC MIXED on the ranked data with appropriate adjustment for p-values. If significant interactions involving ketamine dose were observed, separate follow-up analyses within the high-dose ketamine group and the low-dose ketamine group were also performed. Bonferroni adjustment was applied within but not across hypotheses.

RESULTS

PANSS

The analyses of PANSS data are summarized in Table 2. The initial analysis focused on the PANSS total score. This analysis, depicted in Figure 1, revealed the naltrexone potentiated the effects of the lower, but not the higher, ketamine dose. As presented in Table 2, the ketamine by time interaction, naltrexone by time interaction, and the interaction of ketamine dose, ketamine, naltrexone, and time were significant. For the lower ketamine dose, both the ketamine by time interactive effect (ATS = 1.81, df = 6.63, $p = 0.002$) and the naltrexone by time interactive effect (ATS = 2.55, df = 4.66, $p = 0.005$) were significant. For the higher ketamine dose, the ketamine by time interaction effect was highly significant (ATS = 2.11, df = 89.50, $p < 0.0001$), but the naltrexone and naltrexone by time interaction effects were not significant. Neither the ketamine by time interaction nor the ketamine by naltrexone by time interaction was significant for either dose.

There were significant dose-related ketamine effects on four of the five PANSS factors (positive symptoms (Figure 2), negative symptoms (Figure 3), cognition, and hositility), and naltrexone had no significant effects by itself. The interaction of ketamine dose, ketamine, naltrexone, and time for the emotional discomfort factor data failed to make the Bonferroni-corrected threshold for significance for this outcome ($p < 0.01$; Figure 4). As the interaction was significant at the uncorrected significance level of 0.05, *post hoc* testing was performed. These tests revealed that the 'discomforting' effects of the higher dose of ketamine were not significantly influenced by naltrexone pretreatment, whereas naltrexone pretreatment modestly, but significantly, increased the effects of low-dose ketamine on this outcome measure (ketamine by naltrexone by time interaction: ATS = 2.9, df = 2.7, $p = 0.04$).

VAS and Number of Drinks Scale

The results of the analyses of VAS are summarized in Table 1. Ketamine produced significant dose-related euphoria, drowsiness, and sedation. It also had effects that were deemed significantly similar to those of ethanol in a dose-related fashion. Naltrexone had no significant effects on any of the VAS. None of the interactions between ketamine dose, ketamine, naltrexone, and time reached the significance threshold for this study. However, the four-way interaction for the 'high' VAS was significant at an uncorrected significance level of 0.05, so *post hoc* tests were

Table 2 Summary of Results[a]

