Altered Prefrontal Dopaminergic Function in Chronic Recreational Ketamine Users

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**Objective:** Ketamine is a noncompetitive antagonist at the glutamatergic N-methyl-D-aspartate (NMDA) receptor that is used in human and animal medicine as an injectable anesthetic. The illegal use of ketamine as a recreational drug is rapidly growing. Very little is currently known about the consequences of repeated ketamine exposure in the human brain. Animal studies indicate that the prefrontal dopaminergic system is particularly vulnerable to the toxic effects of repeated administration of NMDA antagonists. In this study, dopamine D1 receptor availability was assessed by using positron emission tomography and the selective D1 receptor radioligand $^{11}$C]NNC 112 in a group of 14 recreational chronic ketamine users and matched healthy subjects.

**Method:** History of ketamine abuse was confirmed in subjects by hair analysis. $^{11}$C]NNC 112 binding potential was measured with kinetic analysis using the arterial input function.

**Results:** Dorsolateral prefrontal cortex D1 receptor availability was significantly up-regulated in chronic ketamine users ($^{11}$C]NNC 112 binding potential: mean=1.68 ml/g, SD=0.40) relative to comparison subjects (mean=1.35 ml/g, SD=0.35). No significant differences were noted in other cortical, limbic, or striatal regions. In the chronic ketamine user group, dorsolateral prefrontal cortex $^{11}$C]NNC 112 binding potential up-regulation was significantly correlated with the number of vials of ketamine (with a vial representing approximately 200–300 mg of ketamine) used per week.

**Conclusions:** Chronic ketamine users exhibited a regionally selective up-regulation of D1 receptor availability in the dorsolateral prefrontal cortex, a phenomenon observed following chronic dopamine depletion in animal studies. These data suggest that the repeated use of ketamine for recreational purposes affects prefrontal dopaminergic transmission, a system critically involved in working memory and executive function.

Ketamine, a noncompetitive antagonist at the glutamatergic N-methyl-D-aspartate (NMDA) receptor, is currently used in human and animal medicine as an injectable anesthetic (1, 2). Ketamine is also a controlled substance, illegally used as a recreational drug (“Special K,” “Vitamin K”). The recreational use of ketamine is prevalent at dance events (3, 4). While no epidemiological study has specifically addressed the scope and growth rate of the nonmedical use of ketamine, the rates of emergency room visits nationwide for use of ketamine grew 20-fold between 1994 and 1999 (5).

At subanesthetic doses, ketamine induces a state of dissociation (including distortion of space, time, and body image) and feelings ranging from euphoria to detachment, an experience described by users as a mind or spiritual exploration (6–8). While the cognitive deficits observed during acute administration of ketamine are well documented (7, 9, 10), very little is known of the long-term effects of repeated ketamine administration in the human brain. High incidence of psychiatric symptoms, such as recurrent hallucinations and psychotic episodes, have been described in subjects abusing phencyclidine (PCP), a more potent noncompetitive NMDA antagonist (11). In chronic ketamine abusers, limited studies suggest the persistence of neurocognitive deficits up to 3 days after use, but these studies are compromised by the polysubstance use in these samples (12, 13).

The animal literature suggests that repeated exposure to noncompetitive NMDA antagonists leads to sustained impairment of performance in numerous cognitive domains, such as working memory tasks (reviewed by Jentsch and Roth [14]). These deficits induced by NMDA antagonists have been linked to reduced function of the prefrontal dopaminergic system, which plays a critical role in sustaining working memory and executive functions (15–19). Monkeys chronically treated with the noncompetitive antagonist MK-801 showed decreased performance on working memory tasks and decreased prefrontal dopamine levels measured with microdialysis (20). Sustained decrease in prefrontal dopamine leads to an up-regulation of prefrontal dopamine D1 receptors, the main dopaminergic receptor in the cortex (21). A positron emission to-