Comment on "Ketamine Has Equal Affinity for NMDA Receptors and the High-Affinity State of the Dopamine D_2 Receptor"

To the Editor:

The recent letter to the editor by Kapur and Seeman (2001) introduces the possibility that ketamine actions at a high affinity state of the dopamine D_2 receptor undermines the use of ketamine "as a proof or as a model for a hypoglutamatergic state." One implication of this statement is that the cognitive and behavioral effects of ketamine in healthy human subjects might be attributable to stimulation of D_2 receptors rather than to the blockade of *N*-methyl-D-aspartate (NMDA) glutamate receptors, considered previously as the primary site of action of ketamine. This hypothesis predicts that those behavioral effects of ketamine that might be most closely associated with consequences of excessive D_2 receptor stimulation, its psychotic and euphoric effects, would be blocked in humans by pretreatment with the D_2 receptor antagonist, haloperidol.

The figure presented below indicates that oral pretreatment with haloperidol 5 mg failed to attenuate the psychotic and euphoric effects of an intravenous infusion of ketamine (bolus 0.23 mg/kg, infusion of 0.65 mg/kg/hr) in 20 healthy human subjects (Krystal et al 1999). The intravenous infusion was administered two hours following the oral medication.

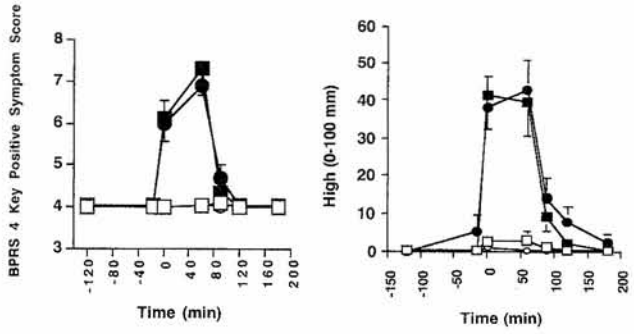

Figure 1. The effects of pretreatment with haloperidol or placebo upon ketamine effects in 20 healthy human subjects who completed four test days as reported previously (Krystal et al 1999). **(Left)** Interactive effects of haloperidol and ketamine upon the Brief Psychiatric Rating Scale four key positive symptom score, a measure of psychosis. Ketamine and the combination of ketamine and haloperidol significantly increased scores relative to placebo, but there was no significant difference between the ketamine and ketamine-haloperidol test days. **(Right)** Results of drug effects upon scores on the visual analog scale measuring "high." Again, ketamine and the combination of ketamine and haloperidol significant increased high relative to placebo, but there were no significant differences between the two ketamine test days. Data are presented as mean ± standard error of the mean. The following symbols were employed: open square: placebo haloperidol and placebo ketamine (saline), filled square: placebo haloperidol and active ketamine, filled circle: active haloperidol and active ketamine, and open circle: active haloperidol and placebo ketamine.

These data do not indicate that the effects of ketamine are attributable to NMDA receptor blockade. However, they appear to suggest that some ketamine effects that might be ascribed to D_2 receptor stimulation do not show the expected blockade by a D_2 receptor antagonist.

The concern raised by Drs. Kapur and Seeman regarding the pharmacologic specificity of the racemic ketamine mixture is not new (Hustveit et al 1995), but it is important and it bears repeating. Experimental psychopharmacology research in humans continues to be stifled by the failure of the pharmaceutical industry to make superior agents, that have demonstrated safety in animals and humans, more broadly available to investigators for use in research studies.

John H. Krystal
D. Cyril D'Souza

Department of Psychiatry
Yale University School of Medicine
Schizophrenia Biological Research Center
VA Connecticut Healthcare System
950 Campbell Avenue
West Haven, CT 06516

PII S0006-3223(01)01258-6

References

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.

Kapur S, Seeman P (2001): Ketamine has equal affinity for NMDA receptor and the high-affinity state of the dopamine D_2 receptor. *Biol Psychiatry* 49:954–955.

Krystal JH, D'Souza DC, Karper LP, et al (1999): Interactive effects of subanesthetic ketamine and haloperidol. *Psychopharmacology* 145:193–204.

Reply

Krystal and D'Souza raise an interesting and valid point regarding the inability of haloperidol to counteract the actions of ketamine in a human acute-infusion model. It is of interest to point out that when it comes to PCP, typical antipsychotics such as haloperidol and pimozide were effective in reducing clinical psychosis in patients who had naturally occurring (rather than experimentally-induced) PCP-psychosis (Giannini et al 1984a; Giannini et al 1984b). We do not wish to suggest that ketamine/PCP are exerting their effects exclusively/primarily via the D^2 receptor, but, that the data raise concerns about whether ketamine/PCP are sufficiently selective models to test the glutamate hypothesis. Therefore, we are glad to join the suggestion by Krystal et al that more selective agents for human-use are needed to provide better tests and models for alterations of the glutamate system.

Shitij Kapur

Department of Psychiatry
University of Toronto
250 College Street
Toronto, Ontario M5T 1R8
Canada

Philip Seeman

Departments of Psychiatry and Pharmacology
University of Toronto
250 College Street
Toronto, Ontario M5T 1R8
Canada

PII S0006-3223(01)01265-3

References

Giannini AJ, Eighan MS, Loiselle RH, Giannini MC (1984a): Comparison of haloperidol and chlorpromazine in the treatment of phencyclidine psychosis. *J Clin Pharmacol* 24:202–204.

Giannini AJ, Nageotte C, Loiselle RH, Malone DA, Price WA (1984b): Comparison of chlorpromazine, haloperidol and pimozide in the treatment of phencyclidine psychosis: DA-2 receptor specificity. *J Toxicol Clin Toxicol* 22:573–579.