Outcome	Ketamine by time interaction[b]	Ketamine dose by ketamine by time[c]	Naltrexone by time[d]	Naltrexone by ketamine by time[e]	Naltrexone by ketamine dose by ketamine by time[f]
PANSS					
PANSS total score	**ATS = 2.09, df = 84.05, $p < 0.0001$**	ATS = 2.09, df = 0.38, $p = 0.7$	**ATS = 2.61, df = 2.72, $p = 0.051$**	ATS = 2.15, df = 2.21, $p = 0.11$	**ATS = 2.15, df = 3.22, $p = 0.036$**
PANSS positive symptom factor	**ATS = 57.8, df = 1.71, $p < 0.0001$**	ATS = 0.23, df = 1.71, $p = 0.76$	ATS = 0.55, df = 2.91, $p = 0.64$	ATS = 1.44, df = 2.58, $p = 0.23$	ATS = 0.46, df = 2.58, $p = 0.69$
PANSS negative symptom factor	**ATS = 34.53, df = 1.92, $p < 0.0001$**	**ATS = 3.57, df = 1.92, $p = 0.03$**	**ATS = 3.76, df = 2.73 $p = 0.01$**	ATS = 1.26, df = 2.38 $p = 0.28$	ATS = 2.47, df = 2.38 $p = 0.07$
PANSS cognitive symptom factor	**ATS = 74.74, df = 1.85, $p < 0.0001$**	ATS = 1.15, df = 1.85, $p = 0.31$	ATS = 1.48, df = 2.19 $p = 0.23$	ATS = 1.16, df = 2.51 $p = 0.32$	ATS = 1.64, df = 2.51 $p = 0.19$
PANSS emotional discomfort factor	**ATS = 3.94, df = 2.50, $p = 0.0125$**	ATS = 1.25, df = 2.50, $p = 0.29$	ATS = 0.76, df = 2.52 $p = 0.50$	ATS = 2.22, df = 2.82 $p = 0.09$	**ATS = 2.86, df = 2.82 $p = 0.04$**
PANSS hostility factor	**ATS = 7.35, df = 2.43, $p = 0.0002$**	ATS = 0.62, df = 2.43, $p = 0.57$	ATS = 1.04, df = 2.05 $p = 0.35$	ATS = 2.51, df = 1.85 $p = 0.09$	ATS = 0.09, df = 1.85 $p = 0.90$
VAS					
VAS high	**ATS = 187.80, df = 1.40, $p < 0.0001$**	ATS = 2.77, df = 1.40, $p = 0.08$	ATS = 1.40, df = 2.02 $p = 0.25$	ATS = 1.36, df = 2.14 $p = 0.26$	**ATS = 3.09, df = 2.14 $p = 0.04$**
VAS drowsy	**ATS = 5.04, df = 2.34, $p = 0.004$**	**ATS = 5.24, df = 2.34, $p = 0.003$**	ATS = 0.41, df = 2.94 $p = 0.74$	ATS = 1.33, df = 2.81 $p = 0.26$	ATS = 0.08, df = 2.81 $p = 0.96$
VAS nervous	**ATS = 3.39, df = 2.23, $p = 0.03$**	ATS = 0.15, df = 2.23, $p = 0.88$	ATS = 2.99, df = 2.76 $p = 0.03$	ATS = 0.58, df = 2.53 $p = 0.60$	ATS = 0.76, df = 2.53 $p = 0.50$
BAES					
BAES stimulant subscale	**ATS = 17.02, df = 1.72, $p < 0.0001$**	**ATS = 3.64, df = 1.75, $p = 0.03$**	ATS = 2.26, df = 2.74 $p = 0.09$	ATS = 0.51, df = 2.29 $p = 0.62$	ATS = 1.99, df = 2.27 $p = 0.13$
BAES sedative subscale	**ATS = 36.57, df = 2.33, $p < 0.0001$**	ATS = 2.67, df = 2.38, $p = 0.06$	ATS = 0.43, df = 2.66 $p = 0.71$	ATS = 0.31, df = 2.90 $p = 0.81$	ATS = 0.46, df = 2.90 $p = 0.71$
HVLT					
Immediate recall	**ATS = 6.31, df = 1.91, $p = 0.002$**	ATS = 2.69, df = 1.91, $p = 0.07$	ATS = 0.45, df = 1.95, $p = 0.63$	ATS = 0.2, df = 1.85, $p = 0.80$	ATS = 0.36, df = 1.85, $p = 0.68$
Delayed recall[g]	ATS = 2.64, df = 1, $p = 0.11$	ATS = 0.38, df = 1, $p = 0.54$	ATS = 1.73, df = 1, $p = 0.19$	ATS = 0.61, df = 1, $p = 0.43$	ATS = 0.43, df = 1, $p = 0.51$

[a]The threshold for statistical significance adopted for this study was $p < 0.01$. Findings with $p < 0.05$ are bolded in the table.
[b]Ketamine by time interaction effects reflect ketamine effects over the test day relative to placebo, irrespective of the ketamine dose.
[c]Ketamine dose by ketamine by time interaction effects indicate the dependency of the ketamine by time interaction upon ketamine dose.
[d]Naltrexone by time interaction effects show the time-dependent effects of naltrexone.
[e]Naltrexone by ketamine by time interaction effects characterize the impact of naltrexone upon ketamine response over time irrespective of ketamine dose.
[f]Naltrexone by ketamine dose by ketamine by time interaction effects reflect whether naltrexone interacts with ketamine over time in a manner that is dependent on the dose of ketamine that is administered.
[g]Two outcome measures could not be analyzed using the ANOVA type statistic, the VAS measuring similarity to ethanol effects and the 'number of drinks' scale. These analyses are presented in the results section.

