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# Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms

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**Abstract**—Ketamine, a racemic mixture consisting of (*S*)- and (*R*)-ketamine, has been in clinical use since 1970. Although best characterized for its dissociative anesthetic properties, ketamine also exerts analgesic, anti-inflammatory, and antidepressant actions. We provide a comprehensive review of these therapeutic uses, emphasizing drug dose, route of administration, and the time course of these effects. Dissociative, psychotomimetic, cognitive, and peripheral side effects associated with short-term or prolonged exposure, as well as recreational ketamine use, are also discussed. We further describe ketamine's pharmacokinetics, including its rapid and extensive metabolism to norketamine, dehydronorketamine, hydroxyketamine, and hydroxynorketamine (HNK) metabolites. Whereas the anesthetic and analgesic properties of ketamine are generally attributed to direct ketamine-induced inhibition of

*N*-methyl-D-aspartate receptors, other putative lower-affinity pharmacological targets of ketamine include, but are not limited to,  $\gamma$ -aminobutyric acid (GABA), dopamine, serotonin, sigma, opioid, and cholinergic receptors, as well as voltage-gated sodium and hyperpolarization-activated cyclic nucleotide-gated channels. We examine the evidence supporting the relevance of these targets of ketamine and its metabolites to the clinical effects of the drug. Ketamine metabolites may have broader clinical relevance than was previously considered, given that HNK metabolites have antidepressant efficacy in preclinical studies. Overall, pharmacological target deconvolution of ketamine and its metabolites will provide insight critical to the development of new pharmacotherapies that possess the desirable clinical effects of ketamine, but limit undesirable side effects.

## I. Introduction

(*R,S*)-Ketamine (hereafter referred to as ketamine) is a phenylcyclohexylamine derivative (mol. wt. = 237.73) consisting of its two optical enantiomers, (*S*)- and (*R*)-ketamine (Adams et al., 1978). It became commercially available for human use in 1970 as a rapid-acting i.v. anesthetic (Dundee et al., 1970). Ketamine was derived from phencyclidine (PCP) with the aim of lessening the serious psychotomimetic/psychodysleptic side effects and abuse potential of the parent drug, which was subsequently removed from the market in 1978 (Mion and Villeveille, 2013). However, ketamine still induces dissociative effects (Domino et al., 1965; Erdemir et al., 1970; Oye et al., 1992; Krystal et al., 1994; Bowdle et al., 1998; Newcomer et al., 1999; Lahti et al., 2001; Pomarol-Clotet et al., 2006) and has abuse potential (Siegel, 1978; Reich and Silvey, 1989; Dalgarno and Shewan, 1996; Stewart, 2001; Morgan and Curran, 2012), although to a lesser extent than PCP. Despite these side effects, ketamine has proven to be a desirable drug due to its short half-life and lack of clinically-significant respiratory depression (Clements et al., 1982; Gorlin et al., 2016). In addition to its well-characterized

anesthetic action in adults, children, and obstetric patients, ketamine possesses analgesic effects (Weisman, 1971), anti-inflammatory effects (Roytblat et al., 1998), and antidepressant activity (Berman et al., 2000; Zarate et al., 2006; also see Wolff and Winstock, 2006).

### A. Clinical Therapeutic Effects

**1. Anesthetic.** Ketamine induces general, dissociative anesthesia in animals (McCarthy et al., 1965; Chen et al., 1966; Bree et al., 1967) and humans (Domino et al., 1965; Corssen and Domino, 1966; Virtue et al., 1967; Miyasaka and Domino, 1968; Domino, 2010). Moreover, ketamine is also used as an adjunct to local anesthetics in veterinary practice and in humans (Green et al., 1981; Bion, 1984; Gomez de Segura et al., 1998; Hawksworth and Serpell, 1998; Kathirvel et al., 2000).

Dissociative anesthesia—a form of anesthesia that lacks complete unconsciousness but is characterized by catatonia, catalepsy, and amnesia—is achieved in humans at ketamine doses ranging from 1 to 2 mg/kg administered i.v. (bolus) or 4–11 mg/kg administered i.m. (Sage and Laird, 1972; Sussman, 1974; Dachs and

**ABBREVIATIONS:**  $\sigma_1R$ , sigma I receptor;  $\sigma_2R$ , sigma II receptor; AMPA,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AUC, area under the curve; CHO, Chinese hamster ovary; CRPS, complex regional pain syndrome;  $D_2R$ ,  $D_2$  receptor; DA, dopamine; DHNK, dehydronorketamine; HCN, hyperpolarization-activated cyclic nucleotide-gated channel; HEK, human embryonic kidney; HK, hydroxyketamine; HNK, hydroxynorketamine; 5-HT, serotonin; IL-6, interleukin 6; mAChR, muscarinic acetylcholine receptor; nAChR, nicotinic acetylcholine receptor; NET, norepinephrine transporter; NMDAR, *N*-methyl-D-aspartate receptor; PCP, phencyclidine; PET, positron emission tomography; SERT, serotonin transporter; VDCC, voltage-dependent calcium channel.

Innes, 1997; Weber et al., 2004; Green et al., 2011; Gao et al., 2016). Peak ketamine plasma concentrations of approximately 1200–2400 ng/ml, or 5–10  $\mu\text{M}$ , are necessary to induce dissociative anesthesia (Little et al., 1972; Idvall et al., 1979; Grant et al., 1983).

The average steady-state plasma concentration necessary to achieve anesthesia with ketamine was reported to be 2200 ng/ml, or 9.3  $\mu\text{M}$  (Idvall et al., 1979). Oral (500 mg; Craven, 2007) or intrarectal (8–15 mg/kg; Idvall et al., 1983; Malaquin, 1984; Malinovsky et al., 1996) administration of ketamine are sufficient to induce sedation and/or general anesthesia in humans.

Awakening from ketamine-induced anesthesia occurs at plasma concentrations ranging from 640 to 1100 ng/ml or 2.7–4.7  $\mu\text{M}$  (Idvall et al., 1979; Reich and Silvy, 1989). White et al. (1985) showed that administration of the racemic mixture of ketamine (5- to 7-minute i.v. infusion of 50 mg/min for a total dose of  $275 \pm 25$  mg) induced general anesthesia in five healthy adult volunteers, as indicated by the absence of an eyelid reflex. Upon termination of the infusion, it took approximately  $11 \pm 3$  minutes for the volunteers to open their eyes (1900–3300 ng/ml or 8.0–14  $\mu\text{M}$  serum concentration), and approximately  $45 \pm 10$  minutes for them to fully regain proper orientation of self, place, and time (3.78–4.62  $\mu\text{M}$  serum concentration; White et al., 1985).

Intranasal (*S*)-ketamine at the doses of 3–9 mg/kg induces sedation in patients (Tsze et al., 2012). As an anesthetic for humans, (*S*)-ketamine is reported to be twice as potent as the racemic mixture and approximately three times more potent than (*R*)-ketamine (White et al., 1985; Schüttler et al., 1987; Himmelseher and Pfenninger, 1998). Specifically, the total i.v. dose required for the induction of anesthesia is  $275 \pm 25$  mg for racemic ketamine,  $140 \pm 21$  mg for (*S*)-ketamine, and  $429 \pm 37$  mg for (*R*)-ketamine (White et al., 1985). Time needed to regain complete orientation of self, place, and time following a 5- to 7-minute i.v. administration of (*S*)-ketamine (25 mg/min; total dose:  $140 \pm 21$  mg) or (*R*)-ketamine (75 mg/min; total dose:  $429 \pm 37$  mg) was  $21 \pm 2$  minutes (500–900 ng/ml or 2.1–3.8  $\mu\text{M}$  serum concentration) and  $18 \pm 3$  minutes (2200–3200 ng/ml or 9.3–13  $\mu\text{M}$  serum concentration), respectively (White et al., 1985). These data indicate that the (*S*)-ketamine isomer is a more potent anesthetic compared with (*R*)-ketamine, given that a three-fold higher dose of (*R*)-ketamine is required to elicit a comparable level of sedation. Additionally, the serum concentration of (*R*)-ketamine that caused half-maximal median frequency decrease ( $\text{IC}_{50}$ ) in electroencephalographic oscillations was measured to be  $2000 \pm 500$  ng/ml ( $8.0 \pm 2.0$   $\mu\text{M}$ ), versus  $1800 \pm 500$  ng/ml ( $7.6 \pm 2.0$   $\mu\text{M}$ ) for the racemic drug and  $800 \pm 400$  ng/ml ( $3.4 \pm 1.7$   $\mu\text{M}$ ) for the (*S*)-ketamine isomer (Schüttler et al., 1987).

**2. Analgesic.** An early report of the analgesic effects of ketamine was provided by Weisman (1971), who observed these effects in pediatric ophthalmologic procedures (Weisman, 1971). Ketamine is described to provide a form of analgesia quantitatively and qualitatively similar to opioids, but with less respiratory depressive effects, as was reported in pediatric patients treated for fractures (Kennedy et al., 1998), burns (see McGuinness et al., 2011), or in cases of traumatic amputation (Bonanno, 2002). When administered i.v. or i.m., ketamine's analgesic effects are associated with plasma concentrations ranging between 70 and 160 ng/ml, or approximately 0.29–0.67  $\mu\text{M}$  (Clements and Nimmo, 1981; Grant et al., 1981; Clements et al., 1982; Flood and Krasowski, 2000).

Intravenous ketamine is used as an analgesic to reduce chronic and acute postoperative pain (Laskowski et al., 2011). Adequate analgesia is achieved at subanesthetic doses of ketamine, as low as 0.15–0.25 mg/kg, when administered i.v. (Roytblat et al., 1993; Backonja et al., 1994; Eide et al., 1994), or 0.5–1 mg/kg when administered i.m. to patients following acute trauma (Hirlinger and Dick, 1984). In addition, ketamine's antinociceptive and analgesic effects have been observed when ketamine is administered as follows: 1) orally at the dose of 0.5 mg/kg twice per day for 15 days (as adjuvant to morphine; Lauretti et al., 1999) or at the single dose of 2 mg/kg (Marchetti et al., 2015); 2) intranasally at a dose ranging from 10 to 50 mg twice per day (Carr et al., 2004); 3) transdermally at the dose of 25 mg released throughout a 24-hour period (Azevedo et al., 2000); 4) s.c. at a dose ranging from 0.05 to 0.15 mg/kg per hour for 7 days (Eide et al., 1995); and 5) rectally at the dose of 10 mg/kg (Tanaka et al., 2000). Following oral dosing, lower ketamine concentrations in the blood may be required to achieve analgesia compared with the other routes of administration (maximum concentration,  $C_{\text{max}} = 45 \pm 10$  ng/ml or  $0.19 \pm 0.04$   $\mu\text{M}$ ; Grant et al., 1981). Continuous infusion of a subanesthetic dose of ketamine (titrated from 10 to 40 mg/h; maintained for 5 days) has been demonstrated to be effective in improving pain in patients suffering from complex regional pain syndrome (CRPS), resulting in plasma concentrations of both (*S*)- and (*R*)-ketamine ranging between 200 and 225 ng/ml (0.84–0.95  $\mu\text{M}$ ; Goldberg et al., 2010; Moaddel et al., 2010).

The use of intranasal (*S*)-ketamine as an analgesic may be of particular relevance in prehospital settings, where i.v. administration is difficult, and in cases where acute administration for injuries is required, because it reduces pain scores within 5 minutes following administration (Johansson et al., 2013). Similar to their differential anesthetic effects, there is evidence supporting that (*S*)-ketamine is a more potent analgesic drug compared with racemic ketamine and (*R*)-ketamine in humans, although (*S*)-ketamine also

produces more side effects (Oye et al., 1992; Mathisen et al., 1995).

3. *Antidepressant*. Evidence of ketamine's antidepressant actions dates back to the 1970s. In preclinical studies, ketamine was found to exert effects similar to those observed following administration of classic antidepressant drugs (i.e., tricyclic antidepressants and monoamine oxidase inhibitors) in rodents (Sofia and Harakal, 1975). In particular, oral administration of ketamine to mice reversed reserpine-induced hyperthermia at the dose of 40 mg/kg and prevented tetrabenazine-induced ptosis with an ED<sub>50</sub> of 27.6 mg/kg (Sofia and Harakal, 1975), which are phenotypes reversed by classical antidepressants (Delini-Stula, 1980). Early evidence of ketamine's possible antidepressant properties in humans was described in 1973 by Khorramzadeh and Lotfy (1973), who reported that i.v. ketamine at the subanesthetic doses of 0.2–1.0 mg/kg (i.v. bolus) resulted in emotional discharge and facilitation of psychotherapy in a cohort of 100 psychiatric inpatients. However, the precise depression symptoms that were improved with ketamine were not well delineated in the context of modern diagnostic criteria and therapeutic definitions. In this study, ketamine was in fact referred to as a general abreactive agent (Khorramzadeh and Lotfy, 1973).

The first placebo-controlled study suggesting ketamine has antidepressant actions was reported in 2000. Based on the results reported in that study, an i.v. 40-minute infusion of 0.5 mg/kg ketamine induced a robust and rapid antidepressant response in patients suffering from depression compared with placebo (Berman et al., 2000). This finding was subsequently replicated in a double-blind, placebo-controlled, randomized clinical trial involving patients suffering from treatment-refractory major depression (Zarate et al., 2006). In particular, Zarate et al. (2006) demonstrated that ketamine exerts an antidepressant effect that becomes evident within 2 hours postinfusion, and lasts for an average of 7 days in patients who have failed to respond to at least two prior classical antidepressant medications. Several other clinical trials have replicated these findings in patients suffering from treatment-refractory depression (e.g., Murrough et al., 2013a; Lapidus et al., 2014). To address the functional unblinding of treatment status due to the dissociative effects of ketamine, which occur even at low subanesthetic doses, Murrough et al. (2013a) used a psychoactive placebo (i.e., midazolam) and demonstrated a higher response rate for the patients who received ketamine (64%) compared with those who received midazolam (28%). Ketamine is also reported to exert antidepressant actions in patients suffering from bipolar depression (Diazgranados et al., 2010a; Zarate et al., 2012b). (S)-ketamine has been shown effective as an antidepressant administered both via i.v. and intranasal routes (Singh et al., 2016a; Daly et al., 2018; Canuso et al., 2018).

Additional studies have shown that ketamine reduces suicidal ideation (Price et al., 2009; DiazGranados et al., 2010b; Ballard et al., 2014) and decreases anhedonia (Lally et al., 2014, 2015; Ballard et al., 2017) in patients suffering from major depression. Intranasal (S)-ketamine also decreased suicidal ideation in patients suffering from depression (Canuso et al., 2018).

The most commonly used subanesthetic antidepressant dose of ketamine (0.5 mg/kg; 40-minute infusion) results in a maximal plasma concentration (C<sub>max</sub>) of ~185 ng/ml or ~0.78 μM ketamine, as calculated from the results of Zarate et al. (2012a). Nevertheless, there is some evidence for antidepressant responses achieved at doses as low as 0.1 mg/kg (5-minute i.v. infusion or i.m. injection), resulting in ketamine C<sub>max</sub> of ~75 ng/ml (0.32 μM—estimated) as reported in a small pilot (n = 15) double-blind, placebo-controlled crossover study in patients suffering from treatment-resistant depression (Loo et al., 2016). Although this study indicated that lower doses of ketamine, which produce fewer side effects, could be effective in the treatment of depression, this finding awaits replication in a larger study.

4. *Anti-Inflammatory*. Inflammation is a critical homeostatic mechanism used by the body to fight infections and to heal tissue injuries (Selye, 1976; Hirsiger et al., 2012). Inflammatory reactions are triggered once immune cells of the innate immune system become activated, whether by invading pathogens or tissue damage. Release of proinflammatory cytokines by these cells then activate members of the adaptive immune system to initiate an inflammatory response (Newton and Dixit, 2012).

Ketamine administration during or prior to surgical operations has been used for a more favorable postoperative outcome, primarily due to its actions to reduce the production of excess proinflammatory cytokines. Anti-inflammatory actions (i.e., reduction of proinflammatory cytokines) of preoperative subanesthetic doses of 0.15–0.25 mg/kg (single i.v. bolus) ketamine were described in humans (Roytblat et al., 1998; Beilin et al., 2007; Russabrov et al., 2008). Ketamine was shown to inhibit immune reaction-induced proinflammatory cytokine production, including nuclear factor κB, and to decrease blood levels of tumor necrosis factor-α, interleukin 6 (IL-6), C-reactive protein, and/or inducible nitric oxide synthase (Larsen et al., 1998; Kawasaki et al., 1999, 2001; Lankveld et al., 2005; Beilin et al., 2007; Loix et al., 2011; De Kock et al., 2013). The ability of ketamine to reduce proinflammatory cytokine levels may be of clinical relevance, given that elevated IL-6 levels have been associated with poor postoperative outcomes (Oka et al., 1992; Hennein et al., 1994; Cremer et al., 1996). However, this possibility awaits systematic investigation.

In addition to its effects on the proinflammatory cytokines, ketamine dose dependently reduces inflammation-induced

nitric oxide production (Shimaoka et al., 1996; Li et al., 1997; Yang et al., 2005). The anti-inflammatory effects of ketamine have been observed when the drug was administered prior to, and following an immune stimulation, indicating that ketamine may be able to prevent exacerbation of inflammation, and also reduce existing inflammation (Loix et al., 2011). There is evidence that ketamine can alleviate postoperative trauma-induced hyperalgesia by modulating the inflammatory response, which is beneficial in the context of chronic postoperative pain (Stubhaug et al., 1997; De Kock et al., 2001; Suzuki et al., 2006; Remerand et al., 2009).

Ketamine has also been shown to correct abnormal inflammatory bone markers in major depressive disorder. In particular, a 40-minute i.v. infusion of ketamine (0.5 mg/kg) increased levels of the osteoprotegerin receptor activator of nuclear factor  $\kappa$ B ligand and osteopontin—predictive markers of bone inflammation—in patients with major depressive disorder, but had no effect in healthy controls (Kadriu et al., 2017). Moreover, serum levels of the proinflammatory cytokines tumor necrosis factor- $\alpha$ , interferon  $\gamma$ , and interleukin 2, 5, and 10 were unaltered following a 40-minute i.v. subanesthetic infusion of ketamine (0.5 mg/kg) in patients suffering from depression, whereas levels of the anti-inflammatory cytokine IL-6 were reported to increase 230 minutes postketamine infusion (Park et al., 2017). However, this effect of ketamine on IL-6 levels was not associated with the antidepressant actions of the drug (Park et al., 2017). It is possible that the infusion itself led to an acute stress-related increase in IL-6 levels, given that this has been observed following saline infusion as well (Cho et al., 2009). Overall, these findings indicate that the anti-inflammatory actions of ketamine occur primarily in the presence of immunostimulation, whereas the drug does not exert any effects on cytokine balance in the absence of an inflammatory reaction (Loix et al., 2011). Thus, ketamine may act as an immunomodulator, and not as an immunosuppressive agent, which is of particular importance because ketamine is commonly administered during the induction of anesthesia, prior to surgery.

