ORIGINAL INVESTIGATION

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Interactive effects of subanesthetic ketamine and haloperidol in healthy humans

Received: 10 November 1998/Final version: 23 February 1999

Abstract Ketamine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist with prominent psychoactive effects in humans. This study evaluated whether the oral administration of haloperidol 5 mg would block the effects of an intravenous ketamine infusion (bolus of 0.26 mg/kg followed by 0.65 mg/kg per hour). Twenty healthy subjects completed 4 test days involving the oral administration of haloperidol or matched placebo 2 h prior to the intravenous infusion of ketamine or saline. Ketamine produced cognitive, behavioral, neuroendocrine, and physiologic effects in the healthy subjects that were similar to previous reports. Haloperidol pretreatment reduced impairments in executive cognitive functions produced by ketamine as measured by proverb interpretations and the Wisconsin Card Sorting Test. However, it failed to block the capacity of ketamine to produce psychosis, perceptual changes, negative symptoms, or euphoria in healthy subjects. These data outline an important, but functionally delineaeted modulation of ketamine effects by dopamine$_2$ receptors and other sites of haloperidol action.

Key words Ketamine · *N*-Methyl-D-asparate · Glutamate · Psychosis · Dissociation · Addiction · Dopamine · Neuroleptic · Memory · Attention · Frontal cortex · Extrapyramidal symptom · Wisconsin Card Sorting Test

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Introduction

The behavioral, cognitive, and electrophysiological effects of antagonists to the *N*-methyl-D-asparate (NMDA) receptor subclass of glutamate receptors in healthy subjects resemble some aspects of the signs and symptoms of schizophrenia and dissociative disorders (Luby et al. 1959; Domino et al. 1965; Øye et al. 1992; Krystal et al. 1994; Malhotra et al. 1996). The NMDA receptor subclass is the site of action of phencyclidine (PCP) and ketamine (Anis et al. 1983). These drugs bind non-selectively to NMDA receptor subtypes (Yamakura et al. 1993; Bresink et al. 1995). Ketamine is 10–50 times less potent than PCP at NMDA receptors, but it has similar effects in preclinical paradigms (Hampton et al. 1982; Byrd 1987; Rothman and Olney 1987; Willetts et al. 1990; Javitt and Zukin 1991). It is available clinically as a racemic mixture of two enantiomers. Its *S*-isomer has 2–4 times greater affinity and selectivity for the NMDA receptor and greater clinical potency than the *R*-isomer (Øye et al. 1991, 1992; Zeilhofer et al. 1992). Ketamine has greatest affinity for NMDA receptors, but it binds to other receptor sites with lower potency (see Krystal et al. 1994).

The similarity between ketamine effects and endogenous psychoses created interest in the capacity of antipsychotic medications to block ketamine effects in healthy humans. Co-administration of typical neuroleptics has been reported to attenuate the psychosis

or delirium associated with ketamine and phencyclidine anesthesia (Helrich et al. 1964; Bovill et al. 1971; Sadove et al. 1971a, b; Becsey et al. 1972; Ebguth et al. 1972; Kamm and Bewes 1978; Lilburn et al. 1978; Geist and Gross 1982). However, the role of neuroleptic treatment in NMDA antagonist-induced psychosis has received relatively little systematic study. Clinical reports suggest that low potency (Luisada and Brown 1976) and high potency (Castellani and Adams 1982) typical neuroleptics treat these psychotic states. However, neuroleptic-resistant symptoms are common in patients presenting with persisting psychoses related to PCP ingestion (Rainey and Crowder 1975; Allen and Young 1978; Fauman and Fauman 1978; Castellani et al. 1982a, b; Berlant 1985). Further, typical neuroleptics do not appear to block the acute effects of NMDA antagonists in laboratory-based studies in schizophrenic patients (Krystal et al. 1995; Lahti et al. 1995; Malhotra et al. 1997).

The current study assessed the interactive effects of subanesthetic ketamine and haloperidol in humans in a double-blind placebo-controlled design. The current study was intended to inform evolving hypotheses concerning the interactions of glutamate and dopamine systems in the regulation of cognitive impairments, positive and negative symptoms resembling schizophrenia, perceptual effects, mood alterations, and neuroendocrine changes produced by ketamine in healthy human subjects. Haloperidol 5mg was selected for this study because we believed that it would be relatively well-tolerated by healthy subjects while producing occupancy of more than 70% of dopamine$_2$ receptors (Nordström et al. 1992). Further, at this dose, this dose of haloperidol has a relative preference for dopamine$_2$ receptor antagonism compared to other actions that might modulate NMDA antagonist effects, such as antagonism of muscarinic receptors (Sturgeon et al. 1981) and antagonism of serotonin$_{2A}$ receptors (Kitaichi et al. 1994).

Materials and methods

Subjects

This research study was approved by the Human Subjects Subcommittee of the VA Connecticut Healthcare System, West Haven, Conn., USA. Subjects were recruited for participation in this study through public advertisement and paid for their participation. Healthy subjects were selected for participation after obtaining written informed consent and following a two-step process to exclude individuals with a history of psychiatric illness, substance abuse disorders, or significant current life stress. The first step involved the administration of a structured diagnostic interview for non-patient populations (Spitzer et al. 1990) supplemented by a clinical interview that further evaluated personal and family history. Based on this assessment, subjects were excluded who gave evidence of a psychiatric or substance abuse disorder, history of clinical consultation for an emotional difficulty, psychiatric illness in a first degree relative, or clinically significant current life stress defined operationally as 3 or greater on the Severity of Psychosocial Stressors Scale for Adults employed in axis IV of DSM-III-R (American Psychiatric Association 1987). The second step was a telephone interview conducted with an individual identified by the subject to confirm information collected from the subject. Subjects were instructed to abstain from consuming psychoactive substances for 4 weeks prior to testing. Urine toxicology screens at initial screening and on test days provided additional confirmatory evidence. None of the subjects reported a history of serious medical illness. All of the subjects had normal results on physical examination and laboratory testing, including liver and thyroid function tests. Subjects were all within normal limits on two measures of vulnerability to psychosis, the Bell Reality Testing Inventory and the Wisconsin Scales of Psychosis Proneness (Chapman et al. 1982; Bell et al. 1985).