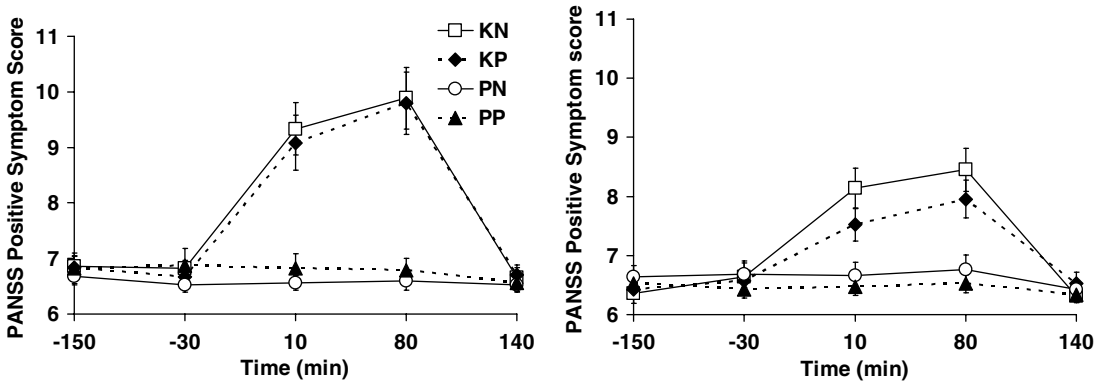

Figure 2 This figure depicts the PANSS positive symptom factor score results. Data are presented as mean values ± SEM. Results of the data analyses are presented in Table 2. The left figure presents the results of the higher perception-altering dose of ketamine and the right figure shows the results from the lower subperceptual dose of ketamine. K = ketamine, N = naltrexone, P = placebo.

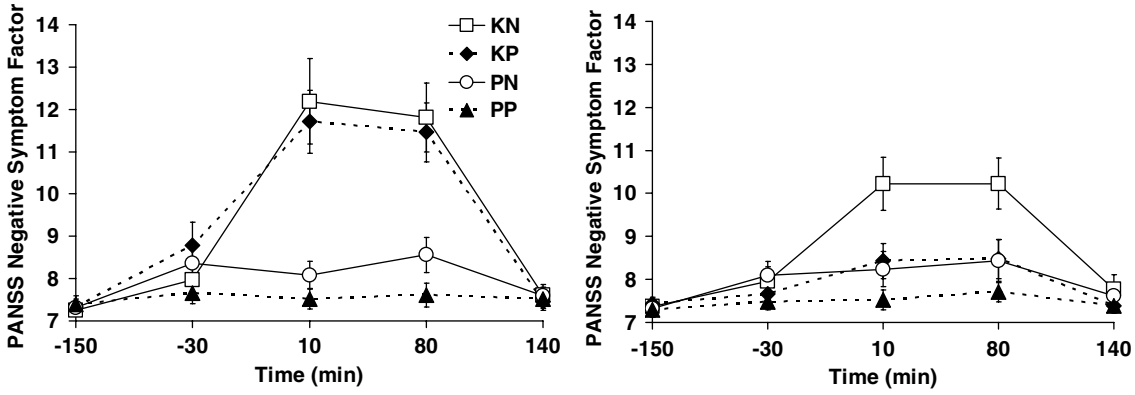

Figure 3 This figure depicts the PANSS negative symptom factor score results. Data are presented as mean values ± SEM. Results of the data analyses are presented in Table 2. The left figure presents the results of the higher perception-altering dose of ketamine and the right figure shows the results from the lower sub-perceptual dose of ketamine. K = ketamine, N = naltrexone, P = placebo.