Relevant doses and plasma concentrations of ketamine used for clinical therapeutic effects are listed in Table 1.

## B. Side Effects

### 1. Psychoactive Effects.

*a. Dissociative and psychotomimetic effects.* Ketamine dose dependently exerts broad influences on consciousness and perception, with some patients reporting dissociative and extracorporeal sensations (out-of-body experiences/illusions) when recovering from ketamine-induced anesthesia (Garfield et al., 1972; White et al., 1980, 1982). Whereas these effects

of ketamine established the drug as a dissociative anesthetic (Domino et al., 1965), the same effects have been noted following subanesthetic doses as well (e.g., Krystal et al., 1994).

The most common psychoactive effects reported after a single subanesthetic i.v. administration of ketamine include dissociation (distortions in visual, auditory, or somatosensory stimuli, or alterations in the perception of self or time), positive psychotomimetic effects (conceptual disorganization, hallucinations, suspiciousness, unusual thought content), and negative psychotomimetic effects (blunted affect, emotional withdrawal, motor retardation). These effects were reported in both randomized controlled studies (e.g., Malhotra et al., 1996; Anand et al., 2000; Berman et al., 2000; Hetem et al., 2000; Abel et al., 2003; Zarate et al., 2006; Diazgranados et al., 2010a; Zarate et al., 2012b; Murrough et al., 2013b, 2015; Downey et al., 2016; Hu et al., 2016; Li et al., 2016) and nonrandomized or open label studies (e.g., Phelps et al., 2009; Mathew et al., 2010; Valentine et al., 2011; Ibrahim et al., 2012; Ionescu et al., 2015). For instance, a randomized, double-blind, placebo-controlled study by Krystal et al. (1994) showed that a 40-minute i.v. infusion of the subanesthetic dose of 0.5 mg/kg ketamine (resulting  $C_{\max}$  estimated to be  $\sim 100$ – $250$  ng/ml or  $0.42$ – $1.1$   $\mu$ M) leads to perceptual aberrations that are consistent with dissociative states, as well as positive and negative psychotomimetic symptoms. These effects emerged within 10 minutes of the beginning of ketamine infusion and subsided within 40 minutes of treatment termination. In contrast, little to no psychoactive effects were observed at the dose of 0.1 mg/kg (resulting in  $\sim 25$ – $50$  ng/ml or  $0.1$ – $0.2$   $\mu$ M plasma ketamine concentration; Krystal et al., 1994). Ketamine (0.3 mg/kg bolus;  $C_{\max} = \sim 120$  ng/ml or  $0.5$   $\mu$ M) has also been shown to exacerbate psychotic symptoms in patients suffering from schizophrenia (Lahti et al., 2001). Similarly, Malhotra et al. (1997) also reported that ketamine increased psychotic symptoms in patients suffering from schizophrenia when given as a single i.v. bolus of 0.12 mg/kg, followed by a 60-minute infusion of 0.65 mg/kg (total dose 0.77 mg/kg).

Experiencing illusions and alterations in hearing, vision, and proprioception has been attributed to the actions of (*S*)-ketamine (Oye et al., 1992; Mathisen et al., 1995; Vollenweider et al., 1997), whereas feelings of relaxation were associated with the actions of (*R*)-ketamine (Vollenweider et al., 1997). In particular, at equimolar doses producing average plasma ketamine levels of  $379 \pm 71$  ng/mg (i.e.,  $1.59 \pm 0.30$   $\mu$ M) and  $389 \pm 74$  ng/mg (i.e.,  $1.64 \pm 0.31$   $\mu$ M) for (*S*)- and (*R*)-ketamine, respectively, the (*S*)-ketamine enantiomer caused acute psychotic reactions at a mean plasma ketamine level of 539 ng/ml (i.e.,  $2.27$   $\mu$ M), whereas (*R*)-ketamine was not associated with these psychotomimetic actions. In contrast, (*R*)-ketamine administration induced a feeling of

TABLE 1  
Relevant doses and plasma concentrations of ketamine for its clinical use and side effects in humans

Clinical Uses and Side Effects	Route of Administration	Ketamine Dose	Plasma C <sub>max</sub>	References
<i>Clinical effects</i>				
General anesthesia	Intravenous Intramuscular Rectal Oral	1.0–2 mg/kg 4–11 mg/kg 8–10.6 mg/kg 500 mg (max)—sedation	1200–2400 ng/ml; 5–10 μM	Sussman (1974), Clements et al. (1982), Idvall et al. (1983), Malaquin (1984), Malinovsky et al. (1996), Dachs and Innes (1997), Yanagihara et al. (2003), Weber et al. (2004), Craven (2007), Gao et al. (2016)
Analgesia	Intranasal Intravenous Intramuscular Intranasal Transdermal Subcutaneous Rectal Oral	For (S)-ketamine: 3–9 mg/kg  0.15 mg/kg 0.5–1 mg/kg 2 × 10–50 mg 25 mg released throughout a 24-hour period 0.05–0.15 mg/kg per hour for 7 days 10 mg/kg 2 mg/kg 0.5 mg/kg	N/R  70–160 ng/ml; 0.29–0.67 μM	Weber et al. (2004), Huge et al. (2010), Reid et al. (2011) Grant et al. (1981), Clements et al. (1982), Hirlinger and Dick (1984), Weksler et al. (1993), Eide et al. (1995), Malinovsky et al. (1996), Stubhaug et al. (1997), Lauretti et al. (1999), Azevedo et al. (2000), Flood and Krasowski (2000), Tanaka et al. (2000), Carr et al. (2004), Marchetti et al. (2015)
Anti-inflammation	Intravenous	0.15–0.25 mg/kg	45 ± 10 ng/ml; 0.19 ± 0.04 μM N/R	Grant et al. (1981)
Antidepressant	Intravenous	0.5 mg/kg; 40-min infusion	185 ng/ml; 0.78 μM	Roytblat et al. (1998), Beilin et al. (2007), Russabrov et al. (2008)
<i>Side effects</i>				
Dissociation	Intravenous	0.5 mg/kg; 40-min infusion	N/R	Zarate et al. (2006)
Psychotomimetic effects in subjects with schizophrenia	Intravenous	0.3 mg/kg bolus  0.12 mg/kg bolus followed by a 60-min infusion of 0.65 mg/kg (total dose 0.77 mg/kg) 40- to 120-min infusion of 0.4–0.8 mg/kg 0.5 mg/kg bolus infusion over length of testing (total dose variable)	100–250 ng/ml; 0.42–1.1 μM 120 ng/ml; 0.5 μM N/R	Krystal et al. (1994) Lahti et al. (2001) Malhotra et al. (1997)
Cognitive and memory impairment	Intravenous	0.25–0.5 mg/kg bolus 1–2 mg/kg 50–150 mg 100–500 mg 30–400 mg	350 ng/ml; 1.5 μM N/R	Malhotra et al. (1996), Newcomer et al. (1999), Morgan et al. (2004), Mathew et al. (2010) Pfenninger et al. (2002) Harris et al. (1975), Driesen et al. (2013)
Abuse (recreational use)	Intramuscular Intravenous Intramuscular Oral Intranasal	0.25–0.5 mg/kg bolus 1–2 mg/kg 50–150 mg 100–500 mg 30–400 mg	N/R N/R	Ghoneim et al. (1985) Siegel (1978), Daigarno and Shewan (1996), Jansen (2000), Arditti et al. (2002), Wolff and Winstock (2006), Bokor and Anderson (2014)

N/R, not reported.

“well-being” and a beneficial effect on mood as measured by the Eigenschaftsworterliste (EWL) mood rating scale (Vollenweider et al., 1997). A clinical study conducted by Mathisen et al. (1995) showed that 56% of patients who suffered from orofacial pain and were treated with (*S*)-ketamine (0.45 mg/kg, i.m.; serum  $C_{\max}$  = ~120 ng/ml or 0.5  $\mu$ M) experienced illusions, whereas only 22% of those treated with (*R*)-ketamine experienced illusions, even though a higher dose of (*R*)-ketamine was used (1.8 mg/kg, i.m.; serum  $C_{\max}$  = ~590 ng/ml or 2.5  $\mu$ M). In this study, the prevalence of illusions among patients treated with (*S*)-ketamine was comparable to that observed among patients treated with (*R,S*)-ketamine at a dose of 0.9 mg/kg, i.m.; serum  $C_{\max}$  = ~297 ng/ml or 1.25  $\mu$ M (Mathisen et al., 1995). Alterations in hearing were reported in 78%, 67%, and 57% of patients treated with (*S*)-, (*R*)-, and (*R,S*)-ketamine, respectively, whereas blurred vision was reported by 100%, 78%, and 85% of patients receiving (*S*)-, (*R*)-, and (*R,S*)-ketamine, respectively. Additionally, treatment with (*S*)-ketamine led to proprioceptive disturbances in 100% of patients, as compared with 56% and 71% of patients receiving either (*R*)- or (*R,S*)-ketamine, respectively (Mathisen et al., 1995). Although 43% of patients treated with (*R,S*)-ketamine reported dreams and hallucinations, neither effect was reported by patients treated with either (*S*)- or (*R*)-ketamine (Mathisen et al., 1995).

A study conducted in healthy volunteers showed no differences in the postanesthetic effects of (*S*)- (140  $\pm$  21 mg), (*R*)- (429  $\pm$  37 mg), or (*R,S*)-ketamine (275  $\pm$  25 mg) in their propensity to elicit floating sensations (average 67% of individuals), diplopia (double vision; 60%), or dizziness (47%; White et al., 1985). These effects occurred at higher plasma concentrations of (*R*)-ketamine compared with (*S*)- and (*R,S*)-ketamine (White et al., 1985; Mathisen et al., 1995).

*b. Memory and cognitive impairment.* In addition to the dissociative and psychotomimetic symptoms, several studies have identified unfavorable effects of subanesthetic administration of ketamine on cognition (also see Ke et al., 2018). Studies have reported that ketamine decreases mental sharpness (Mathew et al., 2010), concentration (Pfenninger et al., 2002), recall and recognition (Malhotra et al., 1996), as well as explicit (episodic and semantic) and implicit (procedural) forms of memory (Harris et al., 1975; Ghoneim et al., 1985; Newcomer et al., 1999; Morgan et al., 2004; Honey et al., 2005; Driesen et al., 2013) either during or shortly after administration (for dosing details, see Table 1).

Vigilance, verbal fluency, and delayed recall are also impaired during/immediately following a 40-minute i.v. infusion of 0.5 mg/kg ketamine (resulting in plasma  $C_{\max}$  estimated to be ~100–250 ng/ml or 0.42–1.1  $\mu$ M); these effects subside shortly after termination of the infusion (Krystal et al., 1994). Global cognitive function and immediate recall appear to remain intact during ketamine infusion (Krystal et al., 1994). Based on results

obtained from cross-sectional studies, long-term ketamine abuse is also associated with cognitive impairments (Morgan and Curran, 2012; Zhang et al., 2018; Morgan et al., 2004). However, the nature of these studies makes it difficult to fully control for the impact of other comorbid or environmental factors (Morgan and Curran, 2012; Zhang et al., 2018).

*c. Abuse.* Whereas the acute psychotropic effects of ketamine may cause discomfort for some individuals (Domino et al., 1965), its dissociative properties have made it desirable for recreational use (Siegel, 1978; Stewart, 2001). However, some users may experience increased agitation or anxiety/panic attacks (Siegel, 1978; Jansen, 2000; Weiner et al., 2000; Arditti et al., 2002). Within 10 minutes following initiation of a 40-minute i.v. infusion of a subanesthetic dose of 0.5 mg/kg ketamine (resulting in plasma  $C_{\max}$  estimated to be ~100–250 ng/ml or 0.42–1.1  $\mu$ M), healthy subjects reported feelings of being “high” (i.e., subjectively comparable to that of alcohol intoxication; Krystal et al., 1994). A lower ketamine dose of 0.1 mg/kg (resulting in plasma  $C_{\max}$  = ~25–50 ng/ml or 0.1–0.2  $\mu$ M) induced a mild euphoria (i.e., buzzing) feeling (Krystal et al., 1994).

Although controlled studies addressing the abuse potential of ketamine are lacking, valuable information about both the acute and chronic effects of ketamine has been derived from reports of recreational use (see Corazza et al., 2013). In general, doses used for recreational ketamine intake may range between 1 and 2 mg/kg (i.v.), 50 and 150 mg (i.m.), 100 and 500 mg (oral), or 30 and 400 mg (intranasal insufflation; Siegel, 1978; Dalgarno and Shewan, 1996; Jansen, 2000; Arditti et al., 2002; Wolff and Winstock, 2006; Bokor and Anderson, 2014). Although the effects of specific doses used for recreational use cannot be directly determined due to a lack of controlled studies assessing these, users report that lower doses induce mild stimulatory, dissociative, and hallucinogenic effects, whereas higher doses yield psychotomimetic symptoms and separation from reality (Stewart, 2001; Wolff and Winstock, 2006).

The most common route of recreational administration is nasal insufflation, with an onset of feeling “high” ranging between 5 and 10 minutes, and lasting between 40 and 75 minutes (Dalgarno and Shewan, 1996; Stewart, 2001; Wolff and Winstock, 2006). At peak levels of intake, users report that ketamine induces a highly dissociative experience marked by an altered state of consciousness and sensory detachment (colloquially referred to as the k-hole), which some describe as being comparable to a near-death experience (Jansen, 1989; Stewart, 2001; Wolff and Winstock, 2006; Bokor and Anderson, 2014).

At plasma concentrations ranging from 50 to 200 ng/ml (0.21–0.84  $\mu$ M; Bowdle et al., 1998), ketamine dose dependently enhances sensory perception (i.e., intensity of sound), emotional connectedness, feelings of unreality, and out-of-body experiences, and may be associated with visual

hallucinations, altered perceptions of self and time, and floating sensations (Hansen et al., 1988; Bowdle et al., 1998; Jansen, 2000; Muetzelfeldt et al., 2008; Wilkins et al., 2012). Undesired effects reported by illicit users include dizziness, blurred vision, slurred speech, vomiting, palpitations, and chest pain (Siegel, 1978; Dalgarno and Shewan, 1996; Weiner et al., 2000; Muetzelfeldt et al., 2008); see section on peripheral effects below. It has been hypothesized that diminished tactile and musculoskeletal sensations caused by ketamine lead to feelings of weightlessness or detachment from oneself, which may contribute to extracorporeal sensations (Collier, 1972; White et al., 1982). Additionally, long-term use of ketamine may lead to flashbacks, attentional and other cognitive dysfunctions, and decreased sociability, but continued use is reinforced by the other psychotropic effects (Siegel, 1978; Jansen, 2000; Zhang et al., 2018). Despite its reinforcing properties, instances of ketamine dependence are relatively scarce (Bobo and Miller, 2002; Lim, 2003; Blier et al., 2012), but have been reported (Morgan and Curran, 2012). There is also evidence to suggest that repeated use of ketamine may lead to drug tolerance (Dalgarno and Shewan, 1996; Jansen and Darracot-Cankovic, 2001; Pal et al., 2002).

**2. Direct and Indirect Peripheral Effects.** At subanesthetic doses (~0.5 mg/kg administered i.v. over 40 minutes), ketamine can lead to vestibular perturbations, including dizziness (Wan et al., 2015) and nausea/vomiting (Ghoneim et al., 1985; Krystal et al., 1994; Morgan et al., 2004). Ketamine's actions on the sympathetic nervous system (Traber and Wilson, 1969; Traber et al., 1970) are associated with broad cardiovascular outcomes (e.g., tachycardia, hypertension, palpitations) evident in both clinical (0.5–1.0 mg/kg i.v.; Strayer and Nelson, 2008; Murrough et al., 2013b) and recreational settings (100–200 mg i.m. or s.c.; Weiner et al., 2000). Although generally considered clinically insignificant, mild respiratory depression is reported at doses ranging from 0.39 to 3.0 mg/kg (Domino et al., 1965; Idvall et al., 1979; Bourke et al., 1987). Additionally, hemodynamic effects (i.e., arterial pressure and heart rate) have not been found to vary significantly among (*S*)-, (*R*)-, and (*R,S*)-ketamine (White et al., 1985), although at least one study suggests that (*S*)-ketamine specifically contributes to (*R,S*)-ketamine's cardiovascular effects, such as increased blood pressure (Geisslinger et al., 1993). Overall, a recent retrospective analysis in individuals who received 684 i.v. ketamine infusions (0.5 mg/kg over 40 minutes) reported that alterations in blood pressure are modest, well tolerated, and clinically insignificant (Riva-Posse et al., 2018).

Ocular effects (e.g., nystagmus, diplopia, dilation) are reported in recreational contexts (Weiner et al., 2000; Stewart, 2001), as well as clinically, at subanesthetic doses of ketamine (e.g., 0.25 mg/kg i.v.; Backonja et al., 1994; Krystal et al., 1994). Some ocular effects (i.e., blurred vision) have been primarily associated with (*S*)-ketamine

(Mathisen et al., 1995). Additionally, musculoskeletal effects (e.g., myoclonus, twitching, spasms, ataxia, fasciculation) have been noted in cases of ketamine abuse (Corssen and Domino, 1966; Felser and Orban, 1982; Wolff and Winstock, 2006; Bokor and Anderson, 2014).

Prolonged recreational use of ketamine is associated with urological complications that include dysuria, increased frequency and urgency of urination, incontinence, pain, hematuria, and ulcerative cystitis (Shahani et al., 2007; Chu et al., 2008; Tsai et al., 2009; Meng et al., 2013; Skeldon and Goldenberg, 2014). It has been suggested that ketamine may have a direct detrimental impact on the interstitial cells of the bladder, since cystoscopy has shown erythema, edema, and epithelial inflammation in long-term ketamine users (Shahani et al., 2007; Chu et al., 2008). Moreover, computer tomography revealed marked bladder wall thickening, mucosal enhancement, and perivesical inflammation associated with recreational ketamine use (Mason et al., 2010). There is at least one case report of subanesthetic ketamine (0.1 mg/kg per hour i.v. administration for 12 hours), being associated with urinary urgency and incontinence (Vickers et al., 2017).

