Effects of Ketamine on Thought Disorder, Working Memory, and Semantic Memory in Healthy Volunteers

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Background: *The* N-*methyl-*D*-aspartate receptor antagonist, ketamine, produces a clinical syndrome of thought disorder, perceptual distortion, and cognitive impairment.*

Methods: *We have administered ketamine to healthy volunteers to characterize the formal thought disorder and specific memory dysfunction associated with ketamine. Ten healthy volunteers underwent a double-blind, placebo-controlled, ketamine infusion (0.12 mg/kg bolus and 0.65 mg/kg/hour). Thought disorder was evaluated with the Scale for the Assessment of Thought, Language and Communication. Cognitive testing involved working and semantic memory tasks.*

Results: *Ketamine produced a formal thought disorder, as well as impairments in working and semantic memory. The degree of ketamine-induced thought disorder significantly correlated with ketamine-induced decreases in working memory and did not correlate with ketamine-induced impairments in semantic memory.*

Conclusions: *This study characterizes the formal thought disorder associated with ketamine and may suggest that ketamine-induced deficits in working memory are associated with ketamine-induced thought disorder.* Biol Psychiatry 1998;43:811–816 *Published 1998 Society of Biological Psychiatry*

Key Words: *N*-methyl-D-aspartate, ketamine, cognition, thought disorder, working memory

Introduction

Several lines of evidence suggest that the *N*-methyl-D-aspartate (NMDA) receptor is involved in the pathogenesis of schizophrenia. Postmortem studies have revealed decreased density of glutamatergic receptors in schizophrenic patients (Kerwin et al 1988; Kornhuber et al 1989), and at least one study of cerebrospinal fluid (CSF) has shown lower levels of glutamate in schizophrenic patients than in healthy controls (Kim et al 1980). Furthermore, administration of NMDA antagonists such as phencyclidine (PCP) to healthy volunteers reproduces many of the symptoms of schizophrenia (Luby et al 1959; Davies and Beech 1960). In schizophrenic patients, administration of PCP exacerbates existing symptoms and may reactivate those in remittance (Luby et al 1959; Ban et al 1961).

The toxicity of PCP (Olney et al 1989) has led to the use of the NMDA antagonist, ketamine, to examine the effects of NMDA antagonism on thought and behavior (Krystal et al 1994; Malhotra et al 1996). At subanesthetic doses, ketamine induces a clinical syndrome characterized by thought disturbance, perceptual alterations, emotional withdrawal, and cognitive dysfunction in healthy volunteers (Krystal et al 1994; Malhotra et al 1996). Because its behavioral profile resembles many of the clinical features of schizophrenia, ketamine has been proposed as a pharmacologic model of the illness.

We have previously found the Brief Psychiatric Rating Scale (BPRS) item, conceptual disorganization, to demonstrate the most significant effect from ketamine (Malhotra et al 1996). Others have similarly found a very marked effect of ketamine on the BPRS factor containing conceptual disorganization (Krystal et al 1994). In terms of specific cognitive effects, we found that ketamine produced marked deficits on two measures of explicit memory, free recall and recognition memory (Malhotra et al 1996). Ketamine has also been associated with impaired performance on delayed recall, another measure of explicit memory, as well as on the semantic memory task of verbal fluency (Krystal et al 1994; Ghoneim et al 1985). All of these memory functions may be considered together as components of memory requiring long-term storage. In addition, ketamine causes deficits on the Wisconsin Card Sorting Test (WCST), a task that includes a significant working memory component (Krystal et al 1994). It has been hypothesized that deficits in specific memory systems are associated with formal thought disorder in schizophrenia. Goldman-Rakic (1994) and others have

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suggested that working memory may underlie thought disorder, while Goldberg and Weinberger (1995) have proposed the involvement of semantic memory.

Previous studies of formal thought disorder and memory dysfunction caused by ketamine raise several methodologic issues. First, thought disorder has been measured with the single BPRS item conceptual disorganization, or the three-item BPRS factor thought disturbance (Krystal et al 1994; Malhotra et al 1996). Many elements of formal thought disorder are poorly measured by these limited ratings. Another issue relates to the cognitive tests that have been utilized. The putative working memory task previously employed, the WCST, involves multiple cognitive processes in addition to working memory (Goldman-Rakic 1994; Axelrod et al 1994). In addition, the attention or vigilance tasks employed in the past have included significant working memory components (Krystal et al 1994; Malhotra et al 1996). Thus, it has been difficult to isolate which cognitive domains are primarily affected by ketamine.

In this study, we further examined the effects of ketamine on thought disorder and memory function. We utilized a comprehensive measure of thought disorder, the Scale for the Assessment of Thought, Language and Communication (TLC). The TLC is a clinical interview based scale that assesses specific aspects of thought disorder, including thought formation and communication (Andreasen 1978). In addition, we examined memory function during ketamine administration with two separate verbal fluency tasks that contain significant semantic memory components, and a working memory task. A simple measure of vigilance involving immediate response to a visual stimulus that minimizes the working memory contribution was also utilized. Further, the relationships between ketamine-induced effects on thought disorder and the two memory tasks were examined to provide information about the relative contributions of working and semantic memory to formal thought disorder under conditions of glutamatergic perturbation.

Methods and Materials

Subjects

Ten subjects (7 men and 3 women, mean age 35.2 ± 17.8 years) were recruited through the National Institutes of Health normal volunteer program to participate in this study. All of the subjects were in good health and underwent a medical evaluation, including a physical exam, an electrocardiogram, and laboratory tests including complete blood count, electrolytes, urinalysis, and liver and thyroid studies. Subjects were found to be free of psychiatric disorders on clinical examination and on a structured diagnostic interview, the Structured Clinical Interview for DSM-III-R (SCID-III-R).

Cognitive and Behavioral Measures

***N*-BACK WORKING MEMORY.** Cognitive testing included a working memory task. Subjects viewed numbers from one to four that consistently appeared in one of four quadrants on a computer screen. They were given a computer keyboard with four keys corresponding to the numbers and quadrants on the screen. Fourteen numbers appeared over a 30-sec interval. Subjects were asked to press the key corresponding to the number then appearing in one condition ("zero back"), to press the key corresponding to the number that immediately preceded the number then appearing in a second condition ("one back"), or to press the key corresponding to the number that preceded the number currently on the screen by two places, in a third condition ("two back"). The test was arranged with a 30-sec rest period followed by each of the three tasks, randomly arranged. Two of these 2-min testing periods were done sequentially and were termed one block. The one back and the two back are tests of working memory that parametrically increase delay time and memory load, while the zero back is considered a simple measure of attention and vigilance (Callicott et al 1998).

VERBAL FLUENCY. Two verbal fluency tests were administered. In one, subjects were given 1 min to generate lists of words in response to single letter prompts (words beginning with the letter "F," the letter "A," and the letter "S"). In the second, they were asked to generate words for 1 min in response to three superordinate categories: "animals," "vegetables," and "fruit" (Benton and Hamsher 1976; Talland 1965).

PSYCHIATRIC SYMPTOMS. Behavioral changes were assessed with the 18-item BPRS (Overall and Gorham 1962). All BPRS ratings were done by a single investigator. BPRS total score was analyzed, as were the empirically derived factors for thought disturbance and withdrawal/retardation (Hedlund and Vieweg 1980). In addition, the item for conceptual disorganization was analyzed.

Formal thought disorder was rated during an interview with the TLC, a structured rating scale (Andreasen 1978). The interviewer asked open-ended questions designed to elicit a quantity of speech from the subject. Speech was further stimulated through the use of a standardized selection of pictures on which the subject was asked to comment at length. All ratings were done by a single investigator. The TLC was analyzed in total and using factors for verbal production and disconnection of thought. These two factors were found to best model thought disorder ratings on the TLC (Harvey et al 1992).

PROCEDURE. The study was done in a double-blind, randomized, placebo-controlled fashion. Placebo and ketamine were administered on 2 separate days not more than 8 and not less than 2 days apart. Subjects were instructed to fast after midnight the night prior to the procedure. On the mornings of the study, bilateral upper extremity intravenous (IV) lines were inserted. Sixty minutes after the IV placement, a 0.12-mg/kg bolus of ketamine or placebo was administered, followed by an hour-long 0.65 mg/kg (maximum dose of 58 mg) ketamine or placebo infusion.