Thirty-four subjects entered the study. Of these, 20 subjects completed the 4 test days. Eight subjects dropped out following a haloperidol test day, predominately due to akathisia that often appeared after research assessments were completed on test days; three subjects terminated their participation following a ketamine test day, and three subjects discontinued their involvement due to scheduling difficulties. Ten male (age: 26.7 ± 3.5 years; weight: 84.0 ± 18.9 kg) and ten female subjects (age: 29.3 ± 7.2 years; weight: 63.0 ± 12.0 kg) completed the study. General intellectual capacities were comparable in the men and women participating in the study as assessed by the Slosson Intelligence Test (men: 127.9 ± 14.4; women: 136.1 ± 11.7; Slosson 1963). Fifteen subjects were Caucasian, two subjects were African-American, and three subjects were of Asian descent. In the group completing 4 test days, test day 1 assignments were as follows: seven subjects received placebo haloperidol and placebo ketamine (placebo day), four subjects received placebo haloperidol/active ketamine (ketamine day), six subjects received active haloperidol/active ketamine (ketamine-haloperidol day), and three subjects received active haloperidol/placebo ketamine (haloperidol day). The relatively small number in the group beginning with haloperidol reflects the relatively high dropout rate from this group following their initial test day.

Ketamine test procedures

Ketamine administration

Subjects completed 4 test days in a randomized and balanced order under double-blind conditions during which they received haloperidol 5 mg (Ortho-McNeill Pharmaceutical, Inc., Raritan, N.J. USA) or matched placebo 2 h before they were administered saline (0.9% NaCl, USP) or ketamine hydrochloride (Parke-Davis, Ann Arbor, Mich., USA) as a 1-min intravenous bolus of 0.26 mg/kg followed by a 1-h intravenous infusion of 0.65 mg/kg. Test days were spaced by 3–7 days. The ketamine dose and administration schedule selected in this study was similar to a previous study (Krystal et al. 1998a).

Behavioral ratings

Symptoms and behaviors characteristic of schizophrenia were assessed using the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962). The BPRS had previously been shown to be sensitive to ketamine effects in humans (Krystal et al. 1994). Four key BPRS items were selected as an index of the positive symptoms of schizophrenia, based on previous reports indicating their utility and validity (Bowers et al. 1980; Kane et al. 1988; Krystal et al. 1993) and inclusion within the empirically derived thought disorder factor of the BPRS (Hedlund and Vieweg 1980). These four key positive symptoms were conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual though content. In

evaluating hallucinatory behavior, bizarre perceptual experiences associated with an identifiable sensory reference were rated as illusory perceptual alterations rather than hallucinations as per Krystal et al. (1998a). Three key BPRS items, blunted affect, emotional withdrawal, and motor retardation, were selected as a measure of the negative symptoms of schizophrenia based on a report of their reliability and validity (Thiemann et al. 1987) and their inclusion within the empirically derived withdrawal-retardation factor of the BPRS (Hedlund and Vieweg 1980). Activation and anxious depression were also assessed using factors derived from the BPRS (Hedlung and Vieweg 1980). The items associated with the activation factor were tension, mannerisms and posturing, and excitement. The items contributing to the anxious depression factor were anxiety, guilt feelings, depressive mood, somatic concern, tension, and motor retardation.

Anxiety, drowsiness, high, irritability, and sadness were assessed using visual analog scales completed by clinician raters. These scales were scored in millimeters from the left hand side of a 100 mm line to a perpendicular mark made by the clinician at a point corresponding to the apparent magnitude of the feeling state reported and exhibited by the subject (range: 0, "not at all," to 100, "most ever"; Charney et al. 1987; Krystal et al. 1994). The BPRS and analog scales were administered prior to haloperidol (-120 min) and ketamine (-15 min) administration, and 5, 60, 90, 120 and 180 min following the initiation of ketamin infusion. Ratings assessed the period following the previous assessment. Thus, the 90-min timepoint reflected the previous 30 min.

The Clinician-Administered Dissociative States Scale (CADSS; Bremner et al. 1998) was a clinician-administered measure of perceptual, behavioral, and attention alterations occuring during dissociative experiences which had been validated in healthy subjects, schizophrenic patients and patients with post-traumatic stress disorder. This scale involved 19 self-report questions and eight observer ratings scored from 0 (not at all) to 4 (extremely). The CADSS was administered at the –150-, 5-, 60-, 90-, 120-, and 180-min timepoints.

This study evaluated immediate, post-distraction, and delayed recall using a simple test employed in prior ketamine studies (Krystal et al. 1994, 1998a). Separate sets of three words, selected on the basis of their comparable frequency of use in the English language and comparable difficulty (Kucera and Francis 1967) were presented at each timepoint. Thus, each set of words was presented once, but recall was assessed three times: immediately following presentation, following a distracting task, and following a 10-min delay. Word lists were presented 150 min prior to ketamine infusion and at the 5-, 90-, 120-, and 180-min timepoints.

Vigilance to visual stimuli was measured using a continuous performance task (Gordon 1983) in which subjects attended to numbers presented sequentially on a screen. The subject pushed a button to signal when a "9" was preceded by a "1". The distractibility task was identical to the vigilance task with the exception that numbers were presented sequentially in three contiguous columns. Subjects had to attend to the middle column and ignore the numbers presented in the outer two columns. The verbal fluency task requires subjects to generate as many words as possible beginning with a specified letter during a 1-min interval.