**3. Long-Term Effects.** Given that ketamine's maintenance of therapeutic efficacy often requires repeated administration of the drug (e.g., Blier et al., 2012; Segmiller et al., 2013; Szymkiewicz et al., 2013), it is important to consider the side effects that may be uniquely associated with chronic ketamine exposure. The effects resulting from long-term ketamine treatment are either poorly defined or scarcely reported (reviewed by Short et al., 2018). To date, repeated ketamine abuse has been most consistently associated with long-lasting memory-related deficits (Morgan et al., 2006; Morgan and Curran, 2012; Zhang et al., 2018). Deaths caused by ketamine overdose, in the absence of multidrug intoxication, are very rare (Gill and Stajic, 2000; Jansen, 2000), although accidental deaths caused by falls from heights, extreme hypothermia, or car accidents involving individuals using ketamine have been reported (Gill and Stajic, 2000; Jansen, 2000; Jansen and Darracot-Cankovic, 2001).

Overall, there is no report, to our knowledge, involving a lethal dose of ketamine in humans. Nevertheless, in rats, intravenous administration of (*R,S*)-ketamine and (*S*)-ketamine at the dose of 40 mg/kg induced significant lethality; whereas, all animals that received (*R*)-ketamine at the same dose survived (Marietta et al., 1977). Although these findings indicate that caution should be taken when using ketamine treatment long-term, there is evidence that repeated administration of subanesthetic doses of ketamine may have beneficial long-term effects. For instance, repeated subanesthetic ketamine has been shown to improve clinical outcomes for treatment-resistant depression (Rasmussen et al., 2013; Loo et al., 2016; Cusin et al., 2017). Repeated ketamine administration has also been associated with attenuation of the acute ketamine-induced dissociation, derealization, and dizziness over time (Grott Zanicotti et al., 2013; Singh et al., 2016b).



Nevertheless, dissociative and psychotomimetic effects have been observed in randomized controlled studies examining the effects of repeated i.v. (Lai et al., 2014; Loo et al., 2016; Singh et al., 2016b), i.m. (Loo et al., 2016), and s.c. (Loo et al., 2016; George et al., 2017) subanesthetic ketamine exposure.

Most, if not all, side effects of ketamine are dose dependent, transient, and self-resolving (Wan et al., 2015; Kishimoto et al., 2016; Loo et al., 2016). However, to more fully assess ketamine's therapeutic utility across clinical contexts, future studies should aim to systematically assess the safety and efficacy of either acute or chronic ketamine treatment, in terms of both short- and long-term outcomes.

**4. Neurotoxicity.** With emerging indications requiring repeated ketamine administration (e.g., antidepressant actions), there are concerns of more profound untoward effects of treatment, including the induction of Olney lesions. First reported in 1989, Olney lesions are characterized by vacuoles occurring in the cytoplasmic compartment of selected neuronal populations, where lysis of mitochondria was reported (Olney et al., 1989, 1991). These neuronal vacuolation events occur primarily in the posterior cingulate and retrosplenial cortices following administration of *N*-methyl-*D*-aspartate receptor (NMDAR) antagonists (e.g., PCP, MK-801, and ketamine) in rats (Olney et al., 1989; Fix et al., 1993; Carliss et al., 2007). At low doses, vacuolation appears to reverse within 24 hours of administration, suggesting that permanent cell damage does not occur when non-competitive (PCP, MK-801, ketamine, and dextrorphan) or competitive (CPP, CGS 19755, and CGP 37849) NMDAR antagonists are used at clinically relevant doses (Olney et al., 1989; Allen and Iversen, 1990; Hargreaves et al., 1994). However, there remains a possibility that high doses (or perhaps repeated administration at low doses) of NMDAR antagonists, such as ketamine, could lead to selective irreversible damage. For instance, pre-clinical studies in rats have shown that administration of a high dose of MK-801 (i.e., 5 mg/kg) leads to necrosis in a small subset of neurons (Allen and Iversen, 1990; Auer, 1996; Kuroda et al., 2015)—an effect that was associated with an age-dependent increase in mortality rate (Auer, 1996). Additionally, studies in nonhuman primates have reported that repeated daily ketamine administration (1 mg/kg per day, i.v.): 1) reduced white matter integrity in fronto-thalamo-temporal connections as assessed by diffusion tensor imaging following a 3-month treatment (Li et al., 2017), and 2) increased cell death in the prefrontal cortex as assessed by terminal deoxynucleotidyl transferase-mediated digoxigenin-deoxyuridine nick-end labeling staining of brain sections obtained from animals treated for 6 months (Sun et al., 2014).

Vacuolation was found to occur following administration of high (i.e., 40–60 mg/kg, s.c.) but not low-to-moderate doses (5–20 mg/kg s.c.) of ketamine in rats (Olney et al., 1989; Jevtovic-Todorovic et al., 2001). Notably, these doses are much higher than the doses

required for the analgesic, anti-inflammatory, or antidepressant actions of the drug. Therefore, the relevance of Olney lesions to human repeated ketamine use is controversial and difficult to assess. One magnetic resonance imaging study reported that recreational ketamine users (total time of ketamine use: 0.5–12 years) presented with cortical atrophy in the frontal, parietal, and occipital lobes, and that measurable atrophies were associated with initiation of drug use occurring 2–4 years prior (Wang et al., 2013). In addition, another study in recreational users (total time of ketamine use: 1–10.5 years) reported a loss of frontal cortical white matter microstructure integrity that was correlated with total lifetime ketamine use (Liao et al., 2010).

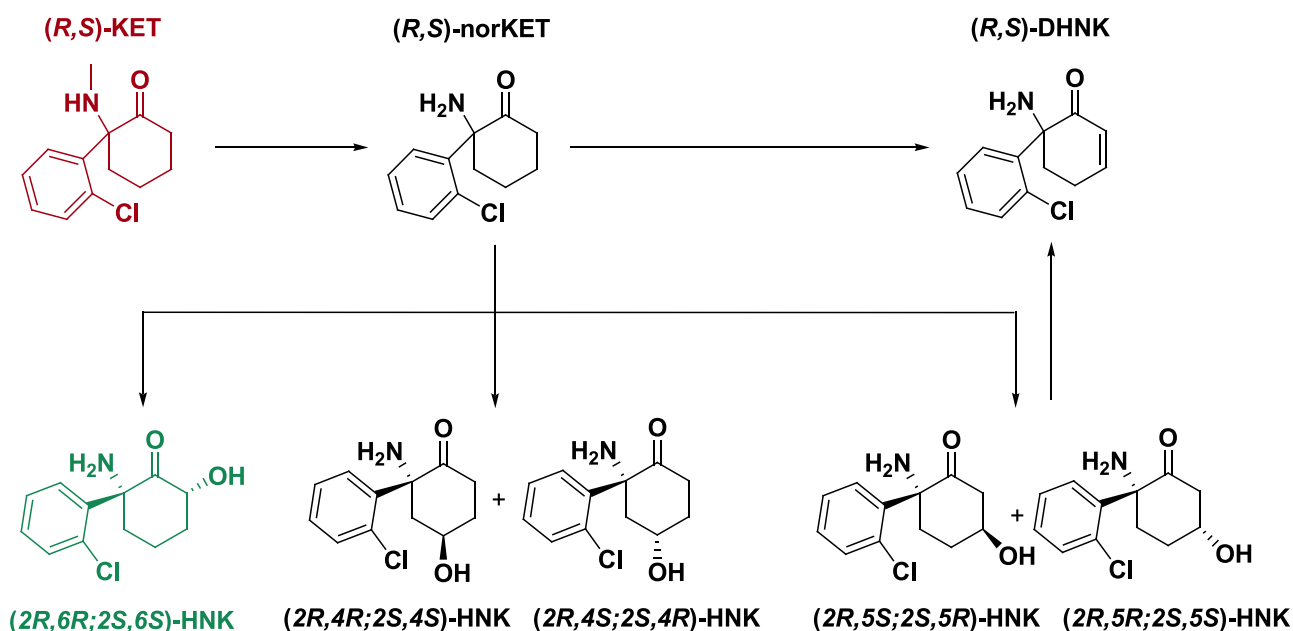
Yeung et al. (2010) reported the presence of hyperphosphorylated tau (microtubule associated protein)-positive cells in the prefrontal and entorhinal cortices of nonhuman primates and mice receiving daily administrations of ketamine (1 mg/kg, i.v. bolus for monkeys and 30 mg/kg, i.p. injections for mice) across a period of 3–6 months. Tau hyperphosphorylation has been associated with the memory decline observed in Alzheimer's disease patients (Augustinack et al., 2002; Huang and Jiang, 2009), possibly indicating a mechanism underlying memory impairment following ketamine use (see *Memory and cognitive impairment* section). Moreover, chronic intermittent administration of (*S*)-ketamine resulted in a loss of parvalbumin immunoreactivity in the hippocampus and prefrontal cortex of mice (Yang et al., 2016), consistent with findings in animal models of psychosis and schizophrenia (Lodge et al., 2009; Gonzalez-Burgos et al., 2015). In line with the lower potency of (*R*)-ketamine to inhibit the NMDARs compared with the (*S*)-ketamine enantiomer (see section *N-Methyl-D-Aspartate Receptors*), chronic intermittent administration of (*R*)-ketamine, unlike that of (*S*)-ketamine (both administered at 10 mg/kg i.p., once per week for a total period of 8 weeks in mice), resulted in no loss of parvalbumin immunoreactivity (Yang et al., 2016). Overall, considering the expanding applications of ketamine, it will be critical to further define the long-term effects of chronic ketamine use.

Relevant doses and plasma concentrations of ketamine that result in untoward side effects in humans are listed in Table 1.

## II. Pharmacokinetics

### A. Metabolism

Ketamine undergoes extensive metabolism (Fig. 1), initially via nitrogen demethylation to norketamine, a reaction that is catalyzed primarily by the cytochrome P450 liver enzymes CYP2B6 and CYP3A4 (Kharasch and Labroo, 1992; Yanagihara et al., 2001; Hijazi and Boulieu, 2002; Portmann et al., 2010; Mossner et al., 2011; Desta et al., 2012; Rao et al., 2016). The demethylation of ketamine occurs in a stereoselective



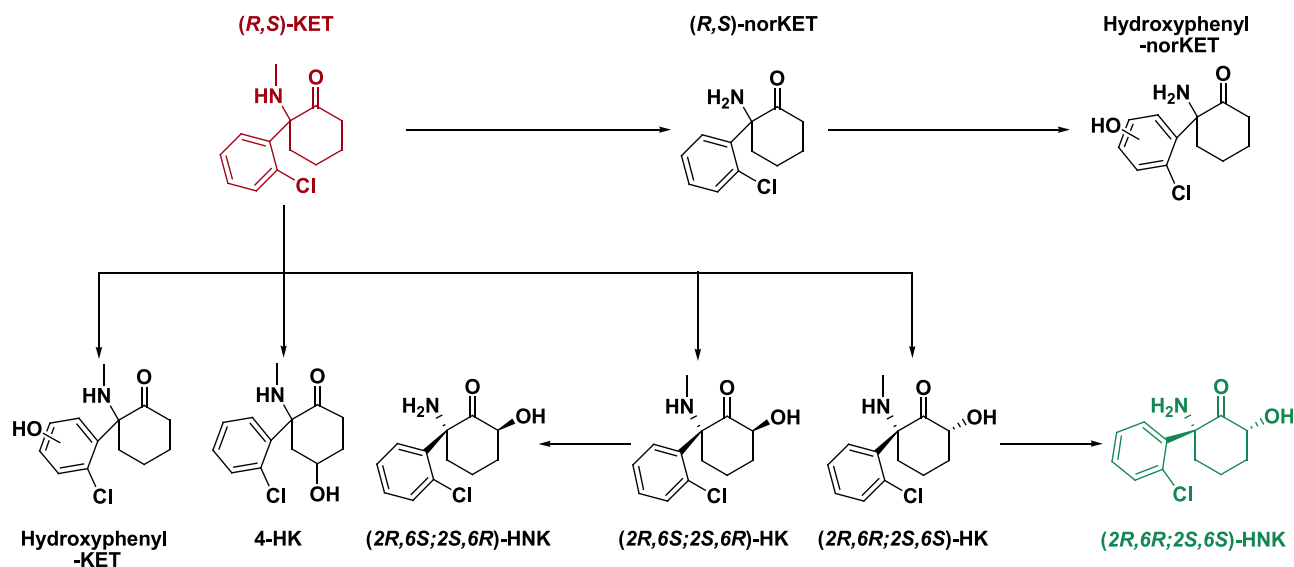
**Fig. 1.** Major metabolic pathways. In the predominant metabolic pathway, racemic ketamine [(*R,S*)-KET] is initially metabolized to norketamine [(*R,S*)-norKET], by either CYP2B6 or CYP3A4. Subsequently, norketamine can be further metabolized to form DHNK or the HNKs. Hydroxylation of norketamine at the six position by CYP2A6 results in (*2R,6S;2S,6S*)-hydroxynorketamine [(*2R,6R;2S,6S*)-HNK]. Alternatively, CYP2B6 or CYP2A6 can hydroxylate norketamine at the four position, resulting in the 4-hydroxy isomers. In the third case, CYP2B6 can hydroxylate norketamine at the five position, resulting in (*2R,5S;2S,5R*)-HNK and (*2R,5R;2S,5S*)-HNK. (*R,S*)-DHNK can result either from direct dehydrogenation from norketamine via CYP2B6 or via dehydration from either diastereomer of the 5-hydroxynorketamines via a nonbiologically catalyzed process.

manner, as CYP3A4 demethylates the (*S*)-ketamine enantiomer more rapidly than the (*R*)-ketamine enantiomer, whereas CYP2B6 demethylates both enantiomers of ketamine with near equal efficiency (Portmann et al., 2010). The individual variability in the metabolism of ketamine (Hijazi and Boulieu, 2002; Cheng et al., 2007; Desta et al., 2012) has been attributed, in part, to differences in the expression of P450 enzymes (Shimada et al., 1994; Hijazi and Boulieu, 2002).

Following demethylation of ketamine to norketamine, norketamine is further metabolized to the hydroxynorketamines (HNKs) and dehydronorketamine (DHNK) (Fig. 1). Early studies noted that the HNKs are formed through the hydroxylation of the cyclohexyl ring of norketamine at various locations (Adams et al., 1981). Several of these HNK metabolites have been detected in humans following ketamine infusion, with (*2R,6R;2S,6S*)-HNK and (*2S,6R;2R,6S*)-HNK being the predominant circulating HNKs in plasma (Moaddel et al., 2010; Zarate et al., 2012a). Metabolism to (*2R,6R;2S,6S*)-HNK is primarily carried out by CYP2A6 and CYP2B6 (Moaddel et al., 2010; Desta et al., 2012). These enzymes are also responsible for the formation of the (*2S,4S;2R,4R*)- and (*2S,5S;2R,5R*)-HNKs. CYP3A4 and CYP3A5 are the principal enzymes identified to catalyze the conversion of norketamine to (*2S,4R;2R,4S*)-HNK, whereas CYP2B6 is predominantly responsible for the catalysis of the conversion of norketamine to (*2S,5R;2R,5S*)-HNK (Desta et al., 2012). The other secondary metabolite is DHNK (Chang and Glazko, 1972; Adams et al., 1981). DHNK is directly formed from norketamine

primarily via the actions of the CYP2B6 enzyme, or from 5-HNK via a nonenzymatic dehydration event (Adams et al., 1981; Bolze and Boulieu, 1998; Turfus et al., 2009; Portmann et al., 2010; Desta et al., 2012).

In addition to the major metabolic pathways of ketamine, there are several other pathways that have also been studied (Fig. 2). One of these pathways is the direct hydroxylation of ketamine to 6-hydroxyketamine (HK) (Woolf and Adams, 1987; Desta et al., 2012). Metabolism of ketamine to (*2R,6R;2S,6S*)-HK is primarily catalyzed by CYP2A6, whereas (*2S,6R;2R,6S*)-HK production is catalyzed by the CYP3A4 and CYP3A5 enzymes (Desta et al., 2012). The formation of (*2R,6R;2S,6S*)-HK is associated with greater hydroxylation of (*S*)-ketamine relative to (*R*)-ketamine, suggesting this reaction is enantioselective (Desta et al., 2012). The (*2R,6R;2S,6S*)-HK metabolite is readily demethylated via CYP2B6 to the corresponding HNK (Desta et al., 2012). However, analogous demethylation from the (*2S,6R;2R,6S*)-HK metabolite is reported to occur very slowly, with a modest contribution from CYP3A5. In addition to 6-HKs, evidence for the production of the 4-HK metabolite has been reported (Adams et al., 1981; Moaddel et al., 2010; Desta et al., 2012; Zarate et al., 2012a). Whereas hydroxylation of the phenyl ring was initially ruled out as being part of the metabolism of ketamine, more recent studies have provided evidence for the formation of such hydroxyphenyl ketamine metabolites via the actions of the CYP2C9 [primarily for the (*R*)-ketamine enantiomer] and flavin-containing mono-oxygenase enzymes [primarily for the (*S*)-ketamine enantiomer; Desta et al., 2012].



**Fig. 2.** Minor metabolic pathways. Although the majority of ketamine is metabolized via the major metabolic pathways (Fig. 1), there are several minor metabolic pathways, which provide unique, albeit low abundance, ketamine metabolites. The aryl ring of ketamine can be directly hydroxylated by flavin-containing mono-oxygenase enzymes or CYP2C9 to provide hydroxyphenyl-ketamine (hydroxyphenyl-KET). 4-Hydroxyketamine has also been observed; however, the metabolic enzymes responsible for this are currently unknown. CYP3A5 can directly hydroxylate ketamine at the six position to provide (2*R*,6*S*;2*S*,6*R*)-HK. Demethylation of (2*R*,6*S*;2*S*,6*R*)-HK with CYP3A5 provides (2*R*,6*S*;2*S*,6*R*)-HNK. CYP2A6 can also directly hydroxylate ketamine to provide (2*R*,6*R*;2*S*,6*S*)-HK, which is then transformed to (2*R*,6*R*;2*S*,6*S*)-HNK. Finally, norketamine can be hydroxylated via an unknown enzyme directly on the aryl ring to provide hydroxyphenyl-norketamine (hydroxyphenyl-norKET).

Lastly, phenolic isomers of HNKs have also been observed, potentially resulting from the hydroxylation of norketamine (Turfus et al., 2009).