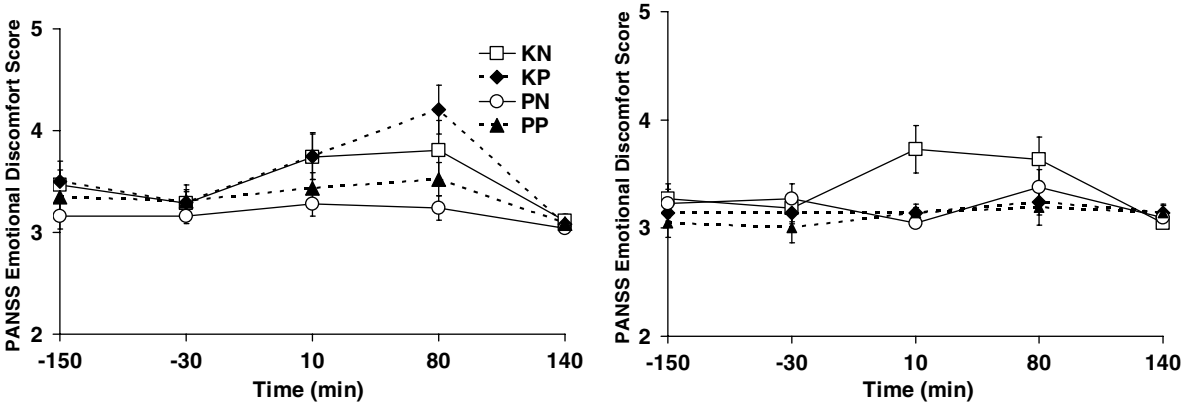

Figure 4 This figure presents the PANSS emotional discomfort factor score results. Data are presented as mean values ± SEM. Results of the data analyses are presented in Table 2. The left figure presents the results of the higher perception-altering dose of ketamine and the right figure shows the results from the lower subperceptual dose of ketamine. K = ketamine, N = naltrexone, P = placebo.

performed (see Figure 5). This analysis revealed a modest, but significant, increase in the euphoric effects of the lower ketamine dose following naltrexone pretreatment (ketamine by naltrexone by time interaction: ATS = 3.78, df = 2.09, $p = 0.02$).

The results for the Number of Drinks Scale, reflecting the number of ethanol drinks that would be anticipated to produce a subjective sense of intoxication comparable to the subjective state at the rating time, are presented in Figure 6. Whereas the ketamine by time interaction was significant (ATS = 2.52, df = 86.32, $p < 0.0001$), there was no significant main effect of naltrexone or significant ketamine dose by ketamine by naltrexone by time interaction.

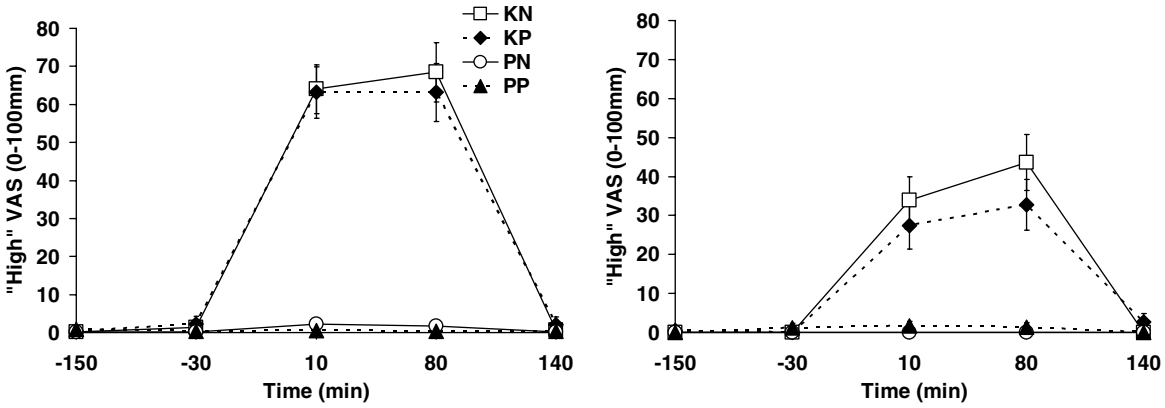

Figure 5 This figure presents the 'high' VAS (range 0–100 mm) results. Data are presented as mean values ± SEM. Results of the data analyses are presented in Table 2. The left figure presents the results of the higher perception-altering dose of ketamine and the right figure shows the results from the lower subperceptual dose of ketamine. K = ketamine, N = naltrexone, P = placebo.

