

The Neurobehavioral Pharmacology of Ketamine: Implications for Drug Abuse, Addiction, and Psychiatric Disorders

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Abstract

Ketamine was developed in the early 1960s as an anesthetic and has been used for medical and veterinary procedures since then. Its unique profile of effects has led to its use at subanesthetic doses for a variety of other purposes: it is an effective analgesic and can prevent certain types of pathological pain; it produces schizophrenia-like effects and so is used in both clinical studies and preclinical animal models to better understand this disorder; it has rapid-acting and long-lasting antidepressant effects; and it is popular as a drug of abuse both among young people at dance parties and raves and among spiritual seekers. In this article we summarize recent research that provides insight into the myriad uses of ketamine. Clinical research is discussed, but the focus is on preclinical animal research, including recent findings from our own laboratory. Of particular note, although ketamine is normally considered a locomotor stimulant at subanesthetic doses, we have found locomotor depressant effects at very low subanesthetic doses. Thus, rather than a monotonic dose-dependent increase in activity, ketamine produces a more complex dose response. Additional work explores the mechanism of action of ketamine, ketamine-induced neuroadaptations, and ketamine reward. The findings described will inform future research on ketamine and lead to a better understanding of both its clinical uses and its abuse.

Key Words: analgesia; anesthesia; animal model; antidepressant; drug abuse; glutamate; ketamine; reward; schizophrenia

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Ketamine was initially developed in the 1960s as a safer alternative to phencyclidine (PCP¹) for anesthetic procedures. It produces a state of dissociation similar to PCP but is shorter-acting, less potent, and less likely to induce agitation and violence (Gill and Stajic 2000; Krystal et al. 1994; Newcomer et al. 1999). The dissociative state allows ketamine-treated patients to be conscious but cognitively separated from the environment and unresponsive to pain. Because of these unique qualities ketamine is ideal for treating burn victims as well as for use in emergency surgical procedures and in acute trauma situations (Bergman 1999; Craven 2007; Domino 2010; Haas and Harper 1992; Sinner and Graf 2008).

In addition to its use as an anesthetic in both animals and humans, ketamine is increasingly used for a variety of other purposes (Domino 2010; Jansen 2000; Sinner and Graf 2008; Wolff and Winstock 2006). Reflecting the increased uses of ketamine, the attention given to the drug in published papers has escalated tremendously. A PubMed search reveals that in 1969 only 19 published articles used “ketamine” as a key word and that the number has increased over the years to well over 500 in 2008–2009 (Figure 1).

This review presents a summary of recent research on the uses and effects of ketamine at subanesthetic doses. The focus is on preclinical animal research as a means to better understand its myriad effects, both in its clinical and preclinical use for various disorders and conditions and in its increasingly popular abuse.

Uses of Ketamine

Anesthesia and Analgesia

A complete discussion of the anesthetic and analgesic effects of ketamine is beyond the scope of this article. However, it is important to mention these effects as they are the clinical actions for which ketamine is most often used.

The first publication on ketamine (called CI-581 at the time) described it as a potent anesthetic that did not produce

¹Abbreviations that appear $\geq 3x$ throughout this article: AMPA, α -amino-3-hydroxy-5methyl-4-isoxazolepropionic acid; AMPAR, AMPA receptor; CPP, conditioned place preference; NMDA, *N*-methyl-D-aspartate; PCP, phencyclidine

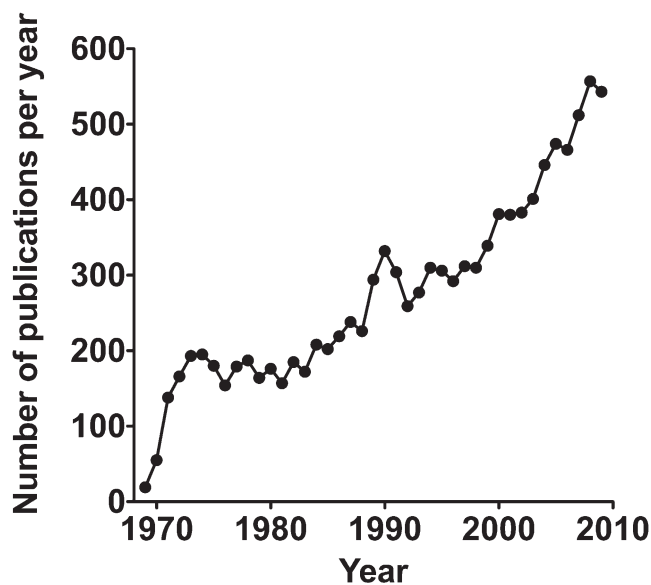


Figure 1 Number of publications on ketamine indexed in PubMed each year from 1969 to 2009, based on key word “ketamine” and publication date. A total of 19 publications appeared in 1969; the number remained below 200 per year through the 1970s, and began an upward trend in the early 1980s. By 2007–2009 publications on ketamine exceeded 500/year.

respiratory depression at anesthetic doses (McCarthy et al. 1965). This feature, which distinguishes ketamine from more traditional central nervous system (CNS) depressant anesthetics, makes it particularly useful for emergency situations (such as battlefield injuries) and procedures in which breathing assistance is unavailable or contraindicated.

Among the other features of ketamine that make it particularly useful are its rapid onset and predictable duration of action; its analgesic, anxiolytic, and amnesic effects; and its mild effects on cardiovascular function (Domino 1990; Haas and Harper 1992; White et al. 1982).

Given these qualities, ketamine soon became, and remains, an important tool in the armamentarium of surgeons and anesthesiologists as well as veterinarians. In fact, one of the biggest sources of ketamine for recreational use is diversion from veterinary sources (Freese et al. 2002; Ross 2008; Wolff and Winstock 2006).

The analgesic properties of ketamine in humans were described soon after its discovery. Domino and colleagues (1965) reported a numbness of the entire body and a complete lack of reaction to “pain-inducing procedures” (including skin crush with hemostats), although sensation to touch was unaffected. But the analgesia was accompanied by strong psychoactive effects, such as changes in mood and body image, vivid dreams and hallucinations, and a psychological state in which subjects appeared to be disconnected from their surrounding environment. The latter prompted Domino and colleagues (1965) to coin the term “dissociative” to describe ketamine and related drugs, apparently inspired by Domino’s wife (Domino 2010).

Although early work focused on relatively high doses of ketamine for analgesia, recent discoveries have led to the use of subanesthetic doses for pain relief (for review, Kronenberg 2002; Visser and Schug 2006). For example, certain types of pathological pain result from a process known as “central sensitization,” in which pain responses become hypersensitive (Latremoliere and Woolf 2009; Woolf 2011). The development of central sensitization involves *N*-methyl-D-aspartate (NMDA¹) receptors. Because, as described below, ketamine is an effective NMDA receptor antagonist, it has been used in the treatment of certain types of pathological pain conditions that involve central sensitization (Craven 2007; Haas and Harper 1992; Hocking and Cousins 2003; Latremoliere and Woolf 2009; Mao 1999; Sinner and Graf 2008; Subramaniam et al. 2004; Woolf 2011).

In the early 1990s it was discovered that ketamine, along with other NMDA receptor antagonists, can inhibit the development of opiate tolerance (Trujillo and Akil 1991, 1994), a finding that has been confirmed by many others (for review, Trujillo 2000). Furthermore, a number of preclinical studies have found that ketamine enhances opiate analgesia (Baker et al. 2002; Dambisya and Lee 1994; Hoffmann et al. 2003; Holtman et al. 2003; Joo et al. 2000; Kosson et al. 2008; Nadeson et al. 2002; Pellissier et al. 2003), leading to its use in combination therapy for pain. Clinical studies show that combinations of ketamine and opioids result in more effective pain relief (and/or lower doses of opiates) and thus fewer side effects (Bell 2009; Bell et al. 2003, 2005; Subramaniam et al. 2004).

Antidepressant Effects

Ketamine has recently been studied for its relevance to the treatment of major depression. Exciting evidence in humans demonstrates that ketamine has very rapid and long-lasting antidepressant effects when administered at subanesthetic doses (Berman et al. 2000; Diazgranados et al. 2011; Zarate et al. 2006). This evidence is supported by research using animal models involving learned helplessness, inescapable stress, forced swim, and tail suspension (for review, Paul and Skolnick 2003; Skolnick 1999; Skolnick et al. 2009).

Remarkably, ketamine’s antidepressant action is evident within hours and lasts for up to 2 weeks postadministration, a finding that has been replicated in humans (Zarate et al. 2006) and rodent models (Yilmaz et al. 2002; Maeng et al. 2008) (however, Popik et al. 2008 were unable to replicate the long-lasting antidepressant effect of ketamine in a rodent model). Ketamine’s rapid and long-lasting antidepressant effects are unusual: currently used medications, such as tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs), have a 3- to 6-week delay in onset and require daily administration to achieve and maintain antidepressant effects (Schatzberg and Nemeroff 2009). However, currently used antidepressants act primarily on monoamine neurotransmitter systems, whereas ketamine acts on glutamate (see details below), resulting in the emergence of theories

about the role of glutamate in major depressive disorder (Hashimoto 2009; Machado-Vieira et al. 2009; Skolnick 1999; Skolnick et al. 2009).

Unfortunately, the usefulness of ketamine as an antidepressant is limited because of adverse side effects, including the psychotomimetic effects described above. Further research is necessary to better understand the mechanisms and antidepressant effects of ketamine and to explore the development of antidepressant glutamatergic compounds that have fewer side effects.

Models of Schizophrenia

Early clinical studies on ketamine and PCP led researchers to believe that these drugs were psychotomimetic and could offer insight into schizophrenia (Davies and Beech 1960; Domino et al. 1965; Luby et al. 1959). Effects of subanesthetic doses include cognitive dysfunction and perceptual changes in healthy volunteers, and exacerbation of symptoms in schizophrenic patients (Adler et al. 1998, 1999; Krystal et al. 1994; Lahti et al. 1995, 2001; Malhotra et al. 1997b; van Berckel et al. 1998). Ketamine's ability to produce both negative and positive symptoms of schizophrenia, as well as cognitive dysfunction, is noteworthy as more traditional stimulant models induce primarily positive symptoms and thus provide an incomplete model of schizophrenia symptomatology (Angrist et al. 1974; Janowsky and Risch 1979; Krystal et al. 2005b).

The effects in humans have led to the use of ketamine (as well as PCP and related drugs) in animal models of schizophrenia, and to the related theory that glutamatergic dysfunction is involved in schizophrenia (more on glutamatergic hypotheses below). In rodent models, the ability of drugs to block the behavioral actions of ketamine is often used as a preclinical assay of antipsychotic effects (Becker et al. 2003; Gilmour et al. 2009; Jentsch and Roth 1999; Lees et al. 2004; Neill et al. 2010). Notably, atypical antipsychotics (drugs such as clozapine, olanzapine, and risperidone, which produce fewer motoric side effects than traditional antipsychotics) are effective at blocking ketamine's behavioral effects in both humans and rodents (Krystal et al. 1999, 2005a; Malhotra et al. 1997a).