Two blocks of the *n*-back attention/working memory test were conducted 45 min prior (−45) to infusion. A group of six blocks was begun 10 min after beginning the infusion and continued for approximately 30 min (+10–+40). Two more blocks were conducted 30 min after the infusion had ended (+90). Verbal fluency was tested only during the infusion, at 40 min (+40). BPRS and TLC were administered 30 min prior to the infusion (−30), 40 min into the infusion (+40), and 30 min after the infusion (+90).

STATISTICAL ANALYSES. Analyses of variance (ANOVAs) were performed using time as a within-subject variable and drug condition as the independent variable. The ANOVA of working memory was calculated using the means of the two preinfusion blocks, the six blocks performed during each infusion, and the two postinfusion blocks. Post hoc Newman–Keuls tests were performed when ANOVA drug by time interactions were significant.

Spearman rank order correlation coefficients were calculated to ascertain the relationship between ketamine-induced changes in the TLC and ketamine-induced changes in the working memory and verbal fluency tasks, as well as between ketamine-induced changes in individual TLC factors and ketamine-induced changes in performance on the memory tasks. Correlation coefficients were also calculated between ketamine-induced changes in TLC scores and ketamine-induced changes in the thought disturbance factor of the BPRS.

Results

Ketamine produced significant increases in TLC total score. The ANOVA revealed a significant effect of time [$F(2,18) = 36.1$, $p < .001$], drug [$F(1,9) = 37.8$, $p < .001$], and the interaction of drug by time [$F(2,18) = 44.5$, $p < .001$] on TLC scores. Post hoc analysis demonstrated a significant difference between TLC scores with ketamine versus placebo at +45 min ($p < .001$) (Figure 1).

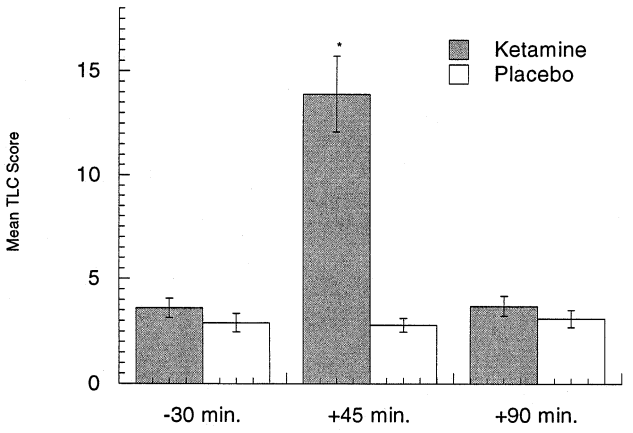

Figure 1. Ketemine significantly increased total TLC score. *$p < .001$.

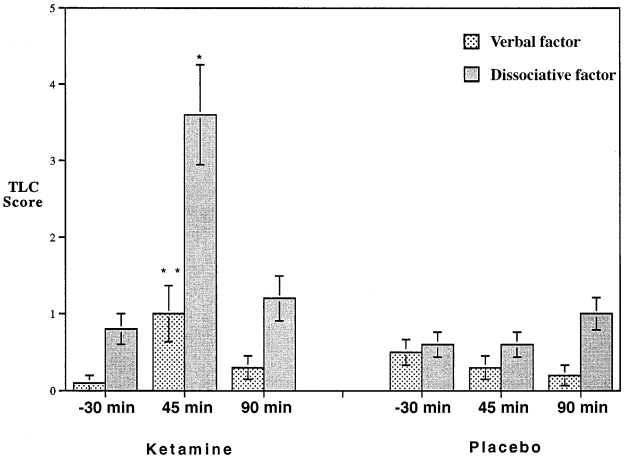

Figure 2. Verbal productivity and disconnection TLC factors were significantly increased by Ketamine. *$p = .009$. **$p < .001$.

We also analyzed the verbal productivity and disconnection factors from the TLC. The verbal productivity factor was significantly affected by ketamine. The ANOVA revealed significant effects for time [$F(2,18) = 3.86$, $p = .040$] and the drug by time interaction [$F(2,18) = 8.27$, $p = .003$]. Post hoc analysis showed a significant difference between ketamine and placebo at +45 min ($p = .009$). The TLC disconnection factor was also significantly affected by ketamine with effects of drug [$F(1,9) = 8.50$, $p = .017$], time [$F(2,18) = 17.8$, $p < .001$], and the interaction of drug by time [$F(2,18) = 15.5$, $p < .001$] being significant. Post hoc analysis showed a significant difference between ketamine and placebo in the disconnection factor at +45 min ($p < .001$) (Figure 2).