Equivalent versions of this task were administered on the 4 test days using letters equated for frequency in English (Borkowski et al. 1967).

The capacity for abstract ideation and the emergence of formal thought disorder were evaluated by assessing the interpretation of proverbs (Gorham 1956). The scoring system described by Gorham has been modified to increase inter-rater reliability and to assess concrete and bizarre responses as described in Krystal et al. (1998a). The concreteness and bizarreness of each response was rated on a 3-point scale, where a value of 0 indicated abstract and typical responses and a value of 2 reflected concrete and highly unusual responses. In addition, failure to respond was coded to reflect whether the subject did not respond secondary to time limitations, physical illness, or refusal. The abstract and bizarre totals were weighted to reflect the total number of responses they represent.

A computerized version of the Wisconsin Card Sorting Test (WCST) developed by Donald Quinlan was employed to examine functions including working memory, mental set shifting, and abstract problem solving (Krystal et al. 1994, 1998a, unpublished). It is a task in which cards are sorted by the number, color, and shape of objects depicted on the card. This task requires the subject to determine the rule governing the matching of cards and to adapt when these rules shift during the task (Milner 1964). To compensate for an unbalanced randomized distribution of first day assignments, eight healthy subjects with very similar demographic characteristics who received ketamine at an identical dose in another study (Krystal et al. 1998a) were added to the analysis of WCST data in the current study. Cognitive tasks were presented in a fixed order in order to increase comparability between test days. The verbal fluency, vigilance and distractibility tests, and the proverb tests were initiated 10 min following the ketamine bolus. The WCST was administered 40 min following the ketamine bolus.

Extrapyramidal motor symptoms were assessed using the Extrapyramidal Symptom Rating Scale (Chouinard et al. 1970) and the Barnes Akathisia Scale (Barnes 1989). Both scales were administered at baseline and at 40 and 120 min following ketamine administration.

Biochemical methods

Plasma levels of prolactin, cortisol, homovanillic acid (HVA), and ketamine were determined. Radioimmunoassay kits were utilized for determining plasma levels of prolactin [Serono Diagnostics, Inc. Norwell, moss, USA; intra-assay and interassay coefficients of variance (CVs) were 3%, and 7%, respectively], cortisol (Baxter Travenol Diagnostics, Incstar Corp, Stillwater minn. USA; intra-assay and interassay variance were 3% and 5%, respectively). Plasma samples for hormonal analysis were run in duplicate pairs. Plasma free levels of HVA (Bacopoulos et al. 1979) were measured by gas chromatography and mass spectrometry using deuterated internal standards.

Data analysis

Data were initially subjected to a repeated measures analysis of variance (RMANOVA) with within-subjects factors of ketamine (ketamine versus placebo), haloperidol (haloperidol versus placebo), and time. If the ketamine by time interaction or the haloperidol by time interaction was significant, but the interactive effects of both drugs and time was not, then a post-hoc RMANOVA comparing the ketamine and ketamine-haloperidol test days was conducted to examine additive interactions. In this presentation, when drug (ketamine or haloperidol), time, and the drug by time interactions all were significant, only the drug by time interactions were reported. The interactive effects of gender was studied as a between subjects factor added to the RMANOVAs. Except when reported, significant gender differences did not emerge in the data analysis. Thus, unless indicated, data were collapsed across genders.

Similarly, the interactive impact of emesis on neuroendocrine data was studied by adding the presence or absence of this behavior as a between-subjects factor in the repeated measures ANOVAs. Post-hoc within-subjects contrasts were employed to compare test days for data from cognitive tasks administered once per test day. Comparison of baseline values was conducted using paired t-tests with Bonferroni corrections to adjust for multiple comparisons. No significant baseline differences emerged. Ketamine effects on the WCST show significant order effects (Krystal et al., unpublished). As a result, WCST data in this report are solely from the first test day for each subject. These data were compared using an ANOVA in a between-subjects design. Post-hoc testing of WCST results was

Table 1 The effects of ketamine and haloperidol upon measures sensitive to frontal cortical impairments in healthy subjects[a]

Assessments	Placebo haloperidol Placebo ketamine	Placebo haloperidol Placebo ketamine	Active haloperidol Active ketamine	Active haloperidol Placebo ketamine
Vigilance[b]				
Number correct	27.9 ± 1.1	26.8 ± 0.9	27.7 ± 0.7	28.3 ± 0.9
Omission errors	2.1 ± 1.1	3.1 ± 0.9	2.9 ± 0.7	1.7 ± 0.9
Commission errors	0.6 ± 0.4	0.7 ± 0.4	1.2 ± 0.4	1.0 ± 0.4
Response latency (ms)	48.2 ± 2.2	47.3 ± 2.4	47.6 ± 2.2	50.1 ± 2.8
Distractibility[c]				
Number correct	27.9 ± 2.4	20.1 ± 1.9***	16.0 ± 2.4***§§§	23.7 ± 2.1
Omission errors	2.1 ± 0.6	9.9 ± 1.9***	14.0 ± 2.4***§§§	6.3 ± 2.1
Commission errors	0.7 ± 0.2	5.3 ± 2.7*	4.4 ± 2.0	2.1 ± 0.9
Response Latency (ms)	45.9 ± 1.9	48.4 ± 2.3	51.2 ± 3.0	48.4 ± 2.4
Verbal fluency[d]				
Words generated	15.6 ± 0.9	14.0 ± 0.9	13.1 ± 1.0	14.0 ± 0.0
Proverb interpretation[e]				
Concreteness	0.2 ± 0.1	0.5 ± 0.1***§§§¶¶¶	0.3 ± 0.1	0.1 ± 0.0
Bizarreness	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
No response	0.2 ± 0.1	1.7 ± 0.7	1.4 ± 0.5	0.1 ± 0.1
Wisconsin Card Sorting Test[f]				
Perseverative errors	21.5 ± 8.4	47.5 ± 8.4^$$$	36.9 ± 7.6$	9.7 ± 1.5
% Perseverative errors	55.9 ± 5.8	64.9 ± 5.4	64.5 ± 4.2	52.4 ± 3.2
Non-persev errors	14.0 ± 3.1	20.8 ± 3.7$$	18.2 ± 3.2$	8.8 ± 1.3
Category criteria met	4.6 ± 0.8	2.3 ± 0.8^^$$$	3.8 ± 0.8$	6.0 ± 0.0
Trials to first category	23.1 ± 9.2	19.0 ± 8.2	22.8 ± 7.3	13.9 ± 1.4

