**Subanesthetic Ketamine: How It Alters Physiology and Behavior in Humans**

Laura M. Rowland

**During the last 20 yr, clinicians and neurobiologists have developed a strong interest in the role of brain glutamatergic activity in behavior.** The primary excitatory neurotransmitter in humans, glutamate, has become the focus of research related to anesthesia, analgesia, cognition, and psychiatric behavior. Ketamine is a rapidly acting, safe antagonist of the glutamate receptor. Because of these properties it has been studied extensively in man. This review considers the clinical applications, potential adverse, neurobiological, and behavioral effects of subanesthetic ketamine in humans.

**General Information**

Ketamine (2-chlorphenyl-2-methylamino-cyclohexanone) is a phencyclidine (PCP) derivative. It was synthesized in 1962 by Calvin Stevens, a scientist working for the Parke-Davis pharmaceutical company. It was created to provide an alternative for PCP. Ketamine is a fast-acting substance.

**Administration:** The FDA approves intravenous (IV) and intramuscular (IM) ketamine administrations. Oral, intranasal, rectal, transdermal, epidural, and subcutaneous routes of administration have been used (8,19,44). For sedation and analgesia, the typical dose for IV administration is 0.2–0.75 mg · kg\(^{-1}\) over 2–3 min followed by a maintenance infusion (e.g., 0.005–0.02 mg · kg\(^{-1}\) · min\(^{-1}\)), and for intramuscular administration is 2–4 mg · kg\(^{-1}\). For anesthesia, the average recommended dose for IV administration is 2 mg · kg\(^{-1}\) (range: 1–4.5 mg · kg\(^{-1}\)) and for IM administration is 10 mg · kg\(^{-1}\) (range: 6.5–13 mg · kg\(^{-1}\)). In anesthesia, ketamine is usually used in conjunction with a benzodiazepine (or other sedatives: volatile anesthetics, propofol) to reduce the risk of emergence reactions and increase cardiovascular stability (11,40).

**Pharmacology:** Ketamine is a glutamate N-methyl-D-aspartate receptor (NMDAR) noncompetitive antagonist. Its primary action is blockade of the PCP binding site within the NMDAR. Specifically, it blocks calcium influx within the ion channel (Fig. 1). At subanesthetic dosing levels, ketamine-induced NMDAR blockade paradoxically causes increased release of prefrontal glutamate (27,41) and dopamine (27,42), and increased striatal dopamine synthesis and transport (38).

Ketamine also binds, with low affinity, to \(\sigma\) (10 times less potent than NMDAR binding) and \(\mu\) (5 times less potent than NMDAR binding) opioid receptors (29). Ketamine also inhibits acetylcholinesterase and affects MAO transporter sites, but at very low capacities. These effects do not substantially contribute to anesthetic, analgesic, or psychotropic properties (18).

**Pharmacokinetics:** Ketamine is a fast-acting substance.
Concentrations in the brain peak 1 min after IV administration according to pharmacokinetic models and brain tissue level studies in nonhuman animals (17). It is rapidly metabolized in the liver (97% prior to excretion) by cytochrome P-450 to norketamine (the major metabolite) and several other hydroxylated norketamine metabolites. Ketamine is not metabolized in the brain. Norketamine concentrations are observed in the brain 1 min following IV administration of ketamine. Norketamine is pharmacologically active, but at a much lower level than ketamine. Ketamine plasma levels have been shown to peak 20 min post-administration with three different subanesthetic doses (30). It has a short elimination half-life, with the α-elimination phase lasting minutes and the β-elimination phase lasting only 2-3 h (18).

Side effects: Potential adverse reactions that can occur with ketamine administration include cardiovascular (frequent: increased BP, tachycardia; less frequent: bradycardia, hypotension; rare: arrhythmias), respiratory (less frequent: depressed respiration; rare: laryngospasms and other obstructions), opthalmic (less frequent: nystagmus, diplopia, and increased intraocular pressure), psychiatric (frequent: hallucinations, delirium, altered mood state, dissociative sensations, vivid dreams, and confusion), central nervous system (frequent: vocalization, tonic and clonic muscle movements, and miscellaneous (less frequent: nausea, vomiting, pain at injection site, and loss of appetite).

Contraindications and precautions: Ketamine is contraindicated in persons for whom an increase in BP would pose a danger (i.e., severe cardiovascular disease, severe hypertension, recent myocardial infarction, history of stroke, cerebral trauma, intracerebral mass or hemorrhage). Precaution should be taken in those persons who have or are suspected to have a psychotic disorder, eye injury, increased intracerebral or intracranial pressure, alcohol or drug abuse/addiction, and thyrotoxic states.

Potential for abuse: Ketamine, commonly referred to by recreational users as “Special K,” “vitamin K,” and “super acid,” is illicitly used worldwide. Reports of ketamine recreational use date back to 1967–1968. During this time it was largely confined to members of the medical community. Evidence suggests that illicit use has grown in the past decade, and other subcultures have used it routinely in nightclubs and raves (9,10). Typical reactions include feeling disconnected from one’s body, losing a sense of time, visual and auditory hallucinations, floating, euphoria, unusual thought content, and paranoia. The intensity of the experience varies depending on the individual. Some have described entering the “K-hole,” which is analogous to a near-death experience. People describe feeling as though they were dead, traveling out of their body through a dark tunnel into light, communicating with God, and hallucinating intensely. Recreational users have also experienced the inability to speak, temporary paralysis, lack of coordination, and increased body temperature (9).

Neurobiological Effects of Ketamine

Studies examining the effects of ketamine on brain metabolism and blood flow, blood oxygen level-dependent (BOLD) signal, and neurochemistry have used [18F-fluoro-deoxy-D-glucose (FDG) and H215O positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and proton magnetic resonance spectroscopy (1H-MRS), respectively.

PET: Several studies have investigated the effects of subanesthetic doses of ketamine on brain metabolic activity in healthy human participants. In an FDG-PET study by Breier et al. (6) it was shown that ketamine infusions (0.12 mg · kg−1 · bolus followed by 0.65 mg · kg−1 · infusion for 1 h) produced increased glucose metabolism in the prefrontal cortex in 17 healthy participants while they performed a simple auditory continuous performance task. Psychotomimetic features, such as disorganized thought, hallucinations, and paranoia were elicited by ketamine. Prefrontal glucose metabolism was positively related to disorganized thought.

Another FDG-PET study by Vollenweider et al. (43) revealed similar findings. The greatest increase in glucose metabolism associated with ketamine infusions (20 mg in 20 ml saline solution for 5 min, followed by 0.02–0.03 mg · kg−1 · min−1 for 60 min) was seen in the anterior cingulate (AC) and frontomedial regions in 15 healthy participants. Lesser increases were also seen in the insula, parietal, somatosensory, motor, and temporoparietal cortices. Ketamine was shown to produce psychotomimetic features, such as disorganized thought, social withdrawal, hallucinations, and flattened affect as determined by the ‘Ego Pathology Inventory,’ ‘Association for Methodology and Documentation in Psychiatry,’ and the ‘Altered States of Consciousness Questionnaire.’ Anterior cingulate and frontomedial metabolism were positively correlated with schizophrenic-like symptoms.

Vollenweider et al. (42) also sought to determine if pure S+ ketamine and R− ketamine produce differential brain metabolic effects in healthy humans using FDG-PET. Typically racemic ketamine (50/50 S+ and R− ketamine) is used as standard medical practice. Findings corroborated and extended previous results by showing increased glucose metabolism in the anterior and posterior cingulate, and the medial and lateral frontal, parietal, somatosensory, motor, and thalamic regions associated with S+ ketamine infusions in 10 healthy, human participants. Like the previous investi-
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gation, S+ ketamine produced psychotic features, as determined with the Ego Pathology Inventory, Association for Methodology and Documentation in Psychiatry, and Altered States of Consciousness Questionnaire, which were related directly to brain glucose metabolism. R− ketamine, however, produced opposite behavioral and metabolic characteristics from S+ ketamine. Participants noted a relaxed state associated with R− ketamine along with decreased glucose metabolism across all regions assessed. It was concluded that the schizophrenia-like features induced with S+ ketamine were probably related to NMDA antagonism, and that the relaxation effects of R− ketamine were probably related to interactions with σ receptors.