These findings provide evidence for the use of ketamine in schizophrenia research, and are leading to a better understanding of the disorder and the development of novel treatments.

Ketamine Abuse

In the 1980s and the 1990s there was a dramatic increase in the recreational use of ketamine (Dillon et al. 2003; Freese et al. 2002; Jansen 1993; Ross 2008; Smith et al. 2002), especially at raves and dance parties, leading to its classification as a "club drug" (Freese et al. 2002; Jansen 2000; Jansen and Darracot-Cankovic 2001; Kelly et al. 2006; Smith et al. 2002). In addition, because of its unique psychoactive

effects, some people use it for psychic exploration, aiming for mystical experiences, self-transcendence, and spiritual growth (Jansen 2000; Jansen and Darracot-Cankovic 2001).

On the streets, ketamine is known as "Special K," "Vitamin K," "cat valium," or "K." It is commercially available as an injectable liquid but most commonly abused in a powder form and either snorted or smoked, although some use it orally or via intramuscular or intravenous injection (Dillon et al. 2003; Freese et al. 2002; Smith et al. 2002).

Ketamine abusers claim that the drug is rewarding and can produce a variety of psychoactive effects. At relatively low doses, users report stimulation and excitement, euphoria, sensory distortions, lucid intoxication, and heightened feelings of empathy (Dillon et al. 2003; Jansen 2000; Jansen and Darracot-Cankovic 2001). At higher doses, ketamine produces a hallucinatory state referred to as a "K-hole," an intense dissociative experience that includes visions and distortion of time, sense, and identity, and sometimes out-of-body, near death, or rebirth experiences. Users often report the K-hole as a frightening or aversive experience (Dillon et al. 2003).

The rise in ketamine abuse is associated with an increase in ketamine-related emergency room visits (Dillon et al. 2003; Jansen 2000; Jansen and Darracot-Cankovic 2001). Because of the drug's dissociative state, burns, falls, drowning, traffic accidents, and "date rape" are some of the consequences linked to ketamine-related impairment (Dillon et al. 2003; Freese et al. 2002; Jansen 2000; Smith et al. 2002). Despite such aversive experiences, case reports of ketamine addiction indicate that ketamine seeking can become compulsive, and users often express concern about the potential for addiction and dependence (Dillon et al. 2003; Jansen and Darracot-Cankovic 2001; Muetzelfeldt et al. 2008).

The potential dangers and increased abuse of ketamine prompted the US Drug Enforcement Administration (DEA) to classify ketamine as a schedule III² drug in 1999 (DEA 1999).

Neurochemical Effects of Ketamine

NMDA Receptors and Glutamate

Glutamatergic transmission is mediated by three ionotropic glutamate receptors: AMPA¹ (α -amino-3-hydroxy-5methyl-4-isoxazolepropionic acid), NMDA, and kainate. It wasn't until the 1980s, nearly 20 years after its discovery, that ketamine was found to exert its physiological and behavioral effects as an antagonist of NMDA receptors (Anis et al. 1983; Lodge et al. 1982).

²According to the DEA website, "Substances in this schedule have a potential for abuse, [which] may lead to moderate or low physical dependence or high psychological dependence" (www.deadiversion.usdoj.gov/schedules; accessed on June 3, 2011).

NMDA receptors are ligand-gated cation channels that open in response to the binding of glutamate and glycine (Collingridge and Watkins 1995; Yamakura and Shimoji 1999). This opening leads to an influx of calcium, which can act in a second messenger cascade and is essential to NMDA receptor function.

PCP and ketamine are NMDA antagonists and selectively bind to the “PCP site,” which is located in the NMDA ion channel (Collingridge and Watkins 1995; Sinner and Graf 2008; Wood et al. 1990; Yamakura and Shimoji 1999). Because of their ability to block NMDA receptor function without inhibiting the binding of glutamate, these drugs are referred to as noncompetitive antagonists. Specifically, ketamine blocks the open ion channel, reduces the amount of open time, and decreases the frequency of channel openings (for review see Sinner and Graf 2008). However, ketamine binds to this site with a lower affinity than PCP (Collingridge and Watkins 1995), reflecting its decreased behavioral effects relative to PCP.

Hypo- or Hyperglutamatergic?

The reigning explanation for the actions of ketamine is the hypoglutamatergic hypothesis: ketamine produces its effects by blocking the ability of glutamate to activate NMDA receptors. More recently, however, it has been suggested that the subjective and behavioral effects of ketamine may result from more complex effects on glutamatergic signaling. According to this hypothesis, ketamine, PCP, and related dissociatives may actually increase glutamate in certain brain areas and thereby produce some of the drugs’ behavioral effects (Adams and Moghaddam 1998; Farber et al. 2002a,b; Krystal et al. 2003; Maeng et al. 2008; Moghaddam et al. 1997; Olney et al. 1999). Thus, rather than producing their effects via a *hypoglutamatergic* mechanism, dissociatives may act via *hyperglutamatergic* actions.

In alignment with the glutamate hyperactivity hypothesis, researchers have demonstrated that NMDA receptor blockade induced by PCP or ketamine results in release of glutamate in the cerebral cortex (Adams and Moghaddam 1998, 2001; Lorrain et al. 2003a,b; Moghaddam et al. 1997; Razoux et al. 2007; Takahata and Moghaddam 2003). GABAergic neurons normally inhibit glutamatergic inputs to the cortex; however, blockade of NMDA receptors on these GABAergic neurons by the dissociatives blocks the inhibition, resulting in activation of the glutamatergic neurons and increased glutamate release. The increased glutamate concentrations produce stimulation of non-NMDA glutamate receptors (AMPA receptors) and the drugs’ cognitive and behavioral effects.