[a]Data are presented as mean ± SEM, variability in sample size across tests reflects tests omitted due to time constraints on particular test days
[b]Based on healthy subjects completing the vigilance task on all 4 test days ($n = 18$)
[c]Based on healthy subjects completing the distractibility task on all 4 test days ($n = 15$)
[d]Based on healthy subjects completing the verbal fluency task on all 4 test days ($n = 19$)
[e]Based on healthy subjects completing the proverb interpretation task on all 4 test days ($n = 19$)
[f]Based on the first test day from healthy subjects ($n = 37$: placebo, $n = 8$; ketamine, $n = 12$; ketamine-haloperidol: $n = 9$; haloperidol: $n = 8$), see ketamine test procedures for description of the sample completing this test
For comparison of the placebo test day to other test days by post-hoc contrasts with Bonferroni adjustments: *$P < 0.05$; **$P < 0.01$; ***$P < 0.005$
For comparisons of the haloperidol day to other test days by post-hoc contrasts with Bonferroni adjustments: $^{\S}P < 0.05$; $^{\S\S}P < 0.01$; $^{\S\S\S}P < 0.005$
For comparisons of the ketamine-haloperidol day to other test days by post-hoc contrasts with Bonferroni adjustments: $^{\P}P < 0.05$; $^{\P\P}P < 0.01$; $^{\P\P\P}P < 0.005$
For comparisons of the placebo test day to other test days by Fishers's protected least significant difference test: $^{\wedge}P < 0.05$; $^{\wedge\wedge}P < 0.01$; $^{\wedge\wedge}P < 0.005$
For comparisons of the haloperidol day to other test days by Fishers's protected least significant difference test: $^{\$}P < 0.05$; $^{\$\$}P < 0.01$; $^{\$\$\$}P < 0.005$

conducted using the Fisher Protected Least Significant Difference (PLSD) multiple comparison test.

Results

Cognitive functions

Vigilance

Vigilance data are presented in Table 1. RMANOVA revealed that ketamine had modest effects on the number of items correctly identified [$F(1,17) = 8.2$, $P = 0.01$] and the number of omission errors [$F(1,17) = 6.5$, $P = 0.02$], but not commission errors, on the continuous performance test of vigilance ($n = 18$). Haloperidol had no effect on vigilance in this study. Adjusting for multiple comparisons in the post-hoc contrasts, there were no significant differences between test days for any vigilance outcome measure. Also, there were no drug effects on response latency.

Distractibility

Both ketamine and haloperidol worsened distractibility, but their interactive effects did not reach significance. The sample size for this test ($n = 15$) was smaller than for vigilance because it was omitted in three subjects who were significantly delayed in completing their assessments. RMANOVA revealed that ketamine [$F(1,15) = 29.1$, $P = 0.0001$] and haloperidol [$F(1,15) = 9.0$, $P = 0.01$] reduced the number of correct

responses on the distractibility task. As described in Table 1, post-hoc within subjects contrasts revealed that both ketamine and the ketamine-haloperidol combination reduced the number of correct responses relative to placebo ($P \leq 0.004$), while the combination also decreased the number of correct responses relative to haloperidol alone ($P = 0.004$). Similarly, both ketamine [$F(1,14) = 28.7$, $P = 0.0001$] and haloperidol [$F(1,14) = 8.9$, $P = 0.01$] increased omission errors and there was a trend for ketamine to produce commission errors [$F(1,14) = 3.6$, $P = 0.08$]. As presented in Table 1, post-hoc within-subjects contrasts revealed that both ketamine and the ketamine-haloperidol combination increased the number of omission errors relative to placebo ($P \leq 0.004$), while the combination also decreased the number of correct responses relative to haloperidol alone ($P = 0.004$). For commission errors, ketamine, but not the ketamine-haloperidol combination, increased errors relative to placebo ($P = 0.02$). There were no significant drug effects on response latency.

Verbal fluency

No significant drug effects on verbal fluency were observed.

Proverb interpretation

Ketamine reduced the capacity for abstract proverb interpretation (Table 1), i.e., it made the thought processes or research subjects concrete [$F(1,18) = 11.1$, $P = 0.004$]. In contrast, haloperidol pretreatment reduced ketamine-induced concreteness without substantially altering this measure relative to placebo [$F(1,17) = 5.6$, $P = 0.03$]. Post-hoc within-subjects contrasts revealed that ketamine increased concreteness relative to both placebo ($P = 0.001$), and haloperidol ($P = 0.0006$) and the ketamine-haloperidol combination ($P = 0.02$). In contrast, the ketamine-haloperidol combination did not differ significantly from placebo or haloperidol. Neither drug significantly altered the bizarreness of proverb interpretations. Ketamine also caused the failure to generate a proverb interpretation [$F(1,19) = 8.9$, $P = 0.008$]. However, haloperidol did not influence responses on this outcome measure. Adjusting for multiple post-hoc comparisons, none of the test days differed significantly on this outcome measure.