Holcomb and colleagues (13) investigated the sequential effects of ketamine administration (0.3 mg · kg\(^{-1}\) bolus injection) on cerebral blood flow using \(^{15}\)O PET in normal, healthy humans. Scans were acquired at baseline, 6, 16, 26, and 36 min post-ketamine administration. Blood flow significantly increased at 6 and 16 min in the AC, middle and inferior frontal cortices, and decreased, relative to whole brain blood flow, in the cerebellum. Participants experienced mild psychotomimetic effects as assessed with the Brief Psychiatric Rating Scale (BPRS). The relationship between the BPRS psychosis subscale and blood flow in a region that included part of the AC and middle frontal regions approached a positive trend level.

**fMRI:** In recent years, several studies have investigated the effects of subanesthetic ketamine on BOLD signal during performance of various cognitive paradigms. Abel et al. (2) investigated the effects of ketamine (0.23 mg · kg\(^{-1}\) bolus, 0.5 mg · kg\(^{-1}\) over 45 min) on BOLD signal during a task that required eight subjects to determine the gender of faces presented on a computer. Ketamine was associated with a decreased BOLD response in the middle occipital and precentral gyri when compared with the placebo condition. Abel et al. (1) extended these findings to include the impact of ketamine administration on processing faces that expressed fear (i.e., emotional faces) compared with neutral faces. The eight subjects were still required to determine the gender of each face irrespective of the condition. Increased BOLD signal in limbic regions was associated with processing of emotional faces in the placebo but not the ketamine condition. These results suggest a neurobiological association with emotional blunting, an effect that is reported with ketamine administration.

One study investigated the effects of ketamine on brain activity during a verbal working memory task with fMRI (15). For that study, 10 healthy subjects performed a working memory task that varied the number of items to be remembered (i.e., memory load) and the method of organizing the information to be remembered (i.e., executive demand) during ketamine administration (target: 50 ng · ml\(^{-1}\) and 100 ng · ml\(^{-1}\) plasma concentration). The combined doses of ketamine resulted in greater BOLD signal in the frontal, parietal, anterior cingulate, and striatal regions only during the executive demand condition. These results suggest that ketamine impairs the executive control of working memory but not maintenance of working memory.

The effects of ketamine on episodic memory have been investigated with two fMRI studies. Honey et al. (14) investigated the effects of ketamine (target: 50 ng · ml\(^{-1}\) and 100 ng · ml\(^{-1}\) plasma concentration) on encoding vs. retrieval of verbal information (i.e., word lists). Findings were dose-dependent. The group given the 100 ng · ml\(^{-1}\) showed the greatest changes. Using a double contrast analysis, the investigators found that the deep-vs.-shallow assessment of encoded words during ketamine administration was associated with increased left ventrolateral prefrontal cortex BOLD signal, compared with the same assessment during the placebo drug condition. Increased BOLD signal was also observed in the right inferior frontal cortex in association with correctly encoded items (i.e., subsequently correctly retrieved) during ketamine administration vs. placebo. For retrieval, increased right frontal and left hippocampal BOLD signals during correct vs. incorrectly recognized words were revealed under ketamine compared with placebo.

An fMRI study by Northoff et al. (31) investigated the effects of ketamine (0.6 mg · kg\(^{-1}\) · h\(^{-1}\)) on episodic word retrieval. Compared with placebo, ketamine was associated with a smaller BOLD signal change in the posterior and anterior cingulate cortices and precuneus during retrieval. The posterior cingulate and precuneus signal changes were related to ketamine-induced psychosis rating scores. These memory studies emphasize the role of glutamatergic function during stimulus encoding and retrieval. They do not, however, clearly demonstrate how alternative pathways do or do not assume greater or lesser behavioral roles during NMDAR antagonism.

Rogers et al. (35) investigated the analgesic effects of ketamine with fMRI. In this study, eight healthy men received ketamine at subanalgiesic (target 50 ng · ml\(^{-1}\) plasma concentration) and analgesic (target 200 ng · ml\(^{-1}\) plasma concentration) doses. They were subjected to alternating blocks of noxious thermal stimuli and non-noxious auditory stimuli. The analgesic dose of ketamine diminished the subjective measures of pain. This was accompanied by BOLD signal reductions in a neural network thought to subserve pain perception; BOLD signal suppression was particularly evident within the thalamus and insula. The changes in response to ketamine administration and auditory stimuli occurred in the superior temporal gyri. This study partially elucidates the analgesic brain effects of ketamine.