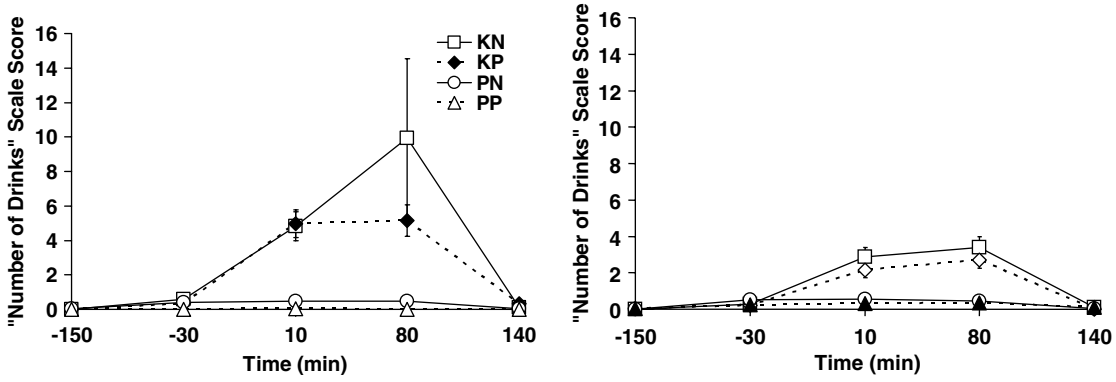

Figure 6 This figure presents the 'number of drinks scale' results. This scale measures the number of standard ethanol drinks needed to produce the current subjective state. Data are presented as mean values ± SEM. Results of the data analyses are presented in Table 2. The left figure presents the results of the higher perception-altering dose of ketamine and the right figure shows the results from the lower subperceptual dose of ketamine. K = ketamine, N = naltrexone, P = placebo.

Biphasic Alcohol Effects Scale

Ketamine produced significant stimulant and sedative effects as measured by the subscales of the BAES, but the effects of either ketamine dose were not significantly modulated by naltrexone pretreatment (Table 2).

Hopkins Verbal Learning Test

Ketamine significantly impaired immediate recall (Table 2). Naltrexone did not have a significant effect and it did not modify the ketamine effect on immediate recall. Controlling for immediate recall tested on the third trial, neither ketamine nor naltrexone impaired delayed recall.

DISCUSSION

The principal finding of this study was that pretreatment with naltrexone increased some effects of a subperceptual subanesthetic dose of ketamine, but this same dose of naltrexone did not alter the effects of a higher perception-altering subanesthetic dose of ketamine when administered to healthy human subjects. This pattern of interaction between naltrexone and ketamine was observed for the total PANSS score. It was also present in secondary analyses of the emotional discomfort factor of the PANSS and the 'high' VAS. This study also found that opiate receptors, particularly the μ-opiate receptor, do not contribute substantially to other cognitive and behavioral effects of ketamine in healthy human subjects. Also, there was no evidence that ketamine effects were antagonized by naltrexone pretreatment. Thus, this study does not provide evidence that any direct effects of either isomer of ketamine are mediated by stimulation of opiate receptors.

The ability of naltrexone pretreatment to increase the 'high' and emotional discomfort produced by low-dose ketamine may suggest a novel mechanism through which it plays a role in the treatment of alcohol dependence. As noted in the introduction, early studies suggested that naltrexone attenuated the euphoric effects of alcohol consumption (O'Malley *et al*, 1996; Volpicelli *et al*, 1995). However, a laboratory study from this period also suggested that naltrexone potentiated sedation and other effects of ethanol associated with descending blood ethanol levels (Swift *et al*, 1994). The current data raise the possibility that naltrexone modestly potentiates feelings of intoxication, both euphoria and emotional discomfort, associated with modest levels of NMDA receptor antagonism, as might be

associated with low levels of ethanol intoxication (Krystal *et al*, 1998).