A population pharmacokinetic model was constructed for ketamine and its metabolites in patients suffering from treatment-resistant bipolar depression in a study that identified norketamine, DHNK, and (2*R*,6*R*;2*S*,6*S*)-HNK as the major circulating metabolites in plasma following a single 40-minute i.v. infusion of ketamine (0.5 mg/kg) (Zhao et al., 2012). These were also the major metabolites identified in plasma of patients suffering from unipolar or bipolar depression (Zarate et al., 2012a) or CRPS (Moaddel et al., 2010) and treated with ketamine. Specifically, norketamine, DHNK, and (2*R*,6*R*;2*S*,6*S*)-HNK were detected in the plasma of patients suffering from treatment-resistant unipolar and bipolar depression as early as 40 minutes after the end of i.v. ketamine administration (0.5 mg/kg delivered during a single 40-minute infusion; Zarate et al., 2012a; Zhao et al., 2012). The average time for metabolites to reach peak plasma concentration was estimated to be approximately 1.33 hours for both (*R*)- and (*S*)-norketamine and 3.83 hours for (*R*)-DHNK, (*S*)-DHNK, and (2*R*,6*R*;2*S*,6*S*)-HNK (Zhao et al., 2012). In plasma samples from these patients, the ratios of (*S*)- to (*R*)-ketamine, (*S*)- to (*R*)-norketamine, and (*S*)- to (*R*)-DHNK were 0.84, 1.0, and 0.67, respectively, during a 40- to 230-minute postinfusion period (Zhao et al., 2012). Similar to these findings, i.v. administration of ketamine (2 mg/kg) in surgical patients resulted in a plasma ratio of (*S*)- to (*R*)-ketamine of 0.91 (Geisslinger et al., 1993). Additionally, CRPS patients receiving continuous i.v. ketamine infusion

at a dose of 40 mg/h over a total period of 5 days had plasma ratios of (*S*)- to (*R*)-ketamine, (*S*)- to (*R*)-norketamine, and (*S*)- to (*R*)-DHNK of 0.77, 0.71, and 0.71, respectively (Moaddel et al., 2010).

Following a 40-minute i.v. ketamine infusion at 0.5 mg/kg in patients diagnosed with treatment-resistant major depressive disorder, peak plasma concentrations were  $204.13 \pm 101.46$  ng/ml or  $0.86 \pm 0.43$   $\mu$ M for ketamine (at 40 minutes),  $73.54 \pm 31.86$  ng/ml or  $0.33 \pm 0.14$   $\mu$ M for norketamine (at 80 minutes),  $13.27 \pm 6.92$  ng/ml or  $0.06 \pm 0.03$   $\mu$ M for DHNK (at 110 minutes), and  $23.19 \pm 11.88$  ng/ml or  $0.097 \pm 0.05$   $\mu$ M for (2*R*,6*R*;2*S*,6*S*)-HNK (at 230 minutes) (Zarate et al., 2012a); see Table 2. In patients with treatment-resistant bipolar depression, peak plasma concentrations were  $177.23 \pm 53.8$  ng/ml or  $0.75 \pm 0.23$   $\mu$ M for ketamine (at 40 minutes),  $69.96 \pm 19.98$  ng/ml or  $0.31 \pm 0.09$   $\mu$ M for norketamine (at 80 minutes),  $50.5 \pm 27.44$  ng/ml or  $0.23 \pm 0.12$   $\mu$ M for DHNK (at 110 minutes), and  $37.59 \pm 14.23$  or  $0.16 \pm 0.06$   $\mu$ M for (2*R*,6*R*;2*S*,6*S*)-HNK (Zarate et al., 2012a; Table 2). In a patient with CRPS receiving chronic ketamine treatment (infusion beginning at 10 mg/h, titrated to 40 mg/h, and lasting 5 consecutive days), significant plasma levels of several HNK metabolites were detected, with (2*R*,6*R*;2*S*,6*S*)- and (2*R*,6*R*;2*S*,6*S*)-HNKs being the major metabolites present in samples obtained on day 3 (Moaddel et al., 2010).

In a study conducted by Cohen et al. (1973), brain concentrations of ketamine metabolites were measured following tail vein administration of ketamine (20 mg/kg) in rats. These authors showed that both ketamine and norketamine rapidly accumulated in the brain with peak

concentrations achieved within 1 minute of administration (Cohen et al., 1973). Subsequently, it was demonstrated that (2*R*,6*R*;2*S*,6*S*)-HNK also accumulates in brain tissue shortly after dosing (Leung and Baillie, 1986; Paul et al., 2014; Moaddel et al., 2015b). Intravenous tail vein injection (2-minute infusion) of 20 mg/kg (*S*)- or (*R*)-ketamine to rats resulted in higher brain levels of (2*S*,6*S*)-HNK relative to (2*R*,6*R*)-HNK, respectively, with maximal concentrations of  $769 \pm 133$  ng/g or  $3.21 \pm 0.55$   $\mu$ mol/kg at 20 minutes for (2*S*,6*S*)-HNK and  $274 \pm 47$  ng/g or  $1.14 \pm 0.20$   $\mu$ mol/kg at 10 minutes for (2*R*,6*R*)-HNK (Moaddel et al., 2015b; Table 2). It was hypothesized that the difference was due to a passive uptake process of these metabolites into the brain (Moaddel et al., 2015b). A ~1:1 ratio for the plasma:brain levels of the corresponding (2*R*,6*R*;2*S*,6*S*)-HNK was observed, indicating that blood-brain barrier penetration or the central nervous system transport process was not mediated by an enantioselective process (Leung and Baillie, 1986; Moaddel et al., 2015b). Importantly, no in situ metabolism was observed when ketamine was incubated with rat brain microsomes (S9 fraction) (Moaddel et al., 2015b). Likewise, ketamine metabolites were below detectable levels in the brain of mice following in vivo intracerebroventricular administration of ketamine (P.Z., R.M., J.N.H., T.D.G., unpublished data), a finding that suggests that local ketamine metabolism does not occur in the brain.

In mice, norketamine, DHNK, and (2*R*,6*R*;2*S*,6*S*)-HNK metabolites were detected in plasma within 10 minutes of i.p. administration of 10 mg/kg ketamine (Can et al., 2016; Zanos et al., 2016). The maximum plasma concentrations were  $561.89 \pm 86.09$  ng/ml or  $2.36 \pm 0.18$   $\mu$ M at 10 minutes for ketamine,  $1098.89 \pm 216.89$  ng/ml or  $4.91 \pm 0.97$   $\mu$ M at 10 minutes for norketamine,  $83.92 \pm 53.63$  ng/ml or  $0.38 \pm 0.24$   $\mu$ M at 30 minutes for DHNK, and  $674.59 \pm 278.23$  ng/ml or  $2.81 \pm 1.16$   $\mu$ M at 10 minutes for (2*R*,6*R*;2*S*,6*S*)-HNK (Zanos et al., 2016), as summarized in Table 2. In the brain, ketamine ( $1162.34 \pm 202.05$  ng/g or  $4.89 \pm 0.85$   $\mu$ mol/kg tissue), norketamine ( $450.94 \pm 199.7$  ng/g or  $2.02 \pm 0.89$   $\mu$ mol/kg tissue), and (2*R*,6*R*;2*S*,6*S*)-HNK ( $498.35 \pm 50.99$  ng/g or  $2.08 \pm 0.21$   $\mu$ mol/kg tissue) were detected within 10 minutes of ketamine administration (Zanos et al., 2016). The maximum brain concentration of ketamine was 51.66% higher than the corresponding plasma concentration, whereas the brain tissue concentrations of norketamine and (2*R*,6*R*;2*S*,6*S*)-HNK were 58.96% and 26.13% lower than the corresponding maximum plasma concentrations, respectively (Zanos et al., 2016). Levels of DHNK in brain tissue were below the limits of quantification, consistent with the findings that DHNK partitions into red blood cells (Moaddel et al., 2016) and has poor penetration of the blood-brain barrier (Can et al., 2016).

### B. Absorption

Ketamine is administered to humans via multiple routes, including i.v., i.m., oral, intranasal, epidural,

and intrarectal (Malinovsky et al., 1996; Andrade, 2017b). The most typical route of administration is via i.v. infusion, which rapidly attains maximum plasma concentrations (e.g., Clements et al., 1982; Weber et al., 2004). Intramuscular administration, which is used in emergency cases of uncooperative patients, neonates, and children, has high bioavailability of 93%, with peak plasma concentrations achieved within 5–30 minutes of administration (e.g., Clements et al., 1982); however, a population pharmacokinetic analysis reported a much lower bioavailability following i.m. administration of ketamine in children (41%; Hornik et al., 2013). In contrast, oral bioavailability of ketamine is limited to 16%–29%, with peak concentration levels of the drug occurring within 20–120 minutes (Grant et al., 1981; Clements et al., 1982; Sekerci et al., 1996; Chong et al., 2009; Rolan et al., 2014; Karch and Drummer, 2015), due to extensive first-pass hepatic metabolism (e.g., Kharasch and Labroo, 1992; Yanagihara et al., 2003). Oral bioavailability of (*S*)-ketamine was calculated to be 8%–11% (Peltoniemi et al., 2012; Fanta et al., 2015), consistent with the greater first-pass metabolism of (*S*)-ketamine relative to (*R,S*)-ketamine. Intranasal and intrarectal ketamine bioavailability is 45%–50% and 25%–30%, respectively (Malinovsky et al., 1996; Yanagihara et al., 2003). Intranasal administration is considered an attractive alternative to the i.v. administration of ketamine because it is less invasive, results in rapid systemic absorption, and is not subject to first-pass hepatic metabolism (Malinovsky et al., 1996).

Following oral administration of (2*S*,6*S*)-HNK in rats (20 mg/kg), maximum plasma concentrations were reached at  $0.4 \pm 0.1$  hour. Oral bioavailability of (2*S*,6*S*)-HNK was estimated to be 46.3% in rats (Moaddel et al., 2015b). In mice, the oral bioavailability of (2*R*,6*R*)-HNK is estimated to be approximately 50% at the dose of 50 mg/kg (P.Z., R.M., J.N.H., T.D.G., unpublished data). The oral bioavailability of other ketamine metabolites remains to be determined.

### C. Distribution

Ketamine is rapidly distributed into highly perfused tissues, including the brain, and has a plasma protein binding between 10% and 50% (Wieber et al., 1975; Dayton et al., 1983; Sinner and Graf, 2008; Peltoniemi et al., 2012, 2016; Karch and Drummer, 2015), resulting in a large steady-state volume of distribution ( $V_d = 3\text{--}5$  l/kg; Karch and Drummer, 2015). A single i.v. bolus administration of an anesthetic dose of racemic ketamine in humans (2 mg/kg) leads to equal plasma concentrations of (*S*)-ketamine and (*R*)-ketamine 1 minute postadministration ( $C_{\max} = \sim 1800$  ng/ml or 7.6  $\mu$ M—estimated from Geisslinger et al., 1993). However, i.v. (bolus) administration of 1 mg/kg (*S*)-ketamine resulted in a higher plasma concentration of the drug 1 minute post-infusion ( $C_{\max} = \sim 2600$  ng/ml: 11  $\mu$ M—estimated from Geisslinger et al., 1993). These results are particularly

TABLE 2  
Pharmacokinetic comparison for (2R,6R) and (2S,6S)-HNK in humans and rodents

Species	Drug	Administration Paradigm	Tissue	$C_{max}$ (R,S)-KET (plasma: $\mu\text{M}$ ; brain: $\mu\text{mol/kg}$ )	$C_{max}$ (R,S)-KET (plasma: ng/ml; brain: ng/g)	$AUC_{0-\infty}$ (R,S)-KET (plasma: h $\cdot\mu\text{M}$ ; brain h: $\mu\text{mol/kg}$ )	$AUC_{0-\infty}$ (R,S)-KET (plasma: h $\cdot\text{ng/ml}$ ; brain h: $\text{ng/g}$ )	$C_{max}$ (2R,6R,2S,6S)-HNK (plasma: $\mu\text{M}$ ; brain: $\mu\text{mol/kg}$ )	$C_{max}$ (2R,6R,2S,6S)-HNK (plasma: ng/ml; brain: ng/g)	$AUC_{0-\infty}$ (2R,6R,2S,6S)-HNK (plasma: h $\cdot\mu\text{M}$ ; brain: h $\cdot\text{ng/g}$ )	References	
Humans	(R,S)-KET	0.5 mg/kg, 40-min i.v. infusion	Plasma	$0.75 \pm 0.23$ (BD)	$177.23 \pm 53.8$ (BD)	$4.10$ (BD)	$975.4$ (BD)	$0.16 \pm 0.06$ (BD)	$37.59 \pm 14.23$ (BD)	$1366$ (BD)	Zarate et al. (2012a), Unpublished data	
	(R,S)-KET	40 mg/kg, i.v. infusion	Plasma	$0.86 \pm 0.43$ (MDD)	$204.13 \pm 101.46$ (MDD)	$3.67$ (MDD)	$873.5$ (MDD)	$0.097 \pm 0.05$ (MDD)	$23.19 \pm 11.88$ (MDD)	$1038$ (MDD)	Unpublished data	
Rats	(R,S)-KET	40 mg/kg, i.v. infusion	Plasma	$34.52 \pm 2.93$	$8206 \pm 697$	$48.01 \pm 21.30$	$11,410 \pm 5064$	$18.59 \pm 2.81$	$4455 \pm 673$	$33,843 \pm 4432$	Moaddel et al. (2015b), Unpublished data	
	(R,S)-norKET	40 mg/kg, i.p. infusion	Brain	$137 \pm 6$	$32,600 \pm 1400$	N/A	N/A	$30 \pm 5$	$7200 \pm 1200$	N/A	Paul et al. (2014)	
	(R)-KET	20 mg/kg, i.v. infusion	Plasma	$14.4 \pm 1.68^a$	$3430 \pm 400^a$	N/A	N/A	$1.44 \pm 0.48^b$	$345 \pm 115^b$	N/A	Moaddel et al. (2015b)	
	(S)-KET	20 mg/kg, i.v. infusion	Brain	$68.84 \pm 8.12^a$	$16,365 \pm 1931^a$	N/A	N/A	$1.14 \pm 0.20^b$	$274 \pm 47^b$	N/A	Moaddel et al. (2015b)	
	(R,S)-norKET	20 mg/kg, i.v. infusion	Plasma	$11.49 \pm 2.25^c$	$2732 \pm 535^c$	N/A	N/A	$5.52 \pm 0.28^d$	$1323 \pm 67^d$	N/A	Paul et al. (2014)	
Mice	(R,S)-norKET	20 mg/kg, i.v. infusion	Brain	$65.25 \pm 1.91^c$	$15,512 \pm 453^c$	N/A	N/A	$3.21 \pm 0.55^d$	$769 \pm 133^d$	N/A	Paul et al. (2014)	
	(2S,6S)-HNK	20 mg/kg, i.v. infusion	Brain	N/A	N/A	N/A	N/A	$16 \pm 3^b$	N/A	N/A	Paul et al. (2014)	
	(R,S)-KET	20 mg/kg, i.v. infusion	Plasma	N/A	N/A	N/A	N/A	$127 \pm 4^d$	N/A	N/A	Paul et al. (2014)	
	(R,S)-KET	20 mg/kg, i.v. infusion	Brain	N/A	N/A	N/A	N/A	$49.89 \pm 1.52^d$	$11,958 \pm 364^d$	$120.91 \pm 25.71^d$	Moaddel et al. (2015b)	
	(R,S)-KET	20 mg/kg, oral	Plasma	N/A	N/A	N/A	N/A	$127.09 \pm 3.51^d$	$30,463 \pm 841^d$	N/A	Moaddel et al. (2015b)	
	(R,S)-KET	20 mg/kg, oral	Brain	N/A	N/A	N/A	N/A	$19.66 \pm 5.05$	$4713 \pm 1211$	$42.22 \pm 5.48$	N/A	Moaddel et al. (2015b)
	(R,S)-KET	10 mg/kg, i.p. injection	Brain	$2.36 \pm 0.36$	$561.89 \pm 86.09$	$0.75$	$177.9$	N/A	$674.59 \pm 278.23$	N/A	Zanos et al. (2016)	
	(R)-KET	10 mg/kg, i.p. injection	Brain	$4.89 \pm 0.85$	$1162.34 \pm 202.05$	$2.07$	$492.2$	$2.81 \pm 1.16$	$498.35 \pm 50.99$	$2.01$	Zanos et al. (2016)	
	(S)-KET	10 mg/kg, i.p. injection	Plasma	$1.40 \pm 0.18^a$	$332.8 \pm 42.99^a$	$0.44^a$	$104.8^a$	$2.08 \pm 0.21$	$678.3 \pm 74.54^b$	$2.49$	Unpublished data	
	(S)-KET	10 mg/kg, i.p. injection	Brain	$7.93 \pm 1.93^a$	$1886 \pm 459.6^a$	$2.48^a$	$591.9^a$	$2.83 \pm 0.31^b$	$590.9 \pm 74.10^b$	$1.85^b$	Unpublished data	
(2S,6S)-HNK	10 mg/kg, i.p. injection	Plasma	$4.32 \pm 1.12$	$1028 \pm 266.7^c$	$1.23^c$	$293.1^c$	$2.47 \pm 0.31^b$	$711.5 \pm 209.4^d$	$2.58^b$	Unpublished data		
(2R,6R)-HNK	10 mg/kg, i.p. injection	Brain	$7.33 \pm 2.36^e$	$1743 \pm 560.6^e$	$2.03^e$	$483.1^e$	$2.21 \pm 0.46^d$	$530.7 \pm 111.2^d$	$4.15^d$	Unpublished data		
			Plasma	N/A	N/A	N/A	N/A	$17.57 \pm 8.72^d$	$4211 \pm 2089^d$	$10.16^d$	Zanos et al. (2016)	
			Brain	N/A	N/A	N/A	N/A	$15.70 \pm 8.98^d$	$3764 \pm 2152^d$	$6.55^d$	Unpublished data	
			Plasma	N/A	N/A	N/A	N/A	$10.79 \pm 4.76^b$	$2587 \pm 1141^b$	$2.43^b$	Unpublished data	
			Brain	N/A	N/A	N/A	N/A	$10.66 \pm 5.85^b$	$2556 \pm 1402^b$	$2.19^b$	Unpublished data	

BD, bipolar disorder; MDD, major depressive disorder.

<sup>a</sup>Reported values represent (R)-KET levels.

<sup>b</sup>Reported values represent (2R,6R)-HNK levels.

<sup>c</sup>Reported values represent (S)-KET levels.