**\(^{1}H\)-MRS:** \(^{1}H\)-MRS is a non-invasive means of measuring certain biochemicals that reflect mechanisms such as neuronal function, cellular inflammation, and glutamate neurotransmission in vivo. A 4 Tesla-\(^{1}H\)-MRS study investigated the effects of a subanesthetic dose of ketamine on brain glutamatergic activity in healthy humans (37). This study tested the hypothesis that NMDAR blockade is associated with increased glutamatergic activity in the cortex. This premise is consistent with nonhuman animal studies (27). It was also predicted that psychotomimetic features induced with ketamine would be positively correlated with increased...


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glutamatergic activity. 1H-spectra were acquired from the bilateral anterior cingulate in 10 subjects before and during ketamine administration (loading dose of 0.27 mg · kg⁻¹ over 10 min followed by a maintenance dose of 0.00225 mg · kg⁻¹ · min⁻¹). As predicted, there was a significant increase in AC glutamine, a putative marker of glutamate neurotransmitter release, with ketamine administration. This increase was not related to psychotomimetic features but was marginally related to selective attention performance. Consistent with rat research (27), an acute hypofunctional NMDAR state induced with ketamine was associated with increased glutamatergic activity in frontal brain regions in humans.

Behavioral Effects of Ketamine

Ketamine has consistently induced psychotomimetic features in normal healthy humans (2,6,12,13,22–26,30,36,42,43). Psychotomimetic features include hallucinatory behavior, suspiciousness/paranoia, disorganized thought, unusual thought, blunted affect, and emotional withdrawal. These features are commonly assessed with standard rating scales like the BPRS (33), the Scale for the Assessment of Negative Symptoms (4), and the Clinician Administered Dissociative States Scale (7).

Cognition: Ketamine also impairs performance on cognitive tests. Impaired attention, working memory, verbal fluency, learning and memory, and executive function have been documented. However, attention, working memory, and verbal fluency results are inconsistent among studies. These inconsistencies are probably attributable to methodological differences among studies. Variations in ketamine dose, route of administration (bolus vs. infusion), and task characteristics are likely to compromise agreement between studies. Another important variable is the time when the tasks were performed during the ketamine administration (i.e., prior, during, or following steady-state levels). Tasks provided immediately following drug injection would be more vulnerable to the drug than those performed 20 or 30 min after the ketamine infusion was begun. A summary of study results including dosing and cognitive process can be found in Table I.

Krystal et al. (25) investigated the psychotomimetic and cognitive effects of two subanesthetic doses of ketamine (0.1 mg · kg⁻¹ and 0.5 mg · kg⁻¹ for 40 min). Verbal fluency, sustained attention assessed with the continuous performance task, executive function assessed with the Wisconsin Card Sorting Test (WCST), the Mini-Mental State Examination, and immediate and delayed word recall were assessed. Ketamine caused impairments on all tests except immediate recall and the Mini-Mental State Examination. The highest dose of ketamine produced the greatest effects.

Krystal et al. (22) has supported and extended previous findings of the WCST performance impairments associated with ketamine administration. This study examined the effects of ketamine on acquisition vs. implementation of WCST rules. Healthy participants were administered 0.26 mg · kg⁻¹ over 2 min followed by 0.65 mg · kg⁻¹ · h⁻¹ of ketamine or placebo during the first session of the WCST (i.e., acquisition of rules). Participants were then administered ketamine or placebo (whichever drug was not received during the first session) during the second session (implementation of rules). Ketamine impaired acquisition, but not implementation of WCST rules. These results suggest that ketamine disrupts learning of new rules but does not impair the implementation of rules learned prior to ketamine exposure.

Malhotra et al. (26) showed that ketamine (0.12 mg · kg⁻¹ bolus followed by 0.65 mg · kg⁻¹ for 1 h) induces deficits in attention, word recognition, and word recall in healthy, normal participants. Ketamine significantly induced psychotomimetic features, but the severity of these features was not related to the cognitive impairments. The lack of a significant correlation between cognitive performance and psychotomimetic ratings suggests that these cognitive deficits were not secondary to induced psychosis.