Naltrexone may potentiate a negative feedback signal on drinking that is both unclear and different than simply increasing the perceived number of alcohol drinks consumed, as this outcome measure was not significantly altered. The low dose ketamine was perceived as similar to 2–3 standard alcohol drinks regardless of naltrexone, whereas the higher ketamine dose was perceived as similar to approximately five standard alcohol drinks when administered by itself and approximately nine standard alcohol drinks when administered following naltrexone (see Figure 6). However, there was no significant interaction between ketamine, naltrexone, and time effects for either ketamine dose for the 'number of drinks' scale data.

The inability of naltrexone to modulate the cognitive and behavioral effects of the higher ketamine dose could signal a limitation on naltrexone's efficacy in treating alcohol dependence. Dosing issues may be very important to the interplay of NMDA receptor antagonists and drugs acting at opiate receptors. Two studies that reported synergy between opiate receptor agonist and NMDA receptor antagonist effects when both drugs were administered at low doses found no interactive drug effects (Young *et al*, 1992) or found the opposite pattern of interactive effects (Hance *et al*, 1989) when higher opiate doses were administered. The multicenter study of alcoholism conducted within the VA failed to find a significant naltrexone effect (Krystal *et al*, 2001) and its research patients drank more heavily at baseline and more rapidly progressed during treatment from their first drink of alcohol to heavy drinking than did the patients in early positive naltrexone trials (Anton *et al*, 1999; O'Malley *et al*, 1992; Volpicelli *et al*, 1992).

Future research may address limitations of the current study. First, the applicability of the findings of this study to alcoholism treatment may be limited by the relatively low dose of naltrexone employed. This study evaluated naltrexone 25 mg due to concern that higher naltrexone doses might produce nausea and vomiting when administered with ketamine. However, clinical trials of naltrexone treatment for alcohol dependence study doses up to 100 mg. Naltrexone, at 25 mg, should have produced a nearly complete blockade of μ-opiate receptors (Lee *et al*, 1988). But, it is possible that higher naltrexone doses would have produced greater effects via δ- or κ-opiate receptors, where it has nearly 16.7-fold and 5.6-fold lower affinity, respectively (Ananthan *et al*, 1999). Second, this study was conducted in healthy human subjects without a family history of alcohol dependence. The presence of a family history of alcohol dependence has been shown to influence ketamine response and the interactive effects of naltrexone and ethanol in healthy human subjects (King *et al*, 1997; Petrakis *et al*, 2004). Different response patterns might have been observed in individuals with a family history of alcohol dependence. Third, this study sequentially evaluated the two ketamine doses in two separate subject groups, raising the possibility that ketamine dose and order effects were confounded in this study and reducing the statistical power for the comparisons across ketamine dose relative to the within subjects analyses.

Overall, the current data describe an interaction between NMDA glutamate receptors and opiate receptors. However, the interactive effects were not very prominent. Thus, the data may suggest that maintaining the tone of endogenous opiate systems is not critical for expressing the cognitive and behavioral effects of NMDA glutamate receptor antagonists.

ACKNOWLEDGEMENTS

This work was supported by the National Institute on Alcohol Abuse and Alcoholism via RO1 AA12308-01, KO5 AA 14906-01, and I-P50 AA-12870-04. It is also supported by the Department of Veterans Affairs via support for the Alcohol Research Center, Schizophrenia Biological Research Center, and National Center for PTSD. The authors thank Angelina Genovese, RN, and Elizabeth O'Donnell, RN, of the Biological Studies Unit of the VA Connecticut Healthcare System for their contributions to the success of this project. The authors also thank Ms Corie Palazollo for her expert assistance in the preparation of this manuscript.

REFERENCES

Ananthan S, Kezar HSI, Carter RL, Saini SK, Rice KC, Wells JL *et al* (1999). Synthesis, opioid receptor binding, and biological activities of naltrexone-derived pyrido- and pyrimidomorphinans. *J Med Chem* **42**: 3527–3538.

Anton RF, Moak DH, Waid LR, Latham PK, Malcolm RJ, Dias JK (1999). Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: results of a placebo-controlled trial. *Am J Psychiatry* **156**: 1758–1764.

Bell MD, Lysaker PH, Beam-Goulet JL, Milstein RM, Lindenmayer JP (1994). Five-component model of schizophrenia: assessing the factorial invariance of the positive and negative syndrome scale. *Psychiatry Res* **52**: 295–303.

Brandt J (1991). The Hopkins Verbal Learning Test: development of a new memory test with six equivalent forms. *Clin Neuropsychol* **5**: 125–142.

Brunner E, Domhof S, Langer F (2002). *Nonparametric Analysis of Longitudinal Data in Factorial Experiments*. Wiley: New York.

Byrd LD, Standish LJ, Howell LL (1987). Behavioral effects of phencyclidine and ketamine alone and in combination with other drugs. *Eur J Pharmacol* **144**: 331–341.

Fidecka S (1987). Opioid mechanisms of some behavioral effects of ketamine. *Pol J Pharmacol Pharm* **39**: 353–360.

France CP, Woods JH (1989). Discriminative stimulus effects of naltrexone in morphine-treated rhesus monkeys. *J Pharmacol Exp Therapeut* **250**: 937–943.

Fratta W, Casu M, Balestrieri A, Loviselli A, Biggio G, Gessa GL (1980). Failure of ketamine to interact with opiate receptors. *Eur J Pharmacol* **61**: 389–391.

Gracy KN, Svingos AL, Pickel VM (1997). Dual ultrastructural localization of mu-opioid receptors and NMDA-type glutamate receptors in the shell of the rat nucleus accumbens. *J Neurosci* **17**: 4839–4848.

Hance AJ, Winters WD, Quam DD, Benthuysen JL, Cadd GG (1989). Catalepsy induced by combinations of ketamine and morphine: potentiation, antagonism, tolerance and cross-tolerance in the rat. *Neuropharmacology* **28**: 109–116.

Huang J, Wang H, Pickel VM (2000). Rostrocaudal variation in targeting of *N*-methyl-D-aspartate and mu-opioid receptors in the rat medial nucleus of the solitary tract. *J Comparat Neurol* **421**: 400–411.

Hustveit O, Maurset A, Oye I (1995). Interaction of the chiral forms of ketamine with opioid, phencyclidine, sigma and muscarinic receptors. *Pharmacol Toxicol* **77**: 355–359.

Jolas T, Aghajanian GK (1997). Opioids suppress spontaneous and NMDA-induced inhibitory postsynaptic currents in the dorsal raphe nucleus of the rat in vitro. *Brain Res* **755**: 229–245.

Kay SR, Opler LA, Lindenmayer JP (1989). The Positive and Negative Syndrome Scale (PANSS): rationale and standardisation. *Br J Psychiatry—Supplement* **7**: 59–67.

Kiefer F, Jahn H, Tarnaske T, Helwig H, Briken P, Holzbach R *et al* (2003). Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism: a double-blind, placebo-controlled study. *Arch Gen Psychiatry* **60**: 92–99.

King AC, Volpicelli JR, Frazer A, O'Brien CP (1997). Effect of naltrexone on subjective alcohol response in subjects at high and low risk for future alcohol dependence. *Psychopharmacology* **129**: 15–22.

Krystal JH, Cramer JA, Kroll W, Kirk G, Rosenheck RA, Group VANCS (2001). Naltrexone in the treatment of alcohol dependence. *N Engl J Med* **345**: 1734–1739.

Krystal JH, D'Souza DC, Petrakis IL, Belger A, Berman R, Charney DS *et al* (1999). NMDA agonists and antagonists as probes of glutamatergic dysfunction and pharmacotherapies for neuropsychiatric disorders. *Harvard Rev Psychiatry* **7**: 125–133.

Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD *et al* (1994). Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry* **51**: 199–214.

Krystal JH, Petrakis IL, Limoncelli D, Webb E, Gueorgueva R, D'Souza DC *et al* (2003a). Altered NMDA glutamate receptor antagonist response in recovering ethanol dependent patients. *Neuropsychopharmacology* **28**: 2020–2028.

Krystal JH, Petrakis IL, Mason G, D'Souza DC (2003b). NMDA glutamate receptors and alcoholism: reward, dependence, treatment, and vulnerability. *Pharmcol Therapeut* **99**: 79–94.

Krystal JH, Petrakis IL, Webb E, Cooney NL, Karper LP, Namanworth S *et al* (1998). Dose-related ethanol-like effects of the NMDA antagonist, ketamine, in recently detoxified alcoholics. *Arch Gen Psychiatry* **55**: 354–360.

Lee MC, Wagner Jr HN, Tanada S, Frost JJ, Bice AN, Dannals RF (1988). Duration of occupancy of opiate receptors by naltrexone. *J Nucl Med* **29**: 1207–1211.

Marek GJ, Aghajanian GK (1998). 5-Hydroxytryptamine-induced excitatory postsynaptic currents in neocortical layer V pyramidal cells: suppression by mu-opiate receptor activation. *Neuroscience* **86**: 485–497.

Martin CS, Earleywine M, Musty RE, Perrine MW, Swift RM (1993). Development and validation of the Biphasic Alcohol Effects Scale. *Alcohol Clin Exp Res* **17**: 140–146.

Martin G, Nie Z, Siggins GR (1997). mu-Opioid receptors modulate NMDA receptor-mediated responses in nucleus accumbens neurons. *J Neurosci* **17**: 11–22.

O'Malley SS, Jaffe AJ, Chang G, Schottenfeld RS, Meyer RE, Rounsaville B (1992). Naltrexone and coping skills therapy for alcohol dependence. A controlled study. *Arch Gen Psychiatry* **49**: 881–887.

O'Malley SS, Jaffe AJ, Rode S, Rounsaville BJ (1996). Experience of a 'slip' among alcoholics treated with naltrexone or placebo. *Am J Psychiatry* **153**: 281–283.

Petrakis IL, Limoncelli D, Guerguieva R, Jatlow P, Boutros NN, Trevisan L *et al* (2004). Altered NMDA glutamate receptor antagonist response in individuals with a family vulnerability to alcoholism. *Am J Psychiatry* **161**: 1776–1782.

Sepulveda J, Ortega A, Zapata G, Contreras E (2002). Acamprosate decreases the induction of tolerance and physical dependence in morphine-treated mice. *Eur J Pharmacol* **445**: 87–91.

Shannon HE, Holtzman SG (1977). Further evaluation of the discriminative effects of morphine in the rat. *J Pharmacol Exp Therapeut* **201**: 55–66.

Smith DJ, Pekoe GM, Martin LL, Coalgate B (1980). The interaction of ketamine with the opiate receptor. *Life Sci* **26**: 789–795.

Spitzer RL, Williams JBW, Gibbon M, First MB (1990). *Structured Clinical Interview for DSM-III-R-Non-Patient Edition (SCID-NP, Version 1.0 with supplement for DSM-IV)*. American Psychiatric Press: Washington, DC.

Stella L, Crescenti A, Torri G (1984). Effect of naloxone on loss of consciousness induced by i.v. anesthetic agents in man. *Br J Anesthes* **56**: 369–373.

Swift RM, Whelihan W, Kuznetsov O, Buongiorno G, Hsuing H (1994). Naltrexone-induced alterations in human ethanol intoxication. *Am J Psychiatry* **151**: 1463–1467.

Trujillo KA, Akil H (1995). Excitatory amino acids and drugs of abuse: a role for *N*-methyl-D-aspartate receptors in drug tolerance, sensitization and physical dependence. *Drug Alcohol Dependence* **38**: 139–154.

Volpicelli JR, Alterman AI, Hayashida M, O'Brien CP (1992). Naltrexone in the treatment of alcohol dependence. *Arch Gen Psychiatry* **49**: 876–880.

Volpicelli JR, Watson NT, King AC, Sherman CE, O'Brien CP (1995). Effect of naltrexone on alcohol 'high' in alcoholics. *Am J Psychiatry* **152**: 613–615.

Yamakura T, Sakimura K, Shimoji K (1999). Direct inhibition of the *N*-methyl-D-aspartate receptor channel by high concentrations of opioids. *Anesthesiology* **91**: 1053–1063.

Young AM, Masaki MA, Geula C (1992). Discriminative stimulus effects of morphine: effects of training dose on agonist and antagonist effects of mu opioids. *J Pharmacol Exp Therapeut* **261**: 246–257.