<sup>d</sup>Reported values represent (2S,6S)-HNK levels.

important when comparing the outcomes of (*S*)-ketamine with those of the racemic ketamine or (*R*)-ketamine, because lower doses of (*S*)-ketamine are required to produce similar or greater ketamine concentrations in the plasma (e.g., White et al., 1985; Mathisen et al., 1995). Notably, there is no interconversion between (*S*)- and (*R*)-ketamine, because administration of (*S*)-ketamine does not result in the formation of (*R*)-ketamine in vivo, and vice versa (Geisslinger et al., 1993; Ihmsen et al., 2001). Plasma of patients suffering from treatment-resistant bipolar depression, who were treated with a 40-minute i.v. infusion of 0.5 mg/kg (*R,S*)-ketamine, had a ratio of (*S*)- to (*R*)-ketamine of 0.84 (Zhao et al., 2012), with peak ketamine concentrations of  $177.23 \pm 53.8$  ng/ml or  $0.75 \pm 0.23$   $\mu$ M (Zarate et al., 2012a).

In mice, administration of subanesthetic doses of either (*S*)- or (*R*)-ketamine (10 mg/kg, i.p.) resulted in similar brain levels of both drugs [area under the curve (AUC)<sub>last</sub> = 483.1 hours.ng/ml or 2.03 hours. $\mu$ mol/kg versus 591.9 hours.ng/ml or 2.48 hours. $\mu$ mol/kg, respectively], with peak levels being  $C_{max} = 1743 \pm 560.6$  ng/g or  $7.33 \pm 2.36$   $\mu$ mol/kg for (*S*)-ketamine and  $1886 \pm 459.6$  ng/ml or  $7.93 \pm 1.93$  for (*R*)-ketamine at 10 minutes postinjection (Zanos et al., 2016). Similarly, there were no differences in (*S*)-ketamine ( $C_{max} = 2732 \pm 535$  ng/ml or  $11.49 \pm 2.25$   $\mu$ M) and (*R*)-ketamine ( $C_{max} = 3430 \pm 400$  ng/ml or  $14.4 \pm 1.68$   $\mu$ M) levels in the plasma of rats 10 minutes following an i.v. administration of 20 mg/kg of each of these enantiomers (Moaddel et al., 2015b).

Direct i.p. administration of (*2R,6R*)-HMK and (*2S,6S*)-HMK in mice results in a 1:1 ratio between circulating plasma and brain tissue concentrations (Table 2), with higher total levels (AUC<sub>last</sub>) of (*2S,6S*)-HMK observed in plasma and brain tissue compared with (*2R,6R*)-HMK (brain: 7.55 versus 3.05 h. $\mu$ mol/kg; plasma: 11.60 versus 3.22 h. $\mu$ M; Zanos et al., 2016; Table 2). Following i.v. administration of (*2S,6S*)-HMK in rats (20 mg/kg), total drug exposure was calculated as AUC<sub>last</sub> =  $28,981 \pm 6162$  h.ng/ml or  $120.91 \pm 25.71$  h. $\mu$ M, with a volume of distribution  $V_d = 7.35 \pm 0.74$  l/kg (Moaddel et al., 2015b). Following oral administration of (*2S,6S*)-HMK to rats (20 mg/kg), total drug exposure was AUC<sub>last</sub> =  $10,120 \pm 1313$  h.ng/ml or  $42.22 \pm 5.48$  h. $\mu$ M (Moaddel et al., 2015b).

#### D. Elimination

Although plasma levels of ketamine are below detectable limits within 1 day following an i.v. antidepressant dose of ketamine (0.5 mg/kg administered over a 40-minute infusion), circulating levels of DHNK and (*2R,6R;2S,6S*)-HMK were observed for up to 3 days after ketamine infusion in patients diagnosed with bipolar depression (Zhao et al., 2012) or treatment-resistant major depression (Zarate et al., 2012a). Norketamine and ketamine were detectable for up to 14 and 11 days, respectively, in the urine of children who received

anesthetic doses of ketamine, with reported concentrations of 0.1–1442 ng/ml (or 0.0004–0.031  $\mu$ M) for norketamine and 2–1204 ng/ml (or 0.008–5.06  $\mu$ M) for ketamine (Adamowicz and Kala, 2005).

In adult humans, ketamine has a high rate of clearance and a short elimination half-life (2–4 hours; Clements et al., 1982; White et al., 1985; Domino, 2010). White et al. (1985) also demonstrated a short elimination half-life (155–158 minutes) for both (*S*)-ketamine and (*R*)-ketamine. Elimination of ketamine is primarily performed by the kidneys, with low levels excreted as ketamine (2%), norketamine (2%), and DHNK (16%) (Haas and Harper, 1992; Lin and Lua, 2004; Adamowicz and Kala, 2005; Karch and Drummer, 2015; Dinis-Oliveira, 2017). The majority of the drug (~80%) is excreted as the glucuronic acid-labile conjugates of HK and HNK (Dinis-Oliveira, 2017), which are eliminated in urine and bile (Chang and Glazko, 1974).

In adult humans, terminal plasma half-life and the clearance rates of ketamine do not significantly differ between i.v. (half-life = 186 minutes; total body clearance = 19.1 ml/min per kilogram) and intramuscular (half-life = 155 minute; total body clearance = 23.2 ml/min per kilogram) routes of administration (Clements et al., 1982). However, there is evidence that repeated administration of ketamine prolongs its elimination time. For example, Adamowicz and Kala (2005) reported that, among three instances of single i.v. infusions of ketamine during a 2-year period (doses ranged from 0.75 to 1.59 mg/kg), the elimination of ketamine was slowed from 2 days following the first infusion to 5 days after the second, and 11 days following the third. Elimination of norketamine remained constant (i.e., 5 days after each infusion; Adamowicz and Kala, 2005).

When compared with adults, ketamine is eliminated approximately twice as fast in children (Haas and Harper, 1992). This is in accordance with evidence supporting a longer duration of anesthesia in adults relative to children following i.m. administration of 6 mg/kg ketamine (Grant et al., 1981, 1983; Akin et al., 2005). Moreover, a negative correlation between age and ketamine dose per body weight required for anesthesia was reported in children (Lockhart and Nelson, 1974). These differences might be due to differences in the enzymatic metabolism of ketamine in children, as compared with adults (Edginton et al., 2006).

In humans, (*S*)-ketamine has a slightly longer elimination half-life than racemic ketamine [~5 hours for (*S*)-ketamine versus 2–4 hours for racemic ketamine; Hagelberg et al., 2010; Peltoniemi et al., 2012], and its systemic clearance is faster when administered alone than when administered in the racemic mixture [ $26.3 \pm 3.5$  ml/kg per minute for (*S*)-ketamine versus  $14.8 \pm 1.7$  ml/kg per minute when administered as the racemic ketamine; Ihmsen et al., 2001]. This may suggest an inhibition of (*S*)-ketamine's clearance by the (*R*)-ketamine enantiomer when the racemic mixture is administered

(Kharasch and Labroo, 1992). Such inhibition could contribute to the prolonged awakening time in patients receiving racemic ketamine relative to those receiving (*S*)-ketamine (White et al., 1985). We note that systemic clearance of (*R*)-ketamine following racemic ketamine administration is  $13.8 \pm 1.3$  ml/kg per minute, which is similar to the (*S*)-ketamine enantiomer ( $14.8 \pm 1.7$  ml/kg per minute; Ihmsen et al., 2001).

Following i.v. administration of (*2S,6S*)-HNK in rats (20 mg/kg), the clearance rate was calculated to be  $704 \pm 139$  ml/kg per hour, with an elimination half-life of  $8.0 \pm 4.0$  hours. Oral administration of this metabolite resulted in an elimination half-life of  $3.8 \pm 0.6$  hours (Moaddel et al., 2015b).

Overall, it is important to note that there are important species differences in regard to half-life values, AUCs,  $C_{\max}$ , and clearance rates of ketamine and its metabolites (see Table 2; also see Zarate et al., 2012a; Zanos et al., 2017c). This should be taken into consideration when comparing the behavioral actions of specific dose regimens for ketamine and its metabolites in mice, rats, and humans. Nevertheless, the brain levels of ketamine and its metabolites following administration of ketamine in humans are not known, and, therefore, direct comparisons are not straightforward.

### III. Pharmacodynamics of Ketamine and Its Metabolites

As aforementioned, ketamine is a NMDAR antagonist, and ketamine's well-characterized analgesic and anesthetic effects are primarily attributed to NMDAR inhibition (Franks and Lieb, 1994). However, ketamine's pharmacological targets are not limited to NMDARs. It has been reported that ketamine interacts with several other receptors and ion channels, including dopamine, serotonin, sigma, opioid, and cholinergic receptors, as well as hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. Ketamine typically has a lower affinity (higher inhibitory constant— $K_i$ —values) for these receptors and channels compared with NMDARs, and independent laboratories have not validated many of the reported findings.

Early pharmacodynamic studies of (*R,S*)-ketamine were conducted in rats and examined the anesthetic effects of the parent compound and its two principal metabolites, (*R,S*)-norketamine and (*2R,6R;2S,6S*)-HNK (Leung and Baillie, 1986). The results demonstrated that a 40 mg/kg i.v. bolus administration of (*R,S*)-ketamine and (*R,S*)-norketamine produced anesthetic actions and increased spontaneous locomotor activity during the post-anesthetic recovery phase, whereas (*2R,6R;2S,6S*)-HNK (same dose) had no anesthetic or hyperlocomotor effects. As a result, (*2R,6R;2S,6S*)-HNK was described as an inactive metabolite, and the majority of the pharmacodynamic assessments were carried out with only (*R,S*)-ketamine and (*R,S*)-norketamine. However, it has been

recently demonstrated that ketamine's HNK metabolites are biologically active (Moaddel et al., 2013; Singh et al., 2013, 2015, 2016c; Paul et al., 2014; Zanos et al., 2016; Cavalleri et al., 2017; Yao et al., 2017; Wray et al., 2018). The (*2S,6S*)- and (*2R,6R*)-HNK metabolites have been shown to exert antidepressant-relevant behavioral responses in rodents (Zanos et al., 2016; Pham et al., 2017a, but see Shirayama and Hashimoto, 2018, as well as Yang et al., 2017). Consistent with the more potent antidepressant actions of (*R*)-ketamine compared with the (*S*)-ketamine enantiomer, (*2R,6R*)-HNK was shown to be a more potent antidepressant than (*2S,6S*)-HNK in several animal tests (Zanos et al., 2016).

#### A. N-Methyl-D-Aspartate Receptors

Historically, the primary recognized receptor target of ketamine is the NMDAR, in which ketamine acts as a noncompetitive open-channel blocker (Lodge et al., 1982; Anis et al., 1983; MacDonald et al., 1987). NMDARs are glutamatergic ion channels made of different combinations of four subunits encoded by one of seven genes: *GluN1*, *GluN2A–D*, and *GluN3A–B* (Vyklicky et al., 2014). NMDARs are highly permeable to calcium ions, which can trigger the activation of a number of intracellular pathways in neurons and glial cells. At resting state, NMDAR channels are tonically blocked by magnesium ( $Mg^{2+}$ ). Efficient receptor activation requires the following: 1) membrane depolarization, which displaces the  $Mg^{2+}$  block, and 2) binding of both glutamate and the coactivator glycine and/or D-serine (Paoletti et al., 2013).

Ketamine was initially characterized as a NMDAR antagonist by David Lodge and colleagues (Lodge et al., 1982; Anis et al., 1983), a finding that was subsequently confirmed by other investigators (Harrison and Simmonds, 1985; Thomson et al., 1985). Ketamine binds to the allosteric phencyclidine (PCP) site that is located within the channel pore of the NMDAR, and thus it blocks the receptor noncompetitively (Kohrs and Durieux, 1998; Mion and Villeveille, 2013). Ketamine has a relatively high (~86%) trapping capability (binding within the ion channel pore following closure of the channel) to block NMDARs, via binding to the same site as PCP (>98% trapping) and MK-801 (100% trapping; Huettner and Bean, 1988; Lerma et al., 1991; MacDonald et al., 1991; Jahr, 1992; Orser et al., 1997). The binding affinity of ketamine to the PCP binding site has been reported to be between 0.18 and 3.1  $\mu$ M in the presence of  $Mg^{2+}$  (Table 3; Wong et al., 1986, 1988; MacDonald et al., 1987; Kornhuber et al., 1989; Reynolds and Miller, 1989; Sharif et al., 1991; Bresink et al., 1995; Lynch et al., 1995; Parsons et al., 1995; Kapur and Seeman, 2001, 2002; Sun and Wessinger, 2004; Seeman et al., 2005; Gilling et al., 2009; Moaddel et al., 2013; Bonifazi et al., 2015; Wallach et al., 2016; Kang et al., 2017; Morris et al., 2017).

NMDAR blockade is thought to underlie the dissociative anesthetic and amnesic effects of ketamine, as well



TABLE 3  
Molecular targets of ketamine and its metabolites

Values represent mean  $\pm$  S.E., unless otherwise indicated.

Receptor/Target	Drug	Action	Proposed Clinical Relevance	Affinity/Potency ( $\mu$ M)	Method	Tissue/System	Species	Reference
NMDAR	(R,S)-KET	Antagonist	Anesthesia, antidepressant effects, amnesia, dissociative effects, abuse potential, cognitive impairment	$K_i = 0.49 \pm 0.05$	RBA— $^3$ HMK-801 binding	Cerebral cortex	Rat	Wong et al. (1986)
				$K_i = 1.09$	RBA— $^3$ HMK-801 binding	Brain	Rat	Wong et al. (1988)
				$K_i = 1.09$	RBA— $^3$ HMK-801 binding	Brain	Rat	Wong et al. (1988)
				$K_i = 1.93$	RBA— $^3$ HITCP binding	Brain	Rat	Wong et al. (1988)
				$K_i = 0.42 \pm 0.03$	RBA— $^3$ HMK-801 binding	Cortex	Human	Kornhuber et al. (1989)
				$K_i = 0.18 \pm 0.03$	RBA— $^3$ HMK-801 binding (no added glutamate or glycine)	Brain	Rat	Reynolds and Miller (1989)
				$K_i = 0.24 \pm 0.10$	RBA— $^3$ HMK-801 binding (added 100 $\mu$ M glutamate and 30 $\mu$ M glycine)	Brain	Rat	Reynolds and Miller (1989)
				$K_i = 0.58 \pm 0.07$	RBA— $^3$ HMK-801 binding	Brain	Mouse	Sharif et al. (1991)
				$K_i = 0.76 \pm 0.047$	RBA— $^3$ HMK-801 binding	Brain	Guinea pig	Sharif et al. (1991)
				$K_i = 0.48 \pm 0.1$	RBA— $^3$ HMK-801 binding	Brain	Dog	Sharif et al. (1991)
				$K_i = 0.71 \pm 0.06$	RBA— $^3$ HMK-801 binding	Cortex	Dog	Sharif et al. (1991)
				$K_i = 0.6 \pm 0.04$	RBA— $^3$ HMK-801 binding	Spinal cord	Rat	Sharif et al. (1991)
				$K_i > 10$	RBA— $^3$ HITCP binding	Rat glioma hybrid cells	Rat	Georg and Friedl (1991)
				$K_i = 1.19 \pm 0.24$	RBA— $^3$ HMK-801 binding	Cortex	Rat	Bresink et al. (1995)
				$K_i = 0.20 \pm 0.02$	RBA— $^3$ HMK-801 binding	Brain (synaptic membranes)	Rat	Parsons et al. (1995)
				$K_i = 1.0 \pm 0.5$	RBA— $^{125}$ I]MK-801 binding	Membranes from HEK293 cells transfected with GluN1/2A receptors	Rat	Lynch et al. (1995)
				$K_i = 2.5 \pm 1.2$	RBA— $^{125}$ I]MK-801 binding	Membranes from HEK293 cells transfected with GluN1/2B receptors	Rat	Lynch et al. (1995)
				$K_i = 2.51 \pm 1.90$	Autoradiographic binding — $^3$ HMK-801	Cerebellum	Rat	Bresink et al. (1995)
				$K_i = 0.5 \pm 0.15$	RBA— $^3$ HMK-801 binding	Striatum	Rat	Kapur and Seeman (2001, 2002)
				$K_i = 0.92$	RBA— $^3$ HMK-801 binding	Brain membranes	Rat	Sun and Wessinger (2004)
				$K_i = 3.1 \pm 0.3$	RBA— $^3$ HMK-801 binding	Striatum	Rat	Seeman et al. (2005)
				$K_i = 1.35 \pm 0.43$	RBA— $^3$ HMK-801 binding	Cortex	Rat	Gilling et al. (2009)
				$K_i = 0.67 \pm 0.15$	RBA— $^3$ HMK-801 binding	Cortex	Human	Gilling et al. (2009)
$K_i = 1.47 \pm 0.68$	Whole-cell patch-clamp recordings —holding potential at -70 mV	HEK293 cells transfected with GluN1/2A receptors	Human	Gilling et al. (2009)				
$K_i = 0.32 \pm 0.02$	RBA— $^3$ HMK-801 binding	Whole brain (excluding cerebellum)	Rat	Wallach et al. (2016), Kang et al. (2017)				
$K_i = 0.25$	RBA— $^3$ HMK-801 binding	Rat brain (minus cerebellum)	Rat	Morris et al. (2017)				
$IC_{50} = 3.91$	RBA— $^3$ HITCP binding	Rat brain (minus cerebellum) synaptoneuroosomal fractions	Rat	Allaoua and Chichportiche (1989)				
$IC_{50} = 5.4 \pm 0.6$	Autoradiographic binding— $^3$ HMK-801	Frontal cortex	Rat	Porter and Greenamyre (1995)				
$IC_{50} = 5.0 \pm 0.6$	Autoradiographic binding— $^3$ HMK-801	Striatum	Rat	Porter and Greenamyre (1995)				
$IC_{50} = 3.9 \pm 0.5$	Autoradiographic binding— $^3$ HMK-801	Entorhinal cortex	Rat	Porter and Greenamyre (1995)				
$IC_{50} = 6.7 \pm 0.8$	Autoradiographic binding— $^3$ HMK-801	Hippocampus (CA1)	Rat	Porter and Greenamyre (1995)				
$IC_{50} = 5.4 \pm 0.6$	Autoradiographic binding— $^3$ HMK-801	Dentate gyrus	Rat	Porter and Greenamyre (1995)				
$IC_{50} = 8.2 \pm 0.6$	Autoradiographic binding— $^3$ HMK-801	Cerebellar granule cell layer	Rat	Porter and Greenamyre (1995)				
$IC_{50} = 1.6 \pm 0.01$	Whole-cell patch-clamp recordings	Cultured superior collicular neurons	Rat	Parsons et al. (1995)				
$IC_{50} > 10$ ; 100 $\mu$ M induced a 65% inhibition of extracellular postsynaptic currents	NMDA (10 $\mu$ M)-evoked currents	Ventral tegmental area	Rat	Wu and Johnson (1996)				
$IC_{50} = 1.03 \pm 0.06$	Glutamate (0.3 $\mu$ M)-evoked GluN1/2A currents	tsA201 cells	Rat	Glasgow et al. (2017)				
$IC_{50} = 0.89 \pm 0.07$	Glutamate (1 mM)-evoked GluN1/2A currents	tsA201 cells	Rat	Glasgow et al. (2017)				
$IC_{50} = 0.59 \pm 0.03$	Glutamate (0.3 $\mu$ M)-evoked GluN1/2B currents	tsA201 cells	Rat	Glasgow et al. (2017)				
$IC_{50} = 0.43 \pm 0.04$	Glutamate (1 mM)-evoked GluN1/2B currents	tsA201 cells	Rat	Glasgow et al. (2017)				
$IC_{50} = 0.43 \pm 0.10$	Whole-cell patch-clamp recordings	Hippocampus	Rat	Parsons et al. (1996)				