Ketamine also produced significant changes in BPRS total scores. The effects of drug [$F(1,9) = 47.1$, $p < .001$], time [$F(2,18) = 41.9$, $p < .001$], and the drug by time interaction [$F(2,18) = 43.9$, $p < .001$] were highly significant. Post hoc analysis showed a significant change in BPRS total scores at +45 min ($p < .001$). Analysis of the BPRS thought disturbance factor revealed a significant effect of drug [$F(1,9) = 33.8$, $p < .001$], time [$F(2,18) = 30.9$, $p < .001$], and the drug by time interaction [$F(2,18) = 30.9$, $p < .001$]. Post hoc analysis showed significant differences between ketamine and placebo in thought disturbance scores at +45 min ($p < .001$). Ketamine did not produce a significant effect on the withdrawal/retardation factor [drug by time: $F(2,18) = 2.57$, $p = .104$].

The BPRS item conceptual disorganization was significantly affected by ketamine. The effects of drug [$F(1,9) = 36.0$, $p < .001$], time [$F(2,18) = 38.8$, $p < .001$], and the drug by time interaction [$F(2,18) = 36.0$, $p < .001$], were highly significant. Post hoc analysis showed a

Table 1. Effects of Ketamine on Cognition

	Preinfusion	Infusion	Postinfusion	F^a	p
Working memory					
One-back task					
Ketamine	13.25 ± 0.5	11.78 ± 0.5[b]	12.75 ± 0.4	6.38	.008
Placebo	12.82 ± 0.5	13.28 ± 0.2	13.48 ± 0.2		
Two-back task					
Ketamine	11.22 ± 0.8	8.98 ± 0.6[b]	11.08 ± 0.6	6.89	.006
Placebo	10.75 ± 1.0	11.85 ± 0.8	11.28 ± 1.1		
Attention					
Zero-back task					
Ketamine	13.85 ± 0.1	13.78 ± 0.05	13.98 ± 0.02	0.86	.440
Placebo	13.75 ± 0.2	13.84 ± 0.1	13.92 ± 0.04		

	Infusion	F^c	p
Verbal fluency			
Letter prompt			
Ketamine	33.4 ± 3.3	8.53	.017
Placebo	45.7 ± 5.3		
Superordinate prompt			
Ketamine	42.3 ± 4.1	12.7	.006
Placebo	52.9 ± 4.2		

[a]Drug × time.
[b]Post hoc $p < .01$.
[c]Drug alone.

significant difference between ketamine and placebo at +45 min ($p < .001$).

All 10 subjects demonstrated increases of the BPRS thought disturbance factor and of TLC total score. Ketamine-induced change scores in the thought disturbance factor correlated significantly with ketamine-induced change scores in the TLC ($r = .84$, $p < .002$).

Ketamine was also associated with decreases in scores on the one-back and two-back tests of working memory (Table 1). There were no significant effects of ketamine administration on the zero-back task (Table 1). Verbal fluency was significantly decreased by ketamine on the letter and on the category prompt tests (Table 1).

Spearman rank order correlation coefficients were calculated between ketamine-induced effects on the TLC versus ketamine-induced effects on working memory and verbal fluency scores. Ketamine-induced effects on the one-back working memory test significantly inversely correlated with ketamine-induced changes on the TLC (Figure 3). Ketamine-induced effects on the two-back working memory task did not significantly correlate with ketamine-induced effects on the TLC (Spearman $r = .13$, $p = .73$). Ketamine-induced changes in verbal fluency did not significantly correlate with ketamine-induced changes on total TLC scores using the letter prompt task (Spearman $r = -.18$, $p = .62$) or the category prompt task (Spearman $r = .05$, $p = .89$).

Discussion

This study confirms and extends previous findings that subanesthetic doses of ketamine cause formal thought disorder and memory dysfunction in healthy volunteers (Krystal et al 1994; Malhotra et al 1996; Ghoneim et al 1985). Ketamine administration significantly elevated ratings on the TLC in healthy volunteers and induced decrements in working memory and semantic memory. Simple vigilance was not significantly affected by ketamine administration.

Previous studies have utilized the BPRS to rate thought disorder induced by ketamine (Krystal et al 1994; Malhotra et al 1996). BPRS measures of formal thought disorder reflect a single item, conceptual disorganization. The TLC allows a more comprehensive examination of thought disorder. Total TLC scores were increased with ketamine administration. In addition, ketamine significantly increased ratings on the verbal productivity and the disconnection factors of the TLC. The increase in the verbal productivity factor was not secondary to an increase in verbal output, as subjects showed increased ratings for poverty of speech as compared to pressure of speech.

We found no significant change in scores on the vigilance task. These data contrast with earlier findings of ketamine-induced effects on attention. This contrast may be due, however, to methodologic differences in testing attention. Krystal et al utilized continuous performance testing (CPT), while we previously used word recognition. As both CPT and word tasks include significant working memory components, these results may reflect the impact of ketamine on working memory rather than on attention (Krystal et al 1994; Malhotra et al 1996).

Our data are consistent with previous studies showing

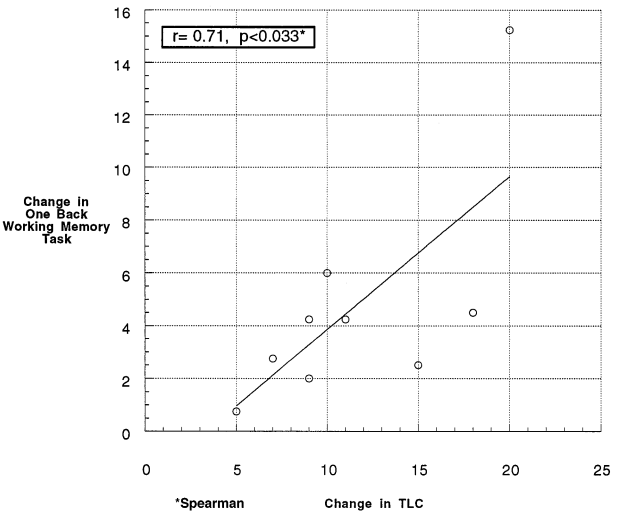

Figure 3. Decrease in performance on one-back working memory task significantly correlated with increase in total TLC.

ketamine-induced effects on working memory. Krystal has previously reported ketamine-induced deficits on the WCST, a task that includes a significant working memory component (Krystal et al 1994). The WCST, however, is not a pure working memory task, making interpretation of the ketamine-induced deficit problematic (Goldman-Rakic 1994).

Our data are also consistent with previous findings of ketamine-induced deficits in verbal fluency (Krystal et al 1994; Ghoneim et al 1985). In contrast, a more recent study of the effects of ketamine found no effect on verbal fluency using either letter or category prompt paradigms (LaPorte et al 1996). Several methodologic discrepancies may explain this disparity. First, LaPorte et al examined schizophrenic subjects. Second, subjects were not tested until 45 min after ketamine bolus. We find that ketamine-induced effects on cognition in schizophrenic patients remit 30 min after ketamine infusion (Malhotra et al 1997). Third, LaPorte et al had a smaller study group, and therefore had less power to detect ketamine-induced effects.

We found that the ketamine-induced decrease in working memory on a one-back task significantly correlated with ketamine-induced effects on the TLC. Our findings offer moderate support for the hypothesized relation between thought disorder and working memory. Similarly we found an association between the conceptual disorganization item of the BPRS and only the one-back task of working memory. The significance of the lack of correlation between thought disorder measures and the two-back task is unclear. The two-back task of working memory is significantly more difficult than the one-back task, and several subjects had very poor performances. These low scores may have masked a potential correlation.

In conclusion, we demonstrated that ketamine induces a spectrum of thought disorder in healthy controls, along with cognitive deficits in two, largely unrelated memory systems, working and semantic memory. In contrast, we showed no deficits in simple vigilance with ketamine administration. Finally, we report a correlation between ketamine-induced deficits in working memory and ketamine-induced thought disorder. While the correlation is limited in scope, these findings lend some support to the hypothesis that working memory is involved in the cognitive pathogenesis of some aspects of thought disorder.

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