In a similar study, Newcomer et al. (30) used three different doses of ketamine (loading dose: 0.27, 0.081, or 0.0243 mg · kg⁻¹; maintenance dose: 0.00225, 0.000675, or 0.0002025 mg · kg⁻¹ · min⁻¹) to assess the drug's effects on psychotomimetic behavior, declarative memory (immediate and delayed paragraph recall, delayed match to sample), selective (Stroop) and sustained (continuous performance task) attention, and verbal fluency. Psychotomimetic features, as well as impairments in paragraph recall and delayed match to sample performance were induced with ketamine. The higher doses produced the greatest effects. Ketamine did not produce deficits in selective or sustained attention, or in verbal fluency.

In contrast to Newcomer et al. (30), an earlier study by Adler and colleagues (3) showed ketamine administration in normal humans to affect verbal fluency. In that study, 10 normal, healthy participants were administered 0.12 mg · kg⁻¹ followed by 0.65 mg · kg⁻¹ for 1 h, and then assessed on working memory (N-back task), verbal fluency, psychotomimetic features, and thought disorder (Scale for the Assessment of Thought, Language, and Communication). Ketamine administration was shown to produce deficits in working memory, verbal fluency, psychotomimetic behavior and thought disorder. The severity of ketamine-induced thought disorder was significantly correlated with working memory deficits.

One study sought to determine whether ketamine-induced memory effects were specifically attributable to deficits in encoding or retrieval (12). Healthy, normal participants learned lists of words prior to and during ketamine infusions (0.5 mg · kg⁻¹ for 1 h), and then were assessed on working memory (N-back task), verbal fluency, psychotomimetic features, and thought disorder (Scale for the Assessment of Thought, Language, and Communication). Ketamine administration was shown to produce deficits in working memory, verbal fluency, psychotomimetic behavior and thought disorder. The severity of ketamine-induced thought disorder was significantly correlated with working memory deficits.

The purpose of another study was to investigate whether ketamine differentially impairs encoding and retrieval of spatial vs. nonspatial information. Rowland et al. (36) investigated the effects of ketamine on spatial learning vs. retrieval in a Virtual Morris Water Task, a...
<table>
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test of hippocampal function. Verbal fluency, working memory, and learning and retrieval of verbal information were also assessed. Ketamine impaired learning of spatial and verbal information, but retrieval of information learned prior to drug administration was preserved. Ketamine did not significantly impair attention, verbal fluency, or verbal or spatial working memory task performance.

Morgan et al. (28) investigated the effects of ketamine on five different aspects of memory function. Working memory, procedural learning, episodic memory, semantic memory, and perceptual priming were assessed with two ketamine doses (0.4 and 0.8 mg·kg$^{-1}$ for 80 min). Ketamine impaired episodic memory, working memory, recognition, and procedural learning; perceptual priming was not affected.

A recent study by Honey and colleagues (16) examined the effects of ketamine on aspects of executive function, specifically focused on working memory and planning. Ketamine administration was targeted to plasma levels of 50 and 100 ng·ml$^{-1}$. Ketamine did not disrupt planning performance on the Tower of London task, nor did it impair spatial working memory performance. Ketamine selectively disrupted the organization of information in verbal working memory, but not the maintenance of information in working memory.

The majority of research provides evidence for ketamine inducing psychotomimetic features, as well as learning and some executive function impairments. Impairments in attention, recognition, and retrieval of already known information appear to be dose-dependent.

**Conclusion**

In the near future there may be a resurgence of ketamine use in adults for analgesia, anesthesia, and sedation in industrialized regions and military environments. A renewed interest in evaluating the cost-benefits ratio of this drug may provide for a greater appreciation of the drug’s advantages and an informed amelioration of its adverse consequences. Its rapid onset, strong safety characteristics, and dose-dependent impact on psychotomimetic symptoms argue in favor of its continued use and application in clinical, investigative, and military settings. Ongoing behavioral and neuroimaging studies may provide a clearer representation of this agent’s pharmacology. Armed with that information, clinicians may be able to use ketamine judiciously and effectively on battlefields, during patient transport, and in field hospitals.

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