Wisconsin Card Sorting Test (WCST)

On test day 1, ketamine impaired performance on the WCST and haloperidol improved aspects of performance on this test. Ketamine increased the number of perseverative errors [$F(1,34) = 10.2$, $P = 0.003$] and reduced the number of category criteria achieved [$F(1,34) = 7.1$, $P = 0.01$], without significantly increasing non-perseverative errors or trials to the successful completion of the first category criterion. Haloperidol significantly increased the number of category criteria achieved [$F(1,34) = 5.0$, $P = 0.03$] and non-significantly reduced perseverative errors [$F(2.9) = 2.9$, $P = 0.1$]. As indicated in Table 1, the number of perseverative errors was increased relative to placebo by ketamine, but not the haloperidol-ketamine combination. Similarly, the number of category criteria achieved was reduced by ketamine, but not the co-administration of ketamine and haloperidol. Thus, although the difference between ketamine and the ketamine-haloperidol test days did not reach significance on these measures, it did appear that haloperidol attenuated ketamine effects.

Learning and memory

Ketamine produced a delay-dependent impairment in word recall [RMANOVA: ketamine by delay by time interaction: $F(8,152) = 18.7$, $P = 0.0001$], with no significant effect on immediate recall and more prominent impairments of post-distraction and delayed recall. There were no significant effects of haloperidol on memory.

Mini-mental state examination (MMSE)

Drug effects on this measure were modest. Ketamine [RMANOVA: ketamine by time interaction: $F(4,76) = 6.2$, $P = 0.003$], but not haloperidol had significant effects on MMSE scores. Although haloperidol did not have significant effects on MMSE performance, there was a non-significant trend for it to worsen the impairment associated with ketamine [ketamine by haloperidol by time: $F(4,76) = 2.3$, $P = 0.09$].

Positive symptoms, negative symptoms, and perceptual alterations

Data from the BPRS 4 key positive symptoms of psychosis, the BPRS 3 key negative symptoms, and the CADSS are presented in Fig. 1.

BPRS

This study replicated previous studies in documenting a capacity of ketamine to produce positive and negative symptoms associated with schizophrenia as well as mood, hostility, and activating effects in healthy subjects. RMANOVAs performed on BPRS total score

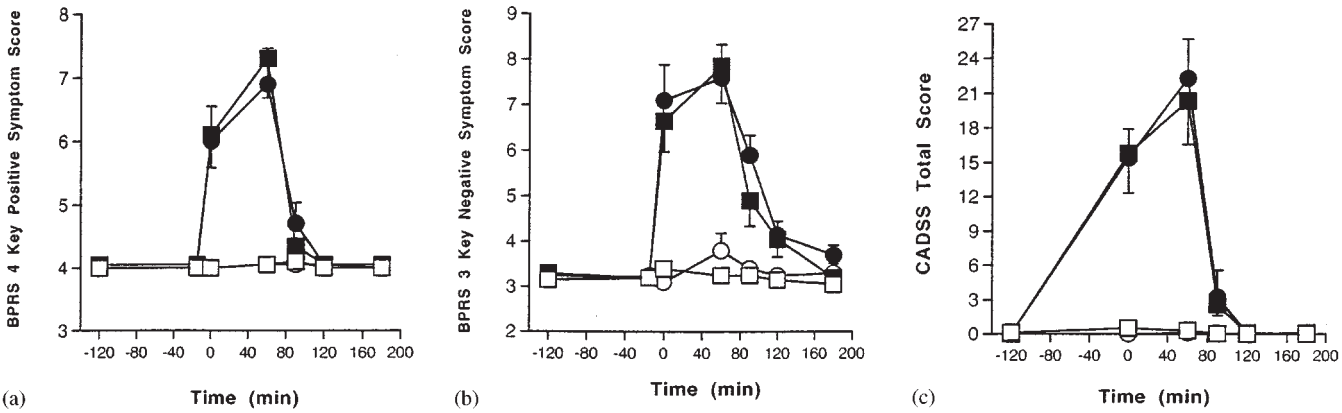

Fig. 1a–c Ketamine and haloperidol effects on symptoms: **a** positive symptoms (BPRS 4 key positive symptom score), **b** negative symptoms (BPRS 3 key negative symptom score), and **c** perceptual alterations (CADSS score). Data are presented as mean values ± SEM. Statistical analyses are presented in the text. Test days are depicted as follows: □ placebo, ■ ketamine, ● ketamine-haloperidol, and ○ haloperidol

[$F(6,114) = 34.3$, $P = 0.0001$], four key positive symptoms of psychosis score [$F(6,114) = 26.2$, $P < 0.0001$], three key negative symptoms score [withdrawal-retardation factor: $F(6,114) = 27.0$, $P < 0.0001$], anxious-depression factor score [$F(6,114) = 23.8$, $P = 0.0001$], hostility-suspiciousness factor score [$F(6,114) = 3.6$, $P = 0.03$], or activation factor score [$F(6,114) = 15.1$, $P < 0.0001$]. There were no significant baseline differences between test days and no significant interactive effects with haloperidol.

CADSS

As previously reported, ketamine significantly increased scores on the CADSS [RMANOVA: ketamine by time interaction: $F(5,95) = 36.9$, $P = 0.0001$]. There were no baseline differences between test days and there were no significant main effects or interactive effects of haloperidol.

Visual analog scales of mood states

Data from the visual analog scales of mood states are presented in Fig. 2.

Anxiety

Ketamine [RMANOVA: ketamine by time: $F(6,114) = 12.6$, $P = 0.0001$] and to a lesser extent, haloperidol [haloperidol by time: $F(6,108) = 3.7$, $P = 0.007$], increased anxiety. There was evidence that haloperidol pretreatment reduced anxiety produced by ketamine. Although the interaction of ketamine, haloperidol, and time did not reach significance [$F(6,114) = 2.0$, $P = 0.1$], anxiety levels on the ketamine test day were significantly greater than on the ketamine-haloperidol test day [drug by time: $F(6,114) = 3.2$, $P = 0.007$]. However, the ketamine-haloperidol test day produced significantly more anxiety than did the haloperidol test day [drug by time: $F(6,114) = 7.45$, $P = 0.0001$].

Drowsiness

Both ketamine [ketamine by time: $F(6,114) = 4.5$, $P = 0.002$] and haloperidol [haloperidol by time: $F(6,114) = 6.4$, $P = 0.0001$] increased drowsiness. The interaction of ketamine, haloperidol, and time was not significant. However, the data suggested that ketamine and haloperidol produced additive sedative effects. RMANOVA revealed that subjects were more drowsy on the ketamine-haloperidol test day than the ketamine test day [$F(6,114) = 2.4$, $P = 0.03$] and a similar non-significant trend was evident for comparison to the haloperidol test day [$F(6,114) = 1.9$, $P = 0.09$].

High

Ketamine [ketamine by time interaction: $F(6,114) = 20.6$, $P = 0.0001$], but not haloperidol, produced a subjective sense of being high. However, haloperidol did not block the ketamine high.

Extrapyramidal motor symptoms

Extrapyramidal symptom scale (ESRS)

ESRS scores are presented in Fig. 3. The RMANOVA revealed a significant ketamine by time interaction [$F(2,38) = 9.2$, $P = 0.0007$] and a non-significant haloperidol effect [$F(1,19) = 3.7$, $P = 0.07$]. There was no significant interaction between these drugs.

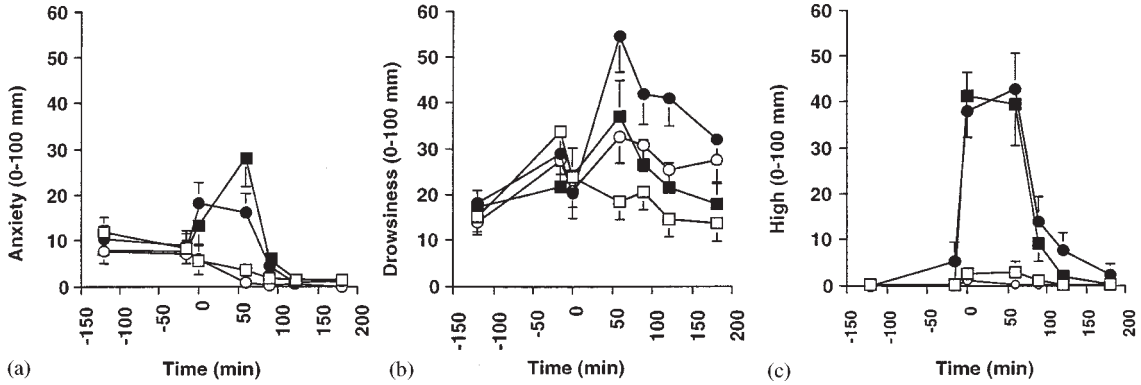

Fig. 2a–c Ketamine and haloperidol effects on mood states assessed by visual analog scales: **a** anxiety, **b** drowsiness, and **c** high. Data are presented as mean values ± SEM. Statistical analyses are presented in the text. Test days are depicted as follows: □ placebo, ■ ketamine, ● ketamine-haloperidol, and ○ haloperidol

Barnes akathesia scale

There were no significant drug effects or interactions as measured by this scale.

Neuroendocrine measures

Cortisol

Cortisol data are presented in Fig. 4. As with previous studies, ketamine significantly increased plasma cortisol levels [RMANOVA: ketamine by time interaction: $F(4,56) = 32.9$, $P = 0.0001$]. Haloperidol also increased plasma cortisol levels [RMANOVA: haloperidol by time interaction: $F(4,56) = 3.2$, $P = 0.05$]. However, there was no significant baseline differences between test days or interactions between haloperidol and ketamine.

Prolactin

Prolactin data are presented for male and female subjects separately in Fig. 5. Haloperidol had greater stimulatory effects on the release of prolactin in females compared to males. However, ketamine potentiated the haloperidol stimulation of prolactin release in males, but not females. As a result, analyses revealed a significant interaction between haloperidol, time and gender [RMANOVA: $F(4,56) = 6.4$, $P = 0.007$]. Because of this gender effect, data from males and females was analyzed separately. The data for females followed the larger sample: there was a haloperidol by time effect [RMANOVA: $F(4,24) = 12.7$, $P < 0.0001$], but no significant ketamine effects. However, in males, the haloperidol by time interaction, the ketamine by time interaction, and the ketamine by haloperidol by time interactions were all significant ($P < 0.05$). In the full sample, the ketamine-haloperidol day prolactin

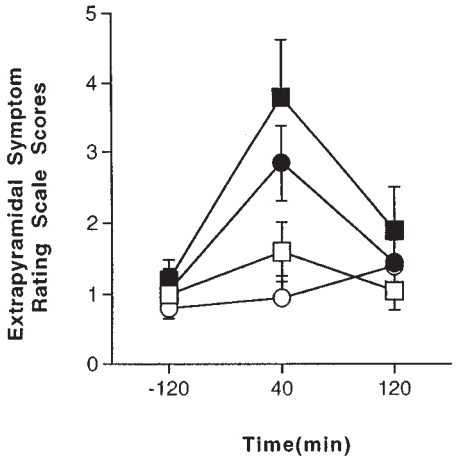

Fig. 3 Ketamine and haloperidol effects on Extrapyramidal Symptom Rating Scale (ESRS) scores. Data are presented as mean values ± SEM. Statistical analyses are presented in the text. Test days are depicted as follows: □ placebo, ■ ketamine, ● ketamine-haloperidol, and ○ haloperidol