In support of this idea, PCP and ketamine have been shown to increase glutamatergic neurotransmission at AMPA receptors (Adams and Moghaddam 1998; Moghaddam et al. 1997; Razoux et al. 2007), and studies have shown that AMPA receptor (AMPA¹) antagonists attenuate certain behavioral and neurochemical effects of dissociatives (Hauber

and Andersen 1993; Hauber and Waldenmeier 1994; Li et al. 2010; Maeng et al. 2008; Takahata and Moghaddam 2003). Together, these results suggest that NMDA receptor blockade leads to the release of glutamate, which acts on AMPA receptors to evoke behavioral effects of the dissociatives.

A role for AMPAR mediation (after glutamate release) has been found for the antidepressant effects of ketamine. When administered before a forced swim test in mice, ketamine and other NMDA receptor antagonists decrease immobility (such a decrease is a sign of antidepressant action), and this effect can be blocked by pretreatment with the AMPAR blocker NBQX (Maeng et al. 2008), as can downstream consequences of ketamine action (Li et al. 2010).

The glutamate hyperactivity hypothesis has been investigated indirectly, using drugs that act on different aspects of glutamate function. For example, as noted above, AMPAR antagonists have been found to inhibit specific effects of ketamine and PCP, suggesting a role for AMPAR activation in the actions of these drugs. Furthermore, group II metabotropic receptor agonists (which can lower glutamate release) can decrease certain motor and cognitive effects of PCP (Krystal et al. 2005a; Lorrain et al. 2003a,b; Moghaddam and Adams 1998).

Although the studies described above suggest that enhanced glutamate release is involved in the effects of dissociatives, other studies, using compounds that inhibit glutamate release, suggest that the hypothesis is incomplete.

Inconsistent Research Results about the Role of Glutamate

Lamotrigine (3,5-diamino-6-[2,3-dichlorophenyl]-1,2,4-triazine) and riluzole (2-amino-6-trifluoromethoxy benzothiazole) are two compounds that inhibit release of glutamate, and both are seeing increased use as potential therapies for psychiatric disorders, including depression, bipolar disorder, and schizophrenia (Amann et al. 2010; Goff 2009; Kugaya and Sanacora 2005; Large et al. 2005; Mathew et al. 2008; Pittenger et al. 2008; Premkumar and Pick 2006; Zarate and Manji 2008).

If the glutamate hyperactivity hypothesis is correct, then riluzole and lamotrigine should inhibit the behavioral actions of dissociatives. However, studies of the effects of these drugs on ketamine-induced behavior have yielded conflicting results. For example, in a study using human participants Anand and colleagues (2000) found that lamotrigine decreased ketamine-induced symptoms of schizophrenia and impairments in learning and memory, but increased the immediate mood-elevating effects of ketamine. Similarly, Brody and colleagues (2003) demonstrated in rats that lamotrigine prevented ketamine-induced disruptions in prepulse inhibition; however, this finding was not replicated in later research (Cilia et al. 2007). Another study demonstrated that lamotrigine increased PCP-induced hyperlocomotion (Williams et al. 2006), an effect that is opposite to the glutamate hyperactivity hypothesis. In related work, Lourenço Da

Silva and colleagues (2003) found no effect of riluzole on the locomotor stimulation produced by MK-801, a potent dissociative drug. Thus, while some studies have obtained findings that are consistent with the hypothesis, others are in contradiction.

In our laboratory we have performed a series of studies to systematically assess the ability of riluzole and lamotrigine to affect the locomotor stimulant actions of ketamine and PCP. Extensive dose response experiments have revealed no consistent effects of these drugs on ketamine- or PCP-induced hyperlocomotion, stereotypy, or ataxia (Trujillo, Smith, and Heller, unpublished results).

In addition, we tested the same hypothesis using the AMPA antagonist GYKI-52466, reasoning that AMPAR blockade should attenuate any behaviors that were due to increased availability of glutamate at AMPA receptors. As with the riluzole and lamotrigine, GYKI-52466 had no effect on ketamine- or PCP-induced hyperlocomotion, stereotypy, or ataxia at a dose that did not, by itself, inhibit locomotor behavior (Trujillo and Smith, unpublished results).

Thus, the findings do not consistently support the glutamate hyperactivity hypothesis. One potential explanation for these mixed findings is that only certain behavioral effects of ketamine are mediated by an increase in glutamate release and subsequent AMPAR activation, and others are mediated by NMDA receptor blockade. This possibility is consistent with the findings of Anand and colleagues (2000), who found that lamotrigine decreased certain effects of ketamine and increased others. Furthermore, the ketamine-induced increase in glutamate release appears delayed relative to the locomotor stimulant effects of ketamine. For example, glutamate release increases significantly only 40 to 60 minutes postadministration (Lorrain et al. 2003a; Moghaddam et al. 1997), whereas the locomotor stimulant effects, stereotypy, and ataxia induced by moderate doses of ketamine occur immediately and subside within 20 minutes (Garcia and Trujillo 2007; Heller and Trujillo 2007; Sullivan and Trujillo 2007). This time discrepancy, along with results of studies using riluzole and lamotrigine, suggests that the motor effects of ketamine are independent of glutamate release.