(continued)



TABLE 3—Continued

Receptor/Target	Drug	Action	Proposed Clinical Relevance	Affinity/Potency ( $\mu\text{M}$ )	Method	Tissue/System	Species	Reference
				$\text{IC}_{50} = 0.92 \pm 0.21$ $2 \text{ mM Mg}^{2+}$	Whole-cell patch-clamp recordings Two-microelectrode recording	Striatum Rat receptors expressed in <i>Xenopus</i> oocytes	Rat Rat	Parsons et al. (1996) Dravid et al. (2007)
				GluN1/2A: $\text{IC}_{50} = 3.31$ GluN1/2B: $\text{IC}_{50} = 0.93$ GluN1/2C: $\text{IC}_{50} = 1.65$ GluN1/2D: $\text{IC}_{50} = 2.42$ $\text{IC}_{50} = 1.97$ $\text{IC}_{50} = 0.71 \pm 0.03$ $\text{IC}_{50} = 6.05 \pm 0.66$	FLIPR calcium influx assay Whole-cell patch-clamp recordings— holding potential at $-70 \text{ mV}$ Whole-cell patch-clamp recordings—holding potential at $0 \text{ mV}$ Whole-cell recordings	HEK293 cells HEK293 cells transfected with GluN1/2A receptors Rat receptor expressed in HEK293 cells	Human Human Human	Gilling et al. (2009) Gilling et al. (2009) Gilling et al. (2009)
				$\text{Mg}^{2+}$ free GluN1/2A: $\text{IC}_{50} = 0.33 \pm 0.01$ ; GluN1/2B: $\text{IC}_{50} = 0.31 \pm 0.02$ ; GluN1/2C: $\text{IC}_{50} = 0.51 \pm 0.01$ ; GluN1/2D: $\text{IC}_{50} = 0.83 \pm 0.02$ $1 \text{ mM Mg}^{2+}$ GluN1/2A: $\text{IC}_{50} = 5.35 \pm 0.34$ ; GluN1/2B: $\text{IC}_{50} = 5.08 \pm 0.02$ ; GluN1/2C: $\text{IC}_{50} = 1.18 \pm 0.04$ ; GluN1/2D: $\text{IC}_{50} = 2.95 \pm 0.02$ $\text{IC}_{50} = 10$ $\text{IC}_{50} = 0.40$ $\text{IC}_{50} = 0.51 \pm 0.04$	Whole-cell recordings	Rat receptor expressed in HEK293 cells	Rat	Kotermanski and Johnson (2009) Kotermanski and Johnson (2009)
	(S)-KET	Antagonist	Anesthesia, antidepressant effects, dissociative effects, cognitive impairment	$\text{IC}_{50} = 0.35$ $K_i = 0.30 \pm 0.013$ $K_i = 0.69 \pm 0.09$ $K_i = 0.42 \pm 0.04$ $K_i = 0.44 \pm 0.10$ $\text{IC}_{50} = 1.6-1.9$ $\text{IC}_{50} = 1.5-2.8$ $\text{IC}_{50} = 1.6-2.1$ $\text{IC}_{50} = 0.80$ $\text{IC}_{50} = 0.9 \pm 1.4$ $2 \text{ mM Mg}^{2+}$ GluN1/2A: $\text{IC}_{50} = 16.10$ GluN1/2B: $\text{IC}_{50} = 1.55$ GluN1/2C: $\text{IC}_{50} = 1.11$ GluN1/2D: $\text{IC}_{50} = 1.50$ $K_i = 1.40 \pm 0.1$ $K_i = 2.57 \pm 0.28$ $K_i = 1.79 \pm 0.31$ $\text{IC}_{50} = 7.2-10$ $\text{IC}_{50} = 8.2-13.7$ $\text{IC}_{50} = 10.9-11.4$ $\text{IC}_{50} = 1.53$ $\text{IC}_{50} = 3.0 \pm 1.4$ $K_i = 3.63 \pm 0.49$ $2 \text{ mM Mg}^{2+}$ GluN1/2A: $\text{IC}_{50} = 50.90$ GluN1/2B: $\text{IC}_{50} = 8.74$ GluN1/2C: $\text{IC}_{50} = 5.6$ GluN1/2D: $\text{IC}_{50} = 7.5$ $\text{IC}_{50} = 2.00$ $K_i = 1.7 \pm 0.050$ $K_i = 2.25 \pm 0.22$ $K_i = 0.87$ $\text{IC}_{50} = 3.0 \pm 0.8$ $\text{IC}_{50} = 1.23$	Extracellular recordings (EPSPs) Whole-cell patch-clamp recordings RBA- $^3$ H/HMK-801 binding RBA- $^3$ H/HMK-801 binding RBA- $^3$ H/HMK-801 binding RBA- $^3$ H/HMK-801 binding RBA- $^3$ H/HMK-801 binding RBA- $^3$ H/HMK-801 binding RBA- $^3$ H/HMK-801 binding RBA- $^3$ H/HMK-801 binding RBA- $^3$ H/HMK-801 binding Whole-cell patch-clamp recordings NMDA ( $\mu\text{M}$ )-evoked currents Two-microelectrode recording	Hippocampus (CA1) Hippocampal neuron culture Forebrain Whole brain (excluding cerebellum) Cortex Whole brain Cortex Cortex Hippocampus (two brain samples only) Frontal cortex (two brain samples only) Occipital cortex (two brain samples only) Hippocampus Cortex Rat receptors expressed in <i>Xenopus</i> oocytes	Rat Rat Rat Rat Rat Pig Pig Human Human Human Rat Rat Rat	Izumi and Zorumski (2014) Emnett et al. (2016) Wallach et al. (2016), Kang et al. (2017) Morris et al. (2017) Ehert et al. (1997) Moaddel et al. (2013) Bonifazi et al. (2015) Temme et al. (2018) Oye et al. (1992) Oye et al. (1992) Oye et al. (1992) Zeilhofer et al. (1992) Ehert et al. (1997) Dravid et al. (2007)
	(R)-KET	Antagonist	Anesthesia, antidepressant effects	$\text{IC}_{50} = 1.53$ $\text{IC}_{50} = 3.0 \pm 1.4$ $K_i = 3.63 \pm 0.49$ $2 \text{ mM Mg}^{2+}$ GluN1/2A: $\text{IC}_{50} = 50.90$ GluN1/2B: $\text{IC}_{50} = 8.74$ GluN1/2C: $\text{IC}_{50} = 5.6$ GluN1/2D: $\text{IC}_{50} = 7.5$ $\text{IC}_{50} = 2.00$	Whole-cell patch-clamp recordings NMDA ( $\mu\text{M}$ )-evoked currents Two-microelectrode recording	Cortex Whole brain Cortex Hippocampus (two brain samples only) Frontal cortex (two brain samples only) Occipital cortex (two brain samples only) Hippocampus	Rat Rat Rat Pig Human Human Human Rat	Ehert et al. (1997) Moaddel et al. (2013) Temme et al. (2018) Oye et al. (1992) Oye et al. (1992) Oye et al. (1992) Zeilhofer et al. (1992)
	(R,S)-norKET	Antagonist	Anesthesia	$\text{IC}_{50} = 1.53$ $\text{IC}_{50} = 3.0 \pm 1.4$ $K_i = 3.63 \pm 0.49$ $2 \text{ mM Mg}^{2+}$ GluN1/2A: $\text{IC}_{50} = 50.90$ GluN1/2B: $\text{IC}_{50} = 8.74$ GluN1/2C: $\text{IC}_{50} = 5.6$ GluN1/2D: $\text{IC}_{50} = 7.5$ $\text{IC}_{50} = 2.00$	Whole-cell patch-clamp recordings NMDA ( $\mu\text{M}$ )-evoked currents Two-microelectrode recording	Cortex Cortex Rat receptors expressed in <i>Xenopus</i> oocytes	Rat Rat Rat Rat	Ehert et al. (1997) Ehert et al. (1997) Dravid et al. (2007)
	(S)-norKET	Antagonist	Anesthesia	$\text{IC}_{50} = 3.0 \pm 0.8$ $\text{IC}_{50} = 1.23$	Whole-cell recordings RBA- $^3$ H/HMK-801 binding RBA- $^3$ H/HMK-801 binding RBA- $^3$ H/HMK-801 binding NMDA ( $\mu\text{M}$ )-evoked currents RBA- $^3$ H/HMK-801 binding	Hippocampal neuron culture Cortex Whole brain Whole brain (excluding cerebellum) Cortex Whole brain (excluding cerebellum)	Rat Rat Rat Rat Rat Rat	Emnett et al. (2016) Ehert et al. (1997) Moaddel et al. (2013) Morris et al. (2017) Ehert et al. (1997) Morris et al. (2017)

(continued)

TABLE 3—Continued

Receptor/Target	Drug	Action	Proposed Clinical Relevance	Affinity/ Potency ( $\mu\text{M}$ )	Method	Tissue/System	Species	Reference
D-serine	(R)-norKET	Antagonist		$K_i = 13 \pm 1.8$	RBA— $^3\text{H}$ HKM-801 binding	Cortex	Rat	Ehert et al. (1997)
				$K_i = 26.46$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Moaddel et al. (2013)
				$K_i = 0.60$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)
	(S)-DHNK	Antagonist	N/A	$\text{IC}_{50} = 39.0 \pm 1.4$	NMDA ( $\mu\text{M}$ )-evoked currents	Cortex	Rat	Ehert et al. (1997)
				$\text{IC}_{50} = 0.85$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)
				$K_i = 38.95$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain	Rat	Moaddel et al. (2013)
	(R)-DHNK	Antagonist	N/A	$K_i = 29.7$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)
				$\text{IC}_{50} = 42.0$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)
				$K_i = 74.55$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain	Rat	Moaddel et al. (2013)
	(2S,6S)-HINK	Antagonist	N/A	$K_i = 42.1$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)
				$\text{IC}_{50} = 59.7$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)
				$K_i = 21.19$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain	Rat	Moaddel et al. (2013)
(2R,6R)-HINK	No effect	N/A	$K_i > 10$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain	Rat	Zanos et al. (2016)	
			$K_i > 100$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)	
			$\text{IC}_{50} = 10.4$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)	
D-serine	(2R,6S)-HINK	Antagonist	Antidepressant	$K_i > 100$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)
				$\text{IC}_{50} > 50$	Whole-cell recordings	Hippocampal neuron culture	Mouse	Suzuki et al. (2017)
				$K_i > 100$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)
	(2S,6R)-HINK	N/A	N/A	$\text{IC}_{50} > 100$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)
				$K_i > 100$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)
				$\text{IC}_{50} > 100$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)
	(2R,5R)-HINK	N/A	N/A	$\text{IC}_{50} > 100$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)
				$K_i > 100$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)
				$\text{IC}_{50} > 100$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)
	(2S,5S)-HINK	N/A	N/A	$\text{IC}_{50} > 100$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)
				$K_i > 100$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)
				$\text{IC}_{50} > 100$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)
(2R,5S)-HINK	N/A	N/A	$\text{IC}_{50} > 100$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)	
			$K_i > 100$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)	
			$\text{IC}_{50} > 100$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)	
(2R,4R)-HINK	N/A	N/A	$\text{IC}_{50} > 100$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)	
			$K_i > 100$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)	
			$\text{IC}_{50} > 100$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)	
(2S,4S)-HINK	N/A	N/A	$\text{IC}_{50} > 100$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)	
			$K_i > 100$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)	
			$\text{IC}_{50} > 100$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)	
(2R,4S)-HINK	N/A	N/A	$\text{IC}_{50} > 100$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)	
			$K_i > 100$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)	
			$\text{IC}_{50} > 100$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)	
(2S,4R)-HINK	N/A	N/A	$\text{IC}_{50} > 100$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)	
			$K_i > 100$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)	
			$\text{IC}_{50} > 100$	RBA— $^3\text{H}$ HKM-801 binding	Whole brain (excluding cerebellum)	Rat	Morris et al. (2017)	
(S)-KET	Transport inhibitor	Antidepressant effects and dissociative side effects	$\text{EC}_{50} = 0.82 \pm 0.29^a$ (intracellular); $0.76 \pm 0.13^b$ (extracellular)	CE-LIF (intracellular); LC-MS (extracellular)	PC-12 cells	Rat-derived cell line	Singh et al. (2015)	
			$\text{EC}_{50} = 0.46 \pm 0.25^a$ (intracellular); $0.57 \pm 0.32^b$ (extracellular)	CE-LIF (intracellular); LC-MS (extracellular)	1321N1 cells	Human-derived cell line	Singh et al. (2015)	
			$\text{IC}_{50} = 0.94 \pm 0.16^a$ (intracellular); $0.70 \pm 0.10^b$ (extracellular)	CE-LIF (intracellular); LC-MS (extracellular)	PC-12 cells	Rat-derived cell line	Singh et al. (2015)	
(R)-KET	$\alpha 7$ nAChR inhibition		$\text{IC}_{50} = 0.75 \pm 0.27^a$ (intracellular); $0.88 \pm 0.25^b$ (extracellular)	CE-LIF (intracellular); LC-MS (extracellular)	1321N1 cells	Human-derived cell line	Singh et al. (2015)	
			$\text{IC}_{50} = 0.115$ (intracellular)	CE-LIF	PC-12 cells	Rat-derived cell line	Singh et al. (2013)	
			$\text{IC}_{50} = 0.035$ (intracellular)	CE-LIF	1321N1 cells	Human-derived cell line	Singh et al. (2013)	
(2S,6S)-HINK	Inhibitor	Anesthesia, antidepressant effects	$\text{IC}_{50} = 0.00018 \pm 0.00004^a$ (intracellular)	CE-LIF	PC-12 cells	Rat-derived cell line	Singh et al. (2016c)	
			$\text{IC}_{50} = 0.00068 \pm 0.00009^a$ (intracellular)	CE-LIF	PC-12 cells	Rat-derived cell line	Singh et al. (2016c)	
			$\text{EC}_{50} = 8.2\text{--}15.6$	Whole-cell recording	Mouse channels expressed in HEK293 cells	Mouse	Chen et al. (2009)	

(continued)

TABLE 3—Continued

Receptor/Target	Drug	Action	Proposed Clinical Relevance	Affinity/Potency ( $\mu\text{M}$ )	Method	Tissue/System	Species	Reference
	(S)-KET			$EC_{50} = 4.1\text{--}7.4$	Whole-cell recording	Mouse channels expressed in HEK293 cells	Mouse	Chen et al. (2009)
GABA uptake	(R,S)-KET	Reversible noncompetitive inhibitor	N/A	$K_i = 6.2 \pm 1.1^c$	RBA— $^3\text{H}$ GABA binding	Striatal synaptosomes	Rat	Mantz et al. (1995)
			Anesthesia (due to observed increased GABA content)	$IC_{50} = \sim 400$	RBA— $^3\text{H}$ GABA binding	Cultured neurons from cerebral hemispheres	Mouse	Wood and Hertz (1980)
				$IC_{50} > 1000$	RBA— $^3\text{H}$ GABA binding	Cultured astrocytes from cerebral hemispheres	Mouse	Wood and Hertz (1980)
				$IC_{50} > 1000$	RBA— $^3\text{H}$ GABA binding	Brain synaptosomes	Mouse	Wood and Hertz (1980)
		Reversible noncompetitive inhibitor	N/A	$IC_{50} = 50$	RBA— $^3\text{H}$ GABA binding	Striatal synaptosomes	Rat	Mantz et al. (1995)
GABA <sub>A</sub> R	(R,S)-KET	Positive modulator	N/A	$EC_{50} = 1200 \pm 600$	Whole-cell recording	Human receptor expressed in HEK293 cells	Human	Flood and Krasowski (2000)
		No effect	N/A	$EC_{50} > 1000$	Human receptor expressed in <i>Xenopus</i> oocytes	Human	Human receptor expressed in <i>Xenopus</i> oocytes	Yamakura et al. (2000)
M1 mAChR	(R,S)-KET	N/R	N/A	$K_i = 45$	RBA	Human receptor expressed in CHO cells	Rat	Hirota et al. (2002)
M2 mAChR	(R,S)-KET	Antagonist	N/A	$IC_{50} = 5.7$	Two-microelectrode recording	Rat receptor expressed in <i>Xenopus</i> oocytes	Rat	Durieux (1995)
M3 mAChR	(R,S)-KET	N/R	N/A	$K_i = 294$	RBA	Human receptor expressed in CHO cells	Human	Hirota et al. (2002)
nAChR (muscle type)	(R,S)-KET	N/R	N/A	$K_i = 246$	RBA	Human receptor expressed in CHO cells	Human	Hirota et al. (2002)
		Antagonist	N/A	$K_i = 16.5 \pm 0.7^a$ (resting); $K_i = 13.1 \pm 1.8^a$ (desensitized)	RBA— $^3\text{H}$ ITCP binding	Human receptor expressed in CHO cells	<i>T. californica</i>	Arias et al. (2002)
		No effect	N/A	No effect	RBA— $^3\text{H}$ tetraecaine binding	membranes	<i>T. californica</i>	Arias et al. (2002)
		Antagonist	N/A	$K_i = 18.2 \pm 1.2^a$ (resting); $K_i = 15.4 \pm 2.3^a$ (desensitized)	RBA— $^3\text{H}$ ITCP binding	AChR native membranes	<i>T. californica</i>	Arias et al. (2002)
		No effect	N/A	$K_i = 19.9 \pm 2.8^a$	RBA— $^3\text{H}$ tetraecaine binding	membranes	<i>T. californica</i>	Arias et al. (2002)
$\alpha$ nAChR	(R,S)-KET	Antagonist	N/A	$K_i = 430 \pm 330^a$	RBA— $^{14}\text{C}$ amobarbital binding	membranes	<i>T. californica</i>	Arias et al. (2002)
		Antagonist	N/A	$EC_{50} = 18.7 \pm 7.4^a$	RBA— $^{125}\text{I}$ TTD photoincorporation	AChR native membranes	<i>T. californica</i>	Arias et al. (2002)
$\beta$ nAChR	(S)-KET	Antagonist	N/A	$EC_{50} = 8.7 \pm 2.2^a$	RBA— $^{125}\text{I}$ TTD photoincorporation	AChR native membranes	<i>T. californica</i>	Arias et al. (2002)
		Antagonist	N/A	$EC_{50} = 15.2 \pm 3.6^a$	RBA— $^{125}\text{I}$ TTD photoincorporation	AChR native membranes	<i>T. californica</i>	Arias et al. (2002)
		Antagonist	N/A	$EC_{50} = 7.4 \pm 4.5^a$	RBA— $^{125}\text{I}$ TTD photoincorporation	AChR native membranes	<i>T. californica</i>	Arias et al. (2002)
$\gamma$ nAChR	(R,S)-KET	Antagonist	N/A	$EC_{50} = 20.4 \pm 10.1^a$	RBA— $^{125}\text{I}$ TTD photoincorporation	AChR native membranes	<i>T. californica</i>	Arias et al. (2002)
		Antagonist	N/A	$EC_{50} = 6.6 \pm 2.9^a$	RBA— $^{125}\text{I}$ TTD photoincorporation	AChR native membranes	<i>T. californica</i>	Arias et al. (2002)
$\delta$ nAChR	(R,S)-KET	Antagonist	N/A	$EC_{50} = 19.4 \pm 6.5^a$	RBA— $^{125}\text{I}$ TTD photoincorporation	AChR native membranes	<i>T. californica</i>	Arias et al. (2002)
		Antagonist	N/A	$EC_{50} = 8.5 \pm 2.4^a$	RBA— $^{125}\text{I}$ TTD photoincorporation	AChR native membranes	<i>T. californica</i>	Arias et al. (2002)
$\alpha 2\beta 2$ nAChR	(R,S)-KET	Antagonist	N/A	$IC_{50} = 92$	Whole-cell recording	Human receptor expressed in <i>Xenopus</i> oocytes	Human	Yamakura et al. (2000)
$\alpha 4\beta 4$ nAChR	(R,S)-KET	Antagonist	N/A	$IC_{50} = 0.24 \pm 0.03$	Whole-cell recording	Chicken receptor expressed in <i>Xenopus</i> oocytes	Chicken	Flood and Krasowski (2000)
		Antagonist	N/A	$IC_{50} = 18$	Whole-cell recording	Human receptor expressed in <i>Xenopus</i> oocytes	Human	Yamakura et al. (2000)
$\alpha 2\beta 4$ nAChR	(R,S)-KET	Antagonist	N/A	$IC_{50} = 29$	Whole-cell recording	Human receptor expressed in <i>Xenopus</i> oocytes	Human	Yamakura et al. (2000)