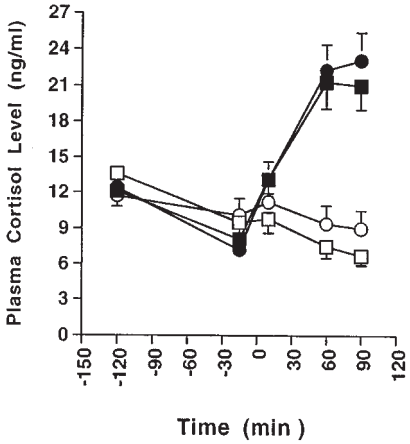

Fig. 4 Ketamine and haloperidol effects on plasma cortisol levels. Data are presented as mean values ± SEM. Statistical analyses are presented in the text. Test days are depicted as follows: □ placebo, ■ ketamine, ● ketamine-haloperidol, and ○ haloperidol

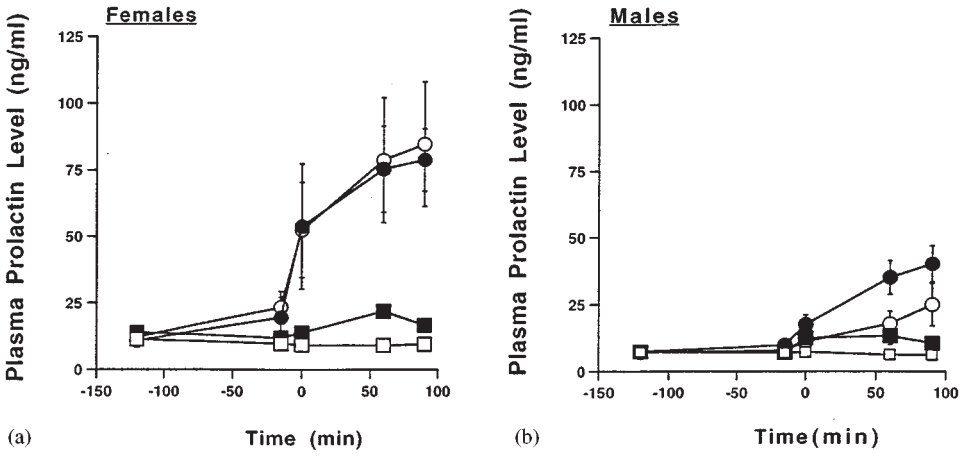

Fig. 5a,b Ketamine and haloperidol effects on plasma prolactin in female subjects **a** and male subjects **b**. Data are presented as mean values ± SEM. Statistical analyses are presented in the text. Test days are depicted as follows: □ placebo, □ ketamine, ● ketamine-haloperidol, and ○ haloperidol

increase was greater than that seen on the haloperidol test day [RMANOVA: drug by time interaction: $F(4,64) = 17.5$, $P < 0.0001$].

HVA

Ketamine [$F(1,17) = 11.5$], but not haloperidol increased plasma HVA levels. However, the interaction of ketamine and time did not reach significance.

Vital signs

Ketamine increased systolic and diastolic blood pressure and pulse in healthy subjects. The RMANOVAs revealed significant effects of ketamine [ketamine by time interaction: systolic, $F(6,114) = 8.7$, $P = 0.0001$; diastolic, $F(6,114) = 7.9$, $P = 0.0001$; pulse, $F(6,114) = 8.9$, $P = 0.0001$]. Neither the haloperidol by time or haloperidol by ketamine by time interactions were significant.

Discussion

The principal finding of this study was that impairments in executive cognitive functions produced by ketamine in healthy subjects and assessed using the WCST and the Gorham's Proverb's test were reduced by pretreatment with haloperidol. In addition, haloperidol reduced the anxiogenic effects of ketamine. However, several other aspects of ketamine response were not reversed by haloperidol, including the production of positive and negative symptoms resembling schizophrenia, perceptual changes similar to dissociative states, amnestic effects, euphoric effects, and attention impairments. In addition, haloperidol increased the sedative and prolactin responses to ketamine. The current findings contrast with a previous study with a very similar experimental design that found that lorazepam 2 mg, PO reduced perceptual and anxiogenic effects of ketamine, while it worsened most aspects of cognitive function (Krystal et al. 1998a). Overall, these data suggest that haloperidol and lorazepam may block different components of acute NMDA antagonist effects. Neither drug reduced the positive or negative symptoms produced by ketamine as assessed by the BPRS.

The capacity of haloperidol to reduce ketamine effects on the WCST and to improve the capacity to interpret proverbs abstractly suggests that these medications interact to modulate cognitive functions associated with networks involving the frontal cortex. These executive functions include vigilance to visual stimuli, distractibility, verbal fluency, abstract reasoning, and the capacity to shift mental set (Goldstein 1949; Milner 1964; Benton 1968; Salmaso and Denes 1982; Wilkins et al. 1987). In the current study, haloperidol had sedative effects that may have been reflected in its enhancement of distractibility, a task that places greater demands upon attention that the vigilance task. The sedative effects of haloperidol may have confounded the evaluation of its capacity to attenuate the increase in distractibility produced by ketamine. However, haloperidol reduced other components of executive function that were impaired by ketamine in this study.