Other Neurochemical Effects of Ketamine

Ketamine affects many neurotransmitter systems other than glutamate. There is, for example, considerable interest in the interactions between ketamine and dopamine as well as ketamine and endogenous opioids. A full consideration of these effects is beyond the scope of this article; summaries are available (Bergman 1999; Seeman 2009; Sinner and Graf 2008; White and Ryan 1996).

Together, the results discussed in this section suggest that the psychoactive and behavioral effects of ketamine may be more complex than either the glutamate hypo- or hyperactivity hypothesis suggests, with perhaps only a subset of responses mediated by an increase in glutamate release and AMPAR activation, others mediated more directly by block-

ade of NMDA receptors, and yet others mediated by neurotransmitters other than glutamate.

Behavioral Effects of Ketamine: Locomotor Activity

Locomotor activation in rodents is an important target in models of drug abuse and certain psychiatric disorders, such as schizophrenia. The effects of ketamine on locomotor behavior have been well characterized, beginning with the 1965 paper reporting that subanesthetic doses of ketamine produced locomotor stimulation accompanied by ataxia in mice and rats (McCarthy et al. 1965). Since then, innumerable studies have replicated the ability of ketamine and related drugs to produce locomotor stimulation, ataxia, and stereotypy at subanesthetic doses.

Because subanesthetic doses of ketamine can induce a schizophrenia-like syndrome in humans, it was a natural extension to consider locomotor activation as a marker of the psychoactive effects of the drug in rodent models of schizophrenia. Consequently, the ability of a drug to block the locomotor effects of ketamine has been used to identify potential antipsychotics. Atypical antipsychotics are particularly effective at blocking ketamine-induced locomotion.

Locomotor activation has also been associated with positive reinforcing effects of drugs, leading to a psychomotor stimulant theory of drug reward (Robinson and Berridge 2001, 2002; Trujillo et al. 1993; Wise 1988; Wise and Bozarth 1987). Drug-induced locomotor activation has therefore sometimes been used as a surrogate marker of drug reward (more on ketamine and reward below).

Data from our laboratory illustrate increases in activity, ataxia, and stereotypy associated with ketamine administration (Figure 2). At a low, subanesthetic dose (15.8 mg/kg), ketamine produces increases in ambulatory activity accompanied by mild ataxia and stereotypy; at a higher dose (50 mg/kg), stimulation, ataxia, and stereotypy dramatically increase. As anesthetic doses are approached (100 mg/kg and higher), ataxia overwhelms the locomotor activation, resulting in a complex progression from low levels of activity to considerable ataxia, stereotypy, and locomotor activation as the anesthesia wears off (not shown).

We have assessed the locomotor responses of Sprague-Dawley rats at subanesthetic doses of ketamine and obtained quite surprising results at the low end of the dose range. We found that the drug reliably depresses locomotor activity, relative to control animals, at doses of 10 mg/kg or less (administered by intraperitoneal [i.p.] injection) (Figure 3). The locomotor depressant effects were not accompanied by noticeable incoordination or ataxia. Therefore, rather than a monotonic increase in activity reported by most laboratories, ketamine produces more complex dose-dependent effects, with decreases in activity at very low subanesthetic doses (5–10 mg/kg), increases at higher doses (15–50 mg/kg), and decreases again at anesthetic levels (100 mg/kg and higher). Moreover, even at stimulant doses, the increase in activity

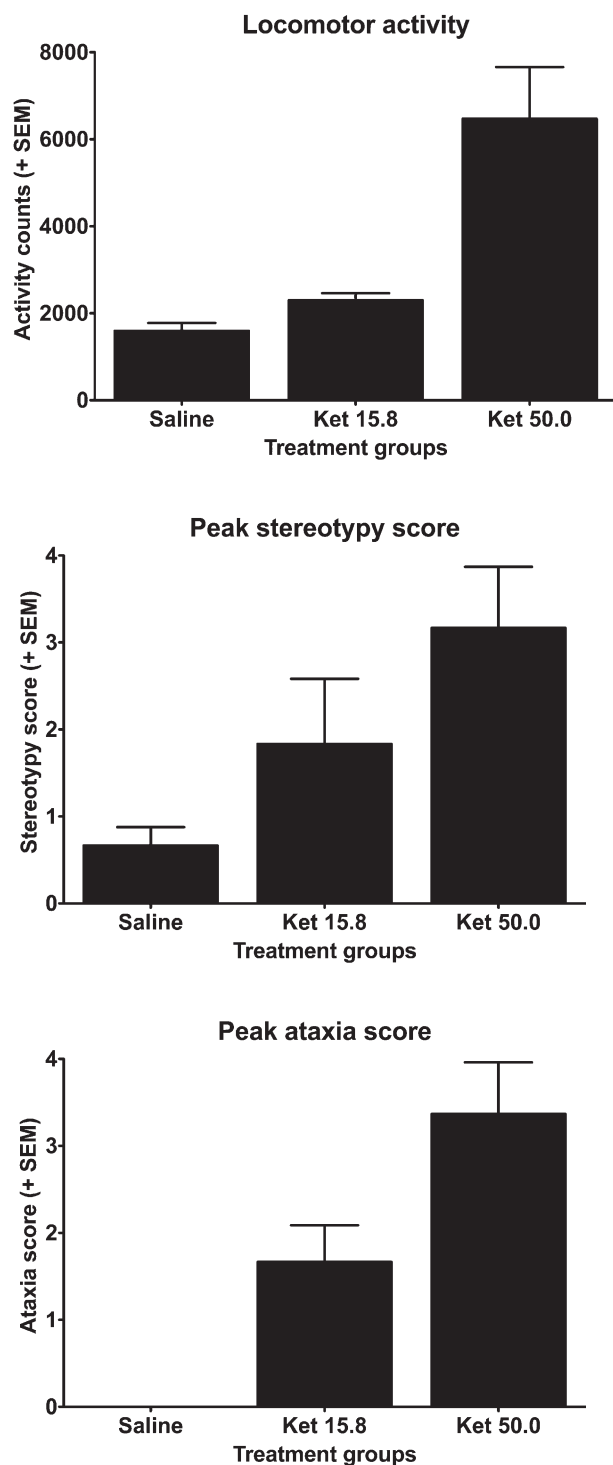


Figure 2 Dose-dependent effects of ketamine (Ket) on motor behavior in laboratory rats. Adult male Sprague-Dawley rats ($n = 6$ /group) were placed in photocell locomotor chambers (Kinder Scientific Open Field Motor Monitor) for a 30-minute habituation, followed by injection of saline (1 ml/kg) or ketamine (15.6 or 50 mg/kg). Ataxia and stereotypy were assessed according to Castellani and Adams (1981). Locomotor activity represents the mean (+SEM) total photocell counts (basic movements) for 60 min after injection in each group. Ataxia and stereotypy are the mean (+SEM) peak scores for each group. SEM, standard error of the mean

was followed by a rebound decrease in behavior, relative to control animals, as the stimulant effect abated (Garcia and Trujillo 2007; Mercado et al. 2009).

In examining the literature, we found at least one reference to locomotor depressant effects of subanesthetic doses of ketamine. Becker and colleagues (2003), in attempting to develop a ketamine-based rodent model of schizophrenia, noted a locomotor depressant effect of the drug at 30 mg/kg (a dose that frequently produces stimulation). However, this result was not studied systematically and was presented as a single figure among others characterizing different behavioral responses to the drug.

Ketamine in Combination with Other Drugs

The locomotor depressant effects of ketamine are most evident when it is administered with other psychomotor stimulants. We examined the interaction of ketamine with methamphetamine, a potent and widely abused psychomotor stimulant that is often used in combination with ketamine (Dillon et al. 2003). The behavioral effects of this combination are largely unknown.

To better understand the effects of ketamine and methamphetamine combined, we explored the locomotor effects of each drug alone and of both mixed together in a “cocktail.” We hypothesized that the combination would produce an effect greater than either drug alone, similar to the “speedball” effect seen with combinations of opiates and psychomotor stimulants (Leri et al. 2003). Methamphetamine administration produced the expected psychomotor stimulation, while ketamine produced a mild depressant effect at lower doses (5 and 10 mg/kg, subcutaneous [s.c.] administration) and stimulation followed by locomotor depression at a higher dose (20 mg/kg s.c.). In contrast to our hypothesis, at all doses ketamine potently inhibited the locomotor stimulant effect of methamphetamine.

Studies of the combined effects of cocaine and ketamine confirm that ketamine can attenuate the behavioral effects of psychostimulants. Uzbay and colleagues (2000) examined the impact of ketamine on cocaine-induced locomotor stimulation and showed that ketamine produced a dose-dependent inhibition of the stimulant effect of cocaine. These results, together with our observations, suggest that ketamine produces potent locomotor depression, an effect that is particularly evident when the drug is administered with psychomotor stimulants.

Research Implications

The finding that ketamine produces locomotor depression at low doses has important implications for preclinical research on the drug. For example, as noted above, locomotor stimulation in rodents is used as an index of the psychotomimetic effects of ketamine, but this effect occurs only at moderate to high doses, whereas the doses used in clinical studies to induce such effects in humans are quite low (Krystal et al. 1994; van Berckel et al. 1998).

Locomotor activity

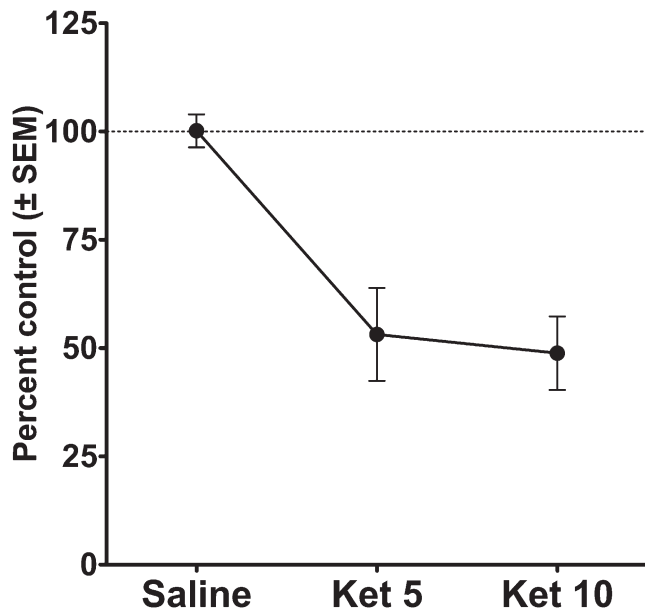


Figure 3 Locomotor depressant effects of low-dose ketamine (Ket) in laboratory rats. Adult male Sprague-Dawley rats ($n = 6/\text{group}$) were injected with saline (1 ml/kg) or ketamine (5 or 10 mg/kg) and immediately placed in photocell locomotor chambers (Kinder Scientific Cage Rack Monitors). Locomotor activity represents the mean (\pm SEM) percent saline control for 15 min after injection in each group. SEM, standard error of the mean

This discrepancy raises the question of whether the low-dose depressant effects in rats may more accurately reflect the clinical research and lead to a better animal model of schizophrenia. Indeed, studies that have examined prepulse inhibition of startle in rats to model schizophrenia-related deficits in sensorimotor gating have typically used ketamine doses in the range that we have found to depress behavior (10 mg/kg or less) (Imre et al. 2006; Mansbach et al. 2001; Mansbach and Geyer 1991; Ong et al. 2005; Swerdlow et al. 1998).

The lower end of the dose range may also be a better target in animal studies of the rewarding effects of ketamine. Studies using conditioned place preference in laboratory rats (see below) have found rewarding effects at low doses, comparable to those that produce locomotor depression. And individuals who use ketamine to enhance their experience at dance clubs and raves aim for doses that do not produce significant incoordination or ataxia. Together, the findings suggest that research should be aimed at better understanding the low-dose depressant effects of ketamine.

Ketamine Neuroadaptations

Repeated administration of psychoactive drugs typically leads to neuroadaptations in the form of tolerance or sensitization.

Tolerance and Sensitization

Tolerance is a decrease in response after repeated use of a drug and sensitization is “reverse tolerance,” or an increase in response. An individual may develop tolerance to some psychoactive and behavioral effects of a drug, and sensitization to others. Furthermore, the development of tolerance and sensitization can be influenced by a variety of factors, such as dose, the interval between doses, and environmental influences.

Tolerance and sensitization are important to the clinical use of drugs as well as drug abuse and addiction. Tolerance to the therapeutic effect of a drug will make it less effective over time, while sensitization to a side effect will produce escalating problems with repeated use. Similarly, tolerance to the desired effect of an abused drug may lead to increases in use to overcome the decreased effect, while sensitization has been linked to the craving that is prominent in addiction.

Early studies on repeated use of ketamine focused on changes induced by high doses and reported that tolerance developed to the anesthetic effect of the drug (Douglas and Dagirmanjian 1975; Hance et al. 1989; Livingston and Waterman 1978; Winters et al. 1988). Follow-up studies on subanesthetic doses of ketamine left an unclear picture of neuroadaptations, with some reports of tolerance, others of sensitization, and others showing no change after repeated administration (Becker et al. 2003; Lannes et al. 1991; Leccese et al. 1986; Nelson et al. 2002; Rocha et al. 1996; Uchihashi et al. 1993).

In light of the inconsistent results, we have begun to examine the changes that take place with repeated administration of subanesthetic doses of ketamine. Our studies demonstrate potent sensitization to the locomotor effects of ketamine. Sensitization occurs at short or long treatment intervals and at a broad range of doses, and, like other drugs of abuse, is enhanced in the presence of specific environmental cues (Heller and Trujillo 2007). Other studies have also reported sensitization to ketamine locomotion (Popik et al. 2008; Uchihashi et al. 1993; Wiley et al. 2008).

Because sensitization has been linked to addiction (Robinson and Berridge 1993, 2001), these results offer insight into the potential addictive properties of ketamine and demonstrate that repeated use can lead to long-term changes in brain function.

Research Implications of Ketamine Neuroadaptations

The development of sensitization to ketamine in some studies and tolerance in others raises an important methodological concern for research on the behavioral pharmacology of dissociative drugs.

Ketamine is the anesthetic of choice for a variety of surgical procedures in laboratory animals. Animals that require surgery before testing, such as those receiving catheter implants for self-administration, often receive high doses of the

drug before behavioral testing. As a result, these animals are experienced with the drug and may have undergone significant brain changes that can influence the outcome of studies.

We recommend the use, when possible, of an alternative anesthetic for animals involved in studies of ketamine or other dissociatives to avoid potentially confounding effects related to tolerance or sensitization.

Ketamine Reward

There are many reasons drugs are abused, but reward is considered to be an essential aspect of addiction (Robinson and Berridge 2000, 2001, 2003; Trujillo and Akil 1995). Two widely used and effective measures of reward in animal models involve self-administration and conditioned place preference (CPP¹).

Self-Administration

In self-administration models, an animal performs a task, such as pressing a lever, to obtain a drug; an increase in the frequency of task performance is an index of the reinforcing properties of the drug. There is a high correspondence between drugs that are readily self-administered by experimental animals and those that are abused by humans (Bozarth 1987; Collins et al. 1984).

The earliest preclinical studies of the rewarding effects of ketamine focused on the propensity for animals to self-administer the drug and showed that ketamine was reinforcing in a small but significant number of self-administration experiments, the first of which involved nonhuman primates. McCarthy and Harrigan (1977) and Moreton and colleagues (1977) found that rhesus monkeys self-administered ketamine in a dose-dependent manner, and the pattern of self-administration behavior was similar to that seen with other drugs of abuse, such as methamphetamine, cocaine, morphine, and heroin. Subsequent studies have replicated the finding that nonhuman primates self-administer ketamine (Broadbear et al. 2004; Carroll and Stotz 1983; Marquis and Moreton 1987; Risner 1982; Winger et al. 1989; Young and Woods 1981).

One potential criticism of this early work is that the animals in these investigations nearly always had considerable experience self-administering other drugs, so it might be argued that they were sensitized or primed for drug self-administration. But similar ketamine self-administration has been observed in monkeys without a history of drug self-administration (Young and Woods 1981). Self-administration of ketamine has also been replicated in other species, including dogs (Risner 1982), baboons (Lukas et al. 1984), and rats (Collins and Woods 2007; Collins et al. 1984; De Luca and Badiani 2011; Marquis et al. 1989; Marquis and Moreton 1987; Rocha et al. 1996; van der Kam et al. 2007, 2009b).

A very recent relevant finding is that ketamine self-administration is highly dependent on environmental

influences. De Luca and Badiani (2011) found that rats readily self-administered ketamine when sessions occurred in an experimental cage, but reduced their self-administration when sessions occurred in the home cage. These results are similar to recent work from our laboratory demonstrating much greater ketamine sensitization when the drug was administered in an experimental cage than in a home cage (Heller and Trujillo 2007). Thus environment is an important factor in the psychoactive effects of ketamine and can modify ketamine reward and neuroadaptations. Future studies should pay attention to environment when evaluating the behavioral and psychoactive effects of ketamine.

Research on self-administration of ketamine is not extensive, but the similar pattern of ketamine self-administration in comparison with other drugs of abuse leads to the conclusion that ketamine is rewarding to laboratory animals. This finding is in contrast to other classes of psychedelic drugs, such as LSD, which are used by humans but are not self-administered by laboratory animals (for review, Fantegrossi et al. 2008).

Conditioned Place Preference

Conditioned place preference is particularly useful in assessing drug reward (Bozarth 1987; Mucha et al. 1982; Tzschentke 1998, 2007). This approach uses an experimental chamber with two compartments distinguished by different cues (visual and/or tactile and/or olfactory). A test drug is reliably paired with one compartment and a placebo with the other. If, after conditioning, the animal spends more time in the drug-associated environment, the drug is considered rewarding. As with self-administration there is a high correspondence between drugs that produce CPP and those abused by humans.

Only in the past 10 years have there been any reported findings regarding the ability of ketamine to produce a conditioned place preference (Gao et al. 2003; Li et al. 2008; Suzuki et al. 2000; van der Kam et al. 2009a; Xu et al. 2006). The earliest work examining ketamine did not focus on its ability to produce a place preference but rather its interaction with other drugs. For example, it was reported that ketamine alone (3 and 10 mg/kg i.p.) produced a significant place preference (Gao et al. 2003; Suzuki et al. 2000) but (at 10 mg/kg i.p.) blocked the development of morphine place preference. In contrast, ketamine (10 mg/kg) produced CPP both alone and in combination with methamphetamine (Xu et al. 2006). In each of these studies, the place conditioning produced by ketamine was statistically significant, but typically less pronounced than that induced by other drugs in the studies, such as morphine (Gao et al. 2003; Suzuki et al. 2000) and MK-801 (Suzuki et al. 1999, 2000).

More recently van der Kam and colleagues (2009a) assessed a variety of doses of ketamine (3.16, 10.0, and 31.6 mg/kg) in place conditioning. Consistent with the previous studies, they noted the development of CPP at 10.0 and 31.6 mg/kg. However, the conditioning was quite modest,

with animals spending only marginally greater time in the drug-paired compartment than the vehicle-paired compartment (although the difference was statistically significant).³

We have begun to examine place conditioning to ketamine in laboratory rats and, like van der Kam and colleagues (2009a), have found that it is modest at best and very sensitive to the specific approaches used. In a series of studies, we were able to show only marginally more time spent in the ketamine-paired (10 mg/kg) compartment relative to the saline-paired compartment (Sullivan and Trujillo 2010). Yet despite the low levels of conditioning, animals became sensitized to the ketamine they received during conditioning. Thus, ketamine sensitization was robust and reliable, while ketamine place conditioning was modest and unreliable.

The results of the studies described here suggest a conflict between those that have used self-administration to study ketamine reward and those that used conditioned place preference. There are several possible explanations for this discrepancy. One likely explanation is that ketamine reward is accompanied by aversive effects that become apparent in CPP studies.

Users of ketamine for recreational purposes often report a mix of reward and aversion (Dillon et al. 2003; Jansen 2000; Jansen and Darracot-Cankovic 2001), an effect that has also been seen in human clinical studies with subanesthetic doses of ketamine (Krystal et al. 1994; van Berckel et al. 1998). Self-administration studies typically use very low doses administered intravenously, with repeated administrations during a single session. Conditioned place preference studies typically use higher doses, with only one i.p. or s.c. administration during a session. The conditions used in self-administration may lead to a bias toward ketamine reward, while CPP methods produce a more balanced expression of reward and aversion.

Further research on ketamine self-administration, conditioned place preference, and other approaches will enhance understanding of ketamine reward and its role in ketamine abuse and addiction.

Conclusion

Ketamine is a fascinating drug that has captured the attention of anesthesiologists, psychiatrists, spiritual seekers, dance partiers, and scientists. In this review we have identified a few aspects of particular interest in current research: the drug's unique anesthetic profile, its analgesic effects across a variety of doses and its ability to prevent pathological pain, its ability to mimic key symptoms of schizophrenia, its rapid and long-lasting antidepressant effects, its ability to evoke mystical or spiritual feelings and insight, and its euphorogenic and rewarding effects.

Although much is known about ketamine's actions, and there has been progress in efforts to understand the mecha-

nisms that underlie its unique effects, there is still much more to be learned. Given the drug's popularity both in clinical use and among recreational users, research on ketamine using both human subjects and animal models will undoubtedly remain a focus of intense investigation well into the future.

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³In contrast to all of these studies, Li and colleagues (2008) reported very strong place conditioning to ketamine (10 mg/kg) in rats.

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