(continued)

TABLE 3—Continued

Receptor/Target	Drug	Action	Proposed Clinical Relevance	Affinity/Potency ( $\mu\text{M}$ )	Method	Tissue/System	Species	Reference
$\alpha 4\beta 2$ nAChR	( <i>R,S</i> )-KET	Antagonist	N/A	IC <sub>50</sub> = 72	Whole-cell recording	Human receptor expressed in <i>Xenopus</i> oocytes	Human	Yamakura et al. (2000)
		Antagonist	N/A	IC <sub>50</sub> = 50 ± 4	Whole-cell recording	Human receptor expressed in <i>Xenopus</i> oocytes	Human	Coates and Flood (2001)
$\alpha 7$ nAChR	( <i>R,S</i> )-KET	Antagonist	Antidepressant effects	IC <sub>50</sub> = 20 ± 2	Whole-cell recording	Human receptor expressed in <i>Xenopus</i> oocytes	Human	Coates and Flood (2001)
		Antagonist		IC <sub>50</sub> = 17.3 ± 2	Whole-cell recording	Human receptor expressed in <i>Xenopus</i> oocytes	Human	Ho and Flood (2004)
$\alpha 3\beta 2$ nAChR	( <i>R,S</i> )-DHNK	Antagonist		IC <sub>50</sub> = 0.055 ± 0.006	Whole-cell recording	KX $\alpha$ 7R1 cells (express rat receptors)	Rat	Moaddel et al. (2013)
	( <i>R,S</i> )-KET	Antagonist	N/A	IC <sub>50</sub> = 50	Whole-cell recording	Human receptor expressed in <i>Xenopus</i> oocytes	Human	Yamakura et al. (2000)
$\alpha 3\beta 4$ nAChR	( <i>R,S</i> )-KET	Antagonist	N/A	IC <sub>50</sub> = 9.5	Whole-cell recording	Human receptor expressed in <i>Xenopus</i> oocytes	Human	Yamakura et al. (2000)
		Antagonist		IC <sub>50</sub> = 3.1	Whole-cell recording	KX $\alpha$ 3 $\beta$ 4R2 cells (express rat receptors)	Rat	Moaddel et al. (2013)
	( <i>R,S</i> )-norKET	Antagonist		IC <sub>50</sub> = 9.1	Whole-cell recording	KX $\alpha$ 3 $\beta$ 4R2 cells (express rat receptors)	Rat	Moaddel et al. (2013)
	( <i>R,S</i> )-DHNK	No significant effect		IC <sub>50</sub> > 200	Whole-cell recording	KX $\alpha$ 3 $\beta$ 4R2 cells (express rat receptors)	Rat	Moaddel et al. (2013)
	(2 <i>S,6S</i> )-HNK			IC <sub>50</sub> > 200	Whole-cell recording	KX $\alpha$ 3 $\beta$ 4R2 cells (express rat receptors)	Rat	Moaddel et al. (2013)
	(2 <i>R,6R</i> )-HNK			IC <sub>50</sub> > 200	Whole-cell recording	KX $\alpha$ 3 $\beta$ 4R2 cells (express rat receptors)	Rat	Moaddel et al. (2013)
D <sub>1-5</sub> R	( <i>S</i> )-KET ( <i>R</i> )-KET	N/A	N/A	No functional effect up to 10 $\mu\text{M}$	RBA	Human receptor expressed in HEK293 cells (for D <sub>1/5</sub> R), or stable fibroblast (for D <sub>2</sub> R) cells	Human	Can et al. (2016)
	( <i>S</i> )-norKET			K <sub>i</sub> = 1.0 ± 0.15	RBA	Striatum	Rat	Kapur and Seeman (2001, 2002)
	( <i>R</i> )-norKET			K <sub>i</sub> = 0.5 ± 0.2 EC <sub>50</sub> = 0.9 ± 0.4	RBA	Human D <sub>2</sub> R expressed in CHO cells	Human	Kapur and Seeman (2002)
	( <i>S</i> )-DHNK			EC <sub>50</sub> = 0.4	RBA/[ <sup>35</sup> S]-GTP- $\gamma$ S	Human D <sub>2</sub> R expressed in CHO cells	Human	Seeman and Kapur (2003)
	( <i>R</i> )-DHNK			K <sub>i</sub> = 0.055 ± 0.012	RBA	Human receptor expressed in CHO cells	Human	Seeman et al. (2005)
	(2 <i>S,6S</i> )-HNK			IC <sub>50</sub> = 2	RBA—[ <sup>35</sup> S]-GTP- $\gamma$ S	Human D <sub>2</sub> R expressed in CHO cells	Human	Seeman and Kapur (2003)
	(2 <i>R,6R</i> )-HNK			IC <sub>50</sub> = 4.6	RBA—[ <sup>3</sup> H]dopamine uptake	Striatum	Rat	Keita et al. (1996)
DAT	( <i>R,S</i> )-KET	Antagonist	N/A	K <sub>i</sub> = 62.9 ± 2.3 <sup>a</sup>	RUA—[ <sup>3</sup> H]dopamine uptake	Striatum	Rat	Nishimura et al. (1998)
		Reversible, noncompetitive inhibition	N/A			Rat transporter expressed in HEK293 cells	Rat	
		Uptake inhibitor	N/A			Human transporter expressed in HEK cells	Human	Can et al. (2016)
	( <i>S</i> )-KET ( <i>R</i> )-KET	No binding or functional activity up to 10 $\mu\text{M}$	N/A	N/A	RBA		Human	
	( <i>S</i> )-norKET			K <sub>i</sub> = 15 ± 5	RBA	Frontal cortex	Rat	Kapur and Seeman (2002)
	( <i>R</i> )-norKET			K <sub>i</sub> = 96.9 ± 3.5	RBA—[ <sup>3</sup> H]BRL43,694	Neuroblastoma cell cultures (N1E-115)	Mouse	Appadu and Lambert (1996)
	( <i>S</i> )-DHNK			K <sub>i</sub> = 420 ± 60	5-HT-induced currents: whole-cell recordings	Human receptor expressed in <i>Xenopus</i> oocytes	Human	Yamakura et al. (2000)
	( <i>R</i> )-DHNK							
	(2 <i>S,6S</i> )-HNK							
	(2 <i>R,6R</i> )-HNK							
5-HT <sub>2R</sub>	( <i>R,S</i> )-KET	N/R	Analgesic effects					
5-HT <sub>3R</sub>	( <i>R,S</i> )-KET	Antagonist	N/A	IC <sub>50</sub> = 910 ± 30	5-HT-induced currents: whole-cell recordings	Human receptor expressed in <i>Xenopus</i> oocytes	Human	Yamakura et al. (2000)
5-HT <sub>3R</sub>	( <i>R,S</i> )-KET	Competitive antagonist	N/A	IC <sub>50</sub> > 100	Whole-cell recording	Human receptor expressed in <i>Xenopus</i> oocytes	Human	Ho and Flood (2004)

(continued)

TABLE 3—Continued

Receptor/Target	Drug	Action	Proposed Clinical Relevance	Affinity/Potency ( $\mu\text{M}$ )	Method	Tissue/System	Species	Reference
SERT	(R,S)-KET	Uptake inhibitor	N/A	$\text{IC}_{50} = 20.2 \pm 2.75$	RUA— $^3\text{H}$ 5-HT uptake	Brain (except cerebellum)	Rat	Martin et al. (1988)
				$\text{IC}_{50} = 18.8$	RUA— $^3\text{H}$ paroxetine	Brain (except cerebellum)	Rat	Martin et al. (1990)
				$K_i = 161.7 \pm 28.3^a$	RUA— $^3\text{H}$ serotonin	Rat transporter expressed in HEK293 cells	Rat	Nishimura et al. (1998)
NET	(S)-KET (R)-KET (S)-norKET (R)-norKET (S)-DHNK (R)-DHNK (2S,6S)-HNK (2R,6R)-HNK (R,S)-KET	N/A	No binding or functional activity up to $10 \mu\text{M}$	$\text{IC}_{50} = 75 \pm 8$	RUA— $^3\text{H}$ 5-HT uptake	Cortical synaptosomes	Rat	Azzaro and Smith (1977)
				$\text{IC}_{50} = 125.2$	RUA— $^3\text{H}$ 5-HT uptake	NE transporter expressed in HEK293 cells	Human	Zhao and Sun (2008)
					REA	Human transporter expressed in HEK cells	Human	Can et al. (2016)
				$K_i = 66.8 \pm 25.9^a$	RUA— $^3\text{H}$ INE	Human transporter expressed in HEK293 cells	Human	Nishimura et al. (1998)
				100 $\mu\text{M}$ —estimated ~50% noncompetitive inhibition	RUA— $^3\text{H}$ INE	Bovine adrenal medullary cells	Bovine	Hara et al. (1998a)
				10–100 $\mu\text{M}$ —estimated ~50% noncompetitive inhibition	RUA— $^3\text{H}$ INE	<i>Xenopus</i> oocytes expressing bovine NE transporters	Bovine	Hara et al. (1998a)
				300 $\mu\text{M}$ —competitive inhibition	RUA— $^3\text{H}$ desipramine	Plasma membranes of bovine adrenal medulla	Bovine	Hara et al. (1998a)
				$\text{IC}_{50} = 290.7$	RUA— $^3\text{H}$ INE	NE transporter expressed in HEK293 cells	Human	Zhao and Sun (2008)
					REA	Human transporter expressed in HEK cells	Human	Can et al. (2016)
				$\mu$ opioid receptor	(S)-KET (R)-KET (S)-norKET (R)-norKET (S)-DHNK (R)-DHNK (2S,6S)-HNK (2R,6R)-HNK (R,S)-KET (S)-KET	Agonist	Analgesia	$K_i = 42.1$
$K_i = 28.6$	REBA— $^3\text{H}$ DPN	Human receptor expressed in CHO cells	Human					Hirota et al. (1999)
$K_i = 11$	REBA— $^3\text{H}$ DAMGO	Whole brain	Rat					Hustveit et al. (1995)
$K_i = 83.8$	REBA— $^3\text{H}$ DPN	Human receptor expressed in CHO cells	Human					Hirota et al. (1999)
$K_i = 28$	REBA— $^3\text{H}$ DAMGO	Whole brain	Rat					Hustveit et al. (1995)
$K_i = 28.1$	REBA— $^3\text{H}$ DPN	Human receptor expressed in CHO cells	Human					Hirota et al. (1999)
$K_i = 25.0$ ; $\text{EC}_{50} = 28.0$	REBA— $^{35}\text{S}$ -GTP- $\gamma$ S	Human receptor expressed in CHO cells	Human					Nemeth et al. (2010)
$K_i = 23.7$	REBA— $^3\text{H}$ DPN	Human receptor expressed in CHO cells	Human					Hirota et al. (1999)
$K_i = 24$	REBA— $^3\text{H}$ U69,593	Whole brain	Rat					Hustveit et al. (1995)
$K_i = 60.0$	REBA— $^3\text{H}$ DPN	Human receptor expressed in CHO cells	Human					Hirota et al. (1999)
$\delta$ opioid receptor	(R,S)-KET (S)-KET (R)-KET	Agonist	Antidepressant effects	$K_i = 100$	REBA— $^3\text{H}$ U69,593	Whole brain	Rat	Hustveit et al. (1995)
				$K_i = 272$	REBA— $^3\text{H}$ DPN	Human receptor expressed in CHO cells	Human	Hirota et al. (1999)
				$K_i = 205$	REBA— $^3\text{H}$ DPN	Human receptor expressed in CHO cells	Human	Hirota et al. (1999)
				$K_i = 130$	REBA— $^3\text{H}$ DPDPE	Whole brain	Rat	Hustveit et al. (1995)
				$K_i = 286$	REBA— $^3\text{H}$ DPN	Human receptor expressed in CHO cells	Human	Hirota et al. (1999)
				$K_i = 130$	REBA— $^3\text{H}$ DPDPE	Whole brain	Rat	Hustveit et al. (1995)
				$\text{IC}_{50} = 66.0 \pm 10.0$	REBA— $^3\text{H}$ + SKF10,047	Spinal cord	Rat	Smith et al. (1987)
				$K_i = 0.15$	REBA— $^3\text{H}$ + SKF10,047	Whole brain	Rat	Hustveit et al. (1995)
				$K_i > 10$	REBA— $^3\text{H}$ DTG	Rat glioma hybrid cells NG108-15	Rat	Georg and Friedl (1991)
				$K_i = 19$	REBA— $^3\text{H}$ + SKF10,047	Whole brain	Rat	Hustveit et al. (1995)
$K_i = 131$	REBA— $^3\text{H}$ + SKF10,047	Whole brain	Rat	Hustveit et al. (1995)				

(continued)

TABLE 3—Continued

Receptor/Target	Drug	Action	Proposed Clinical Relevance	Affinity/Potency ( $\mu\text{M}$ )	Method	Tissue/System	Species	Reference
$\sigma_1\text{R}$	( <i>R,S</i> )-KET			$K_i = 139.60 \pm 6.13$	RBA— $^3\text{H}$ (+) pentazocine	Liver membrane	Rat	Robson et al. (2012)
$\sigma_2\text{R}$	( <i>R,S</i> )-KET			$K_i = 26.30 \pm 2.98$	RBA— $^3\text{H}$ -o-tolylguanidine	Liver membrane	Rat	Robson et al. (2012)
TTX-sensitive VGSC	( <i>R,S</i> )-KET	Antagonist	Local anesthesia	$\text{IC}_{50} = 146.7 \pm 8.4$ (tonic)	Whole-cell recording	Dorsal root ganglion	Rat	Zhou and Zhao (2000)
TTX-resistant VGSC	( <i>R,S</i> )-KET	Antagonist		$\text{IC}_{50} = 866.2 \pm 34.7$ (tonic), $314.8 \pm 12.4$ (phasic)	Whole-cell recording	Dorsal root ganglion	Rat	Zhou and Zhao (2000)
VGSC	( <i>R,S</i> )-KET	Antagonist		$\text{IC}_{50} = 800$ (tonic), 2300 (phasic)	Two-microelectrode recording	Rat channels expressed in <i>Xenopus</i> oocytes	Rat	Wagner et al. (2001)
				$\text{IC}_{50} = 222.0$ $K_i = 11.5$	$^{22}\text{Na}^+$ -stimulated influx (measure sodium uptake)	Brain (minus cerebellum) synaptoneurosomal fractions	Rat	Allaoua and Chicheportiche (1989)
				$\text{ED}_{50} = 11.00$	Single channel recordings	Cortical synaptosome bilayer	Human	Frenkel and Urban (1992)
	( <i>S</i> )-KET	Antagonist		$\text{IC}_{50} = 240 \pm 60^a$ (neuronal), $59 \pm 10^a$ (skeletal)	Whole-cell recording	Rat channels expressed in HEK293 cells	Rat	Haeseler et al. (2003)
	( <i>R</i> )-KET	Antagonist		$\text{IC}_{50} = 333 \pm 89^a$ (neuronal), $181 \pm 49^a$ (skeletal)	Whole-cell recording	Rat channels expressed in HEK293 cells	Rat	Haeseler et al. (2003)
L-type VDCC	( <i>R,S</i> )-KET	Antagonist	Antidepressant effects	$\text{IC}_{50} = 1000$	Whole-cell recording	Tracheal smooth muscle	Pig	Yamakage et al. (1995)
	( <i>R,S</i> )-KET			$\text{IC}_{50} = 9.2$	Whole-cell recording	Atrial myocytes	Bullfrog	Hatakeyama et al. (2001)

CE-LIF, capillary electrophoresis-laser-induced fluorescence; D<sub>1-5</sub>R, dopamine receptor subtypes 1–5; DAMGO, [D-Ala<sup>2</sup>, N-MePhe<sup>4</sup>, Gly-<sup>o</sup>ll-enkephalin; DAT, dopamine transporter; DPDPE, [D-Pen<sup>2</sup>, D-Pen<sup>5</sup>]enkephalin; DPN, diprenorphine; DTG, 1,3-Di-*o*-tolylguanidine; EPSP, excitatory postsynaptic potential; FLIPR, fluorescence imaging plate reader; GABA<sub>A</sub>R, GABA receptor A; GTP $\gamma$ S, guanosine 5'-*3*-*O*-(thio)triphosphate; HEK, human embryonic kidney cells; 5-HT<sub>2</sub>R, serotonin receptor subtype 2; KET, ketamine; LC-MS, liquid chromatography–mass spectrometry; NMDA, *N*-methyl-D-aspartate; norKET, norketamine; NE, norepinephrine; REA, radioligand-binding assay; RUA, radioligand uptake assay; TCP, [1-(2-thienyl)cyclohexyl] piperidine; TID, 3-(Trifluoromethyl)-3-(3-iodophenyl) diazine; TTX, tetrodotoxin; VGSC, voltage-gated sodium channel.