The beneficial cognitive effects of acute haloperidol may have therapeutic implications. Ketamine enhances glutamate and dopamine release in components of cortico-striato-thalamic circultry primarily as a consequence of NMDA receptor antagonism (Rao et al. 1989; Carlsson and Carlsson 1990; Moghaddam et al. 1997). Ketamine also has modest, but detectable, affinity and activity at the dopamine transporter at subanesthetic doses (Snell et al. 1984; Kuhar et al. 1990; Irifune et al. 1991). Consistent with recent study in rodents, haloperidol pretreatment may have prevented ketamine-induced impairments in cognitive functions associated with the frontal cortex by blocking the consequences of excessive dopamine$_2$ receptor stimulation (Arnsten et al. 1994; Verma and Moghaddam 1996), while permitting the possible beneficial effects of

enhanced dopamine$_1$ and dopamine$_5$ receptor stimulation to continue unimpeded (Arnsten et al. 1994, 1995; Williams and Goldman-Rakic 1995). Because ketamine may model cognitive dysfunction associated with schizophrenia arising from reductions in NMDA receptor function, the potential role of selective dopamine$_{1/5}$ receptor agonists as nootropic agents deserves further examination. However, NMDA antagonist-induced impairments in working memory appear more transient than increases in prefrontal cortex and nucleus accumbens extracellular dopamine levels (Adams and Moghaddam 1998). These data question the role of dopamine in mediating as opposed to moderating ketamine effects on cognition. Therefore, further research is needed to identify mechanisms underlying the beneficial cognitive effects of haloperidol observed in this study.

Haloperidol did not block the positive or negative symptoms produced by ketamine in healthy subjects. As noted earlier, this finding is consistent with the limited impact of chronic haloperidol treatment on ketamine effects in schizophrenic patients (Lahti et al. 1995). It is possible that the failure of haloperidol to block these symptoms reflects a limitation in the relevance of the NMDA receptor deficit model for schizophrenia. Alternatively, it is possible that this study did not fully test the hypothesis that dopamine$_2$ receptor antagonism reduces the psychotogenic effects of NMDA antagonists because it evaluated single doses of both ketamine and haloperidol. Further, haloperidol actions at other sites, such as dopamine$_3$ (Lévesque et al. 1992) and σ (Hanner et al. 1996) receptors, may have contaminated the interpretation of dopamine$_2$ receptor antagonist effects in the current study. In particular, haloperidol may have potentiated some ketamine effects by reducing NMDA receptor function via its σ receptor actions (Whittemore et al. 1997) or via a distinct site on NMDA receptors (Lynch and Gallagher 1996). However, it may be the case that ketamine effects better model of positive and negative symptoms that are resistant to typical neuroleptic treatment than they model symptoms that are responsive to typical neuroleptics (Krystal et al. 1998c).

The failure of haloperidol to block the euphoric effects of ketamine may have implications for addictive disorders. Both ketamine and PCP are abused drugs (Siegel 1978; Smith et al. 1978). The failure of haloperidol to alter ketamine-induced euphoria is consistent with preclinical research suggesting that the rewarding properties of NMDA antagonists are not dopamine$_2$ receptor antagonist-sensitive (Carlezon and Wise 1996). However, the current findings raise further questions about the utility of drugs acting at dopamine$_2$ receptors in the treatment of individuals who abuse NMDA antagonists or perhaps other drugs, such as ethanol, that block NMDA receptors (Krystal et al. 1998b).

This study documents the existence of ketamine effects of ESRS scores, a clinical measure of extrapyramidal side effects. NMDA antagonists produces both stereotypy and catalepsy in animals, although NMDA antagonists also reduce neuroleptic-induced Parkinsonism (Koek et al. 1988; Kretschmer et al. 1992). In the current study, ketamine-induced extrapyramidal symptoms were accompained by psychomotor retardation. However, the psychomotor effects of ketamine at the doses studied were modest. For example, ketamine did not increase response latency in the continuous performance test of attention. Late-appearing akathesia occurred in a subset of healthy subjects who received haloperidol on the evening of test days. Although subjects received close follow-up and were provided with benztropine to reduce these symptoms in anticipation of this effect, akathisia was an important source of study non-completion in this group of healthy subjects. It is possible that dropouts among healthy subjects experiencing extrapyramidal symptoms following the administration of haloperidol may have biased the data against finding these symptoms in study completers.

This study found gender differences in the interaction of ketamine and haloperidol. In this sample, ketamine increased prolactin significantly in male, but not female subjects. In contrast, haloperidol had greater effects on prolactin in female than male subjects. Gender-related differences in prolactin regulation are consistent with preclinical studies suggesting that estrogen modulates the effects of NMDA antagonists upon tuberoinfundibular dopaminergic neurons (Wagner et al. 1993).

Several limitations influence the interpretation of this study. First, pilot data (available upon requent) suggest that plasma ketamine and haloperidol levels were not at steady state during the period of behavioral assessment. Therefore, it is conceivable that the current results reflect this state.

In summary, the current study replicated a growing body of research describing ketamine effects on cognitive function, symptoms resembling schizophrenia, perceptual effects similar to dissociative states, and euphoric effects that have been described as similar to the effects of ethanol. The beneficial effects of haloperidol pretreatment upon cognitive effects of ketamine is consistent with the animal literature and supportive of the importance of interactions between dopaminergic and glutamatergic systems. However, the failure of haloperidol pretreatment to block the schizophrenia-like symptoms produced by ketamine suggests that novel pharmacologic approaches will be needed to block these effects.

Acknowledgements The authors thank Ms. Sally Vegso for excellent statistical support. They also thank Mr. Jonathan White, the staff of the Schizophrenia Research Program, Ms. Angelina Genovese, Ms. Patricia Barry, Ms. Elizabeth O'Donnell, and the Staff of the Biological Studies Unit of the VA Connecticut Healthcare System for their contributions to this study. This study was supported by funding from the Department of Veterans Affairs

through the Schizophrenia Biological Research Center (D. Charney, B.S. Bunney) and VA-Yale Alcoholism Research Center (J. Krystal, B. Rounsaville), West Haven, Conn. and by a Merit Review Grant from the Department of Veterans Affairs (J. Krystal). Additional funding care from research grant MH-30929 (D. Charney, J. Leckman) and MH44866 (P. Goldman-Rakic) from the National Institute of Mental Health Bethesda, Md.

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