<sup>a</sup>Values reported as mean  $\pm$  S.D.

as the antidepressant, analgesic, and altered psychotomimetic effects induced by the drug (White et al., 1980; Oye et al., 1992; Yeung et al., 2010; Li et al., 2010; Autry et al., 2011; Miller et al., 2014). Ketamine-induced cognitive deficits are also hypothesized to be due to NMDAR inhibition (Shaffer et al., 2014). (*S*)-ketamine has an approximately fourfold higher affinity/potency for the PCP site of the NMDAR compared with the (*R*)-isomer, and twice that of the racemic mixture [(*S*)-ketamine:  $K_i = 0.3\text{--}0.69\ \mu\text{M}$ ; (*R*)-ketamine:  $K_i = 1.4\text{--}2.57\ \mu\text{M}$ ; and (*R,S*)-ketamine:  $K_i = 0.18\text{--}3.1\ \mu\text{M}$ , in the presence of extracellular  $\text{Mg}^{2+}$  (Ebert et al., 1997; Kohrs and Durieux, 1998; Moaddel et al., 2013; Zanos et al., 2016; Temme et al., 2018)]. The effects of (*S*)-ketamine and (*R*)-ketamine were also assessed on NMDA receptor-activated cation currents of whole-cell voltage-clamped cultured rat hippocampal neurons (Zeilhofer et al., 1992). These authors showed that both enantiomers exhibited voltage- and use-dependent blockades of NMDAR currents, with (*S*)-ketamine being about twice as potent compared with (*R*)-ketamine ( $\text{IC}_{50} = 0.80$  versus  $1.53\ \mu\text{M}$ , respectively; Zeilhofer et al., 1992). Moreover, (*S*)-ketamine has 2.5–3 times higher potency to inhibit NMDA-evoked currents in cat dorsal horn neurons compared with the (*R*)-ketamine enantiomer (Lodge et al., 1982). This higher affinity/potency of the (*S*)-ketamine isomer is hypothesized to explain why (*S*)-ketamine is a more potent anesthetic than (*R,S*)-ketamine (Yamakura and Shimoji, 1999). Consistent with these stereospecific differential potencies to inhibit the NMDAR by ketamine's isomers, the  $\text{ED}_{50}$  value for induction of hypnosis (loss of righting reflex) was lower for (*S*)-ketamine and (*R,S*)-ketamine (3.5 and 5.6 mg/kg, respectively) compared with (*R*)-ketamine (10.3 mg/kg; Marietta et al., 1977). Similarly, Ryder et al. (1978) showed that (*S*)-ketamine is an  $\sim 3$  times more potent analgesic, 1.5 times more potent hypnotic (loss of righting reflex) and 1.8 times more potent locomotor stimulant agent compared with (*R*)-ketamine. In particular, the median effective analgesic (s.c.) doses were found to be 6.5, 3.7 and 11 mg/kg for (*R,S*)-ketamine, (*S*)-ketamine and (*R*)-ketamine, respectively (Ryder et al., 1978). The median hypnotic doses for (*R,S*)-ketamine, (*S*)-ketamine and (*R*)-ketamine were calculated to be 45, 38 and 56 mg/kg, respectively (Ryder et al., 1978). In addition, (*S*)-ketamine (25 mg/kg, s.c.) induced a more profound disruption in sensorimotor gating compared with the (*R*)-ketamine (25 mg/kg, s.c.) enantiomer in the rat pre-pulse inhibition paradigm, although (*R*)-ketamine also showed a subtle effect in this study compared with the control-treated rats (Littlewood et al., 2006). In agreement with this finding, Yang et al. (2015) showed disruption of sensorimotor gating and hyperlocomotion to only occur from administration of (*S*)-ketamine, but not (*R*)-ketamine in mice. Subanesthetic concentrations of ketamine (40-minute i.v. infusion; 0.5 mg/kg), which exert antidepressant actions in patients suffering from major depression (Zarate et al., 2012a),

resulted in a maximum of  $31\% \pm 18\%$  NMDAR occupancy (Shaffer et al., 2014). This occupancy is similar to the NMDAR occupancy estimated ( $32\% \pm 6\%$  maximum; Shaffer et al., 2014) following an antidepressant-relevant dose of ketamine in rats (10 mg/kg, i.p.; Yeung et al., 2010). Nevertheless, (*R*)-ketamine was reported to be a more potent and longer-lasting antidepressant compared with the (*S*)-ketamine enantiomer in several rodent models (Zhang et al., 2014; Yang et al., 2015; Zanos et al., 2016; Fukumoto et al., 2017), when using a 30-fold dose range (Zanos et al., 2016). There do not appear to be differences in brain exposure of the two enantiomers (Zanos et al., 2016; Fukumoto et al., 2017), thus challenging the NMDAR inhibition hypothesis as the sole mediator of the antidepressant actions of ketamine.

In membrane fractions of postmortem human brain homogenates,  $\text{IC}_{50}$  values for [ $^3\text{H}$ ]MK-801 displacement by (*S*)- and (*R*)-ketamine were reported to be 1.6–1.9 and 7.2–10  $\mu\text{M}$ , respectively, in the presence of extracellular  $\text{Mg}^{2+}$  (Oye et al., 1992). Similarly, in rat cortical tissue (*S*)-ketamine inhibited NMDA (10  $\mu\text{M}$ )-evoked currents with an  $\text{IC}_{50}$  of  $0.9 \pm 1.4\ \mu\text{M}$ , whereas (*R*)-ketamine was a less potent inhibitor with an  $\text{IC}_{50}$  of  $3.0 \pm 1.4\ \mu\text{M}$  (Ebert et al., 1997). Whole-cell patch-clamp electrophysiological recordings obtained from human embryonic kidney (HEK)293T cells transfected with different NMDAR subunits revealed that, in the absence of extracellular  $\text{Mg}^{2+}$ , ketamine inhibits the NMDARs containing GluN1/GluN2A ( $\text{IC}_{50} = 0.33 \pm 0.01\ \mu\text{M}$ ) and GluN1/GluN2B ( $\text{IC}_{50} = 0.31 \pm 0.02\ \mu\text{M}$ ) subunit compositions with a modestly higher potency than GluN1/GluN2C ( $\text{IC}_{50} = 0.51 \pm 0.01\ \mu\text{M}$ ) and GluN1/GluN2D ( $\text{IC}_{50} = 0.83 \pm 0.02\ \mu\text{M}$ ) subunits (Kotermanski and Johnson, 2009). In contrast, in the presence of physiologic levels of  $\text{Mg}^{2+}$  (1 mM), ketamine blocks NMDAR containing GluN1/GluN2C ( $\text{IC}_{50} = 1.18 \pm 0.0\ \mu\text{M}$ ) and GluN1/GluN2D ( $\text{IC}_{50} = 2.95 \pm 0.02\ \mu\text{M}$ ) subunits, with a higher potency than the GluN1/GluN2A ( $\text{IC}_{50} = 5.35 \pm 0.34\ \mu\text{M}$ ) and GluN1/GluN2B ( $\text{IC}_{50} = 5.08 \pm 0.02\ \mu\text{M}$ ) subunits (Kotermanski and Johnson, 2009). Nevertheless, Yamakura et al. (1993) failed to identify differences in ketamine-induced inhibition of the different NMDAR receptor subunits in *Xenopus* oocytes injected with subunit-specific mRNAs synthesized in vitro. These findings highlight a lack of clarity on any differential effects of ketamine on NMDAR subtypes composed of different subunits.

Studies have shown that (*S*)-ketamine inhibits NMDARs composed of GluN1/GluN2C ( $\text{IC}_{50} = 1.11\ \mu\text{M}$ ) and GluN1/GluN2D ( $\text{IC}_{50} = 1.50\ \mu\text{M}$ ) with higher potency than those composed of GluN1/GluN2A ( $\text{IC}_{50} = 16.10\ \mu\text{M}$ ) in the presence of 2 mM  $\text{Mg}^{2+}$  (Dravid et al., 2007). (*S*)-ketamine's potency to inhibit GluN1/GluN2B ( $\text{IC}_{50} = 1.55\ \mu\text{M}$ ) is reported to be similar to its potency to inhibit GluN1/GluN2C- and GluN1/GluN2D-containing NMDARs in the presence of 2 mM  $\text{Mg}^{2+}$  (Dravid et al., 2007). These findings indicate that any preferential potency of

ketamine is likely not the result of higher affinity of ketamine to bind to the GluN2C-NMDARs per se, but may be due to differential capacity for  $Mg^{2+}$  binding, or interactions between the drug and  $Mg^{2+}$  within the channel (Kotermanski and Johnson, 2009; Kotermanski et al., 2009). Thus, ketamine may differentially block specific NMDAR subtypes in the brain depending upon local  $Mg^{2+}$  concentrations. In support of this concept, in the absence of  $Mg^{2+}$ , ketamine blocks GluN2B-containing NMDARs with a higher potency compared with the NMDARs containing other GluN2 subunits, as measured using recombinant NMDAR GluN2A–D subunits expressed in *Xenopus* oocytes (Dravid et al., 2007).

In the presence of extracellular  $Mg^{2+}$ , ketamine's *N*-demethylated metabolite, norketamine, also inhibits the NMDAR. (*S*)-norketamine has a reported  $K_i$  of 1.70–2.25  $\mu M$  for NMDARs in the spinal cord and the cerebral cortex, whereas (*R*)-norketamine has an approximately eight times lower binding affinity ( $K_i = 13.0$ – $26.46 \mu M$ ; Ebert et al., 1997; Moaddel et al., 2013); also see Table 3. In accordance with these findings, (*S*)-norketamine ( $IC_{50} = 3.0 \pm 0.8 \mu M$ ) more potently inhibited NMDA (10  $\mu M$ )-evoked currents than (*R*)-norketamine ( $IC_{50} = 39 \pm 1.4 \mu M$ ) in rat cerebral cortical neurons (Ebert et al., 1997). Therefore, because NMDAR inhibition was considered the primary mechanism of action of ketamine, the clinical effects of the drug were initially attributed to ketamine and norketamine (Leung and Baillie, 1986; Hirota and Lambert, 2011; Singh et al., 2014).

DHNK and HNK metabolites display weak or no ability to displace [ $^3H$ ]MK-801 binding to NMDARs. (*R*)-DHNK has lower affinity than (*S*)-DHNK (59.7–74.6 and 39.0–42.0  $\mu M$ , respectively) for displacing [ $^3H$ ]MK-801 binding to the NMDAR (Moaddel et al., 2013; Morris et al., 2017). (*2S,6S*)-HNK has a  $K_i = 10.4$ – $21.0 \mu M$  for displacing [ $^3H$ ]MK-801 binding, whereas (*2R,6R*)-HNK does not bind to the NMDAR-PCP site with appreciable affinity ( $K_i > 100 \mu M$ ; Moaddel et al., 2013; Morris et al., 2017). In addition, at concentrations up to 10  $\mu M$ , neither (*2S,6S*)-HNK nor (*2R,6R*)-HNK functionally inhibit NMDA-evoked currents in rat hippocampal interneurons (Zanos et al., 2016). Lack of functional NMDAR inhibition by (*2R,6R*)-HNK at 10  $\mu M$  was also reported by Suzuki et al. (2017). At a higher concentration (50  $\mu M$ ), (*2R,6R*)-HNK moderately (~40%) inhibited NMDAR-mediated miniature excitatory postsynaptic currents recorded from cultured hippocampal neurons in the absence of  $Mg^{2+}$ . This finding supported the contention that, at concentrations higher than those relevant to antidepressant treatment and in the absence of  $Mg^{2+}$ , (*2R,6R*)-HNK might functionally inhibit NMDARs (Suzuki et al., 2017; Zanos et al., 2017a). Notably, at the same concentration (50  $\mu M$ ) and under the same experimental conditions, ketamine induced >90% inhibition of NMDAR-mediated miniature excitatory postsynaptic currents recorded from hippocampal neurons

(Suzuki et al., 2017). (*2R,6S*)-, (*2S,6R*)-, (*2R,5R*)-, (*2S,5S*)-, (*2S,5S*)-, (*2R,5S*)-, (*2S,5R*)-, (*2R,4S*)-, (*2S,4R*)-, (*2R,4R*)-, and (*2S,4S*)-HNKs do not have significant affinity to displace [ $^3H$ ]MK-801 binding ( $K_i > 100 \mu M$ ; Morris et al., 2017).

There is also evidence that, by reducing extracellular levels of D-serine, ketamine's enantiomers and its metabolites may indirectly decrease the activation of NMDARs (Singh et al., 2013). D-serine, an endogenous NMDAR coagonist that binds to the glycine<sub>B</sub> site, is required for activation of the NMDAR complex (Paoletti et al., 2013) and is produced by enzymatic L-serine enantioconversion catalyzed by serine racemase (Wolosker et al., 2008). Incubation of PC-12 cells with increasing concentrations of (*S*)- and (*R*)-ketamine exerted differential effects on the intracellular and extracellular D-serine levels. Specifically, application of (*S*)-ketamine was associated with increased intracellular D-serine ( $EC_{50} = 0.82 \pm 0.29 \mu M$ ) and decreased extracellular levels of D-serine ( $IC_{50} = 0.82 \pm 0.29 \mu M$ ; Singh et al., 2015). In contrast, (*R*)-ketamine decreased both intracellular ( $IC_{50} = 0.94 \pm 0.16 \mu M$ ) and extracellular levels of D-serine ( $IC_{50} = 0.70 \pm 0.10 \mu M$ ; Singh et al., 2015; Table 3). Similar findings were observed using 1321N1 cells and primary hippocampal and cortical neuronal cells. Singh et al. (2015) also demonstrated that inhibition of the amino acid transporter, ASCT2, resulted in qualitatively similar effects to those induced by (*S*)-ketamine on D-serine levels. In addition, coincubation with sub-saturating concentrations of an ASCT2 inhibitor and (*S*)-ketamine resulted in an additive effect in both PC-12 cells and primary neuronal cells in regard to D-serine levels, indicating that the effects of (*S*)-ketamine might be due to an inhibition of the amino acid transporter systems.

The differential effects of ketamine's enantiomers on D-serine levels might contribute to their differential behavioral effects. Indeed, whereas (*S*)-ketamine is a more potent anesthetic and analgesic drug (Marietta et al., 1977; White et al., 1985) than (*R*)-ketamine, (*R*)-ketamine is a more potent and longer-lasting antidepressant than (*S*)-ketamine in several animal tests (Zhang et al., 2014; Yang et al., 2015; Zanos et al., 2016; Fukumoto et al., 2017). In fact, D-serine plays a role in synaptic plasticity (Henneberger et al., 2010), and baseline plasma D-serine levels are negatively correlated with ketamine treatment response in patients suffering from major depression (Moaddel et al., 2015a), indicating a possible role of D-serine levels in the antidepressant responses of ketamine (also see Hashimoto, 2014). In vivo, sub-chronic (14-day) administration of ketamine to rats was shown to reduce serine racemase mRNA levels in the forebrain (Watanabe et al., 2010). However, a single administration of ketamine at the dose of 50 mg/kg resulted in an enhancement of serine racemase mRNA levels in the striatum, hippocampus, and cortex of rats (Takeyama et al., 2006), an effect that is



predicted to induce an increase rather than a decrease in D-serine levels. Indeed, a single administration of (R)-ketamine (10 mg/kg, i.p.) slightly, but significantly increased cortical D-serine/L-serine ratio in mice (Ma et al., 2017). Therefore, further *in vivo* confirmation of the effects of ketamine and its enantiomers on D-serine levels is warranted.

DHNK has also been shown to modify D-serine levels. Singh et al. (2013) demonstrated that incubation of PC-12 and 1321N1 cells with 5–90 nM DHNK decreased the relative intracellular D-serine concentrations. Because DHNK is not produced in the brain and does not cross the blood-brain barrier in ketamine-treated rodents (Can et al., 2016; Moaddel et al., 2016), the behavioral relevance of this metabolite's actions on D-serine levels is not clear (Zanos et al., 2016).

HNKs are also capable of reducing intracellular D-serine concentrations in PC-12 cells, with (2*S*,6*S*)-HNK being more potent than (2*R*,6*R*)-HNK ( $IC_{50}$ s are reported to be  $0.18 \pm 0.04$  and  $0.68 \pm 0.09$  nM, respectively; Singh et al., 2016c). It is possible that the HNK-induced reduction of intracellular D-serine levels may also result in a reduction of extracellular levels of this amino acid. However, modulation of extracellular levels of D-serine may not be an important determinant of the antidepressant effects of HNKs, because at least in mice, (2*R*,6*R*)-HNK exerts more potent antidepressant actions than (2*S*,6*S*)-HNK (Zanos et al., 2016) and DHNK (Safat et al., 2015). In addition, electrophysiological studies failed to identify any inhibitory effects of antidepressant-relevant concentrations of these metabolites on NMDAR function (Zanos et al., 2016, 2017b; Suzuki et al., 2017), as decreased extracellular D-serine levels would predict. Moreover, acute D-serine administration induces ketamine-like antidepressant behavioral and biochemical responses in rats (Wei et al., 2017), further complicating the possible functional role of decreased extracellular D-serine levels following ketamine administration. Further verification, possibly using human brain-derived cells or measuring extracellular D-serine levels *in vivo* following administration of ketamine and/or its metabolites, would be informative in determining the functional relevance of these results.

### B. Hyperpolarization-Activated Cyclic Nucleotide-Gated Channels

HCN channels are voltage-gated cation channels (HCN1–HCN4; Luthi and McCormick, 1998; Wahl-Schott and Biel, 2009). Activation of these channels by membrane hyperpolarization is facilitated by cyclic nucleotides, including cAMP. In the central nervous system, HCN channels play a major role in controlling neuronal excitability, synaptic activity, and rhythmic oscillations (Shah, 2014).

There is a report of subunit-specific inhibitory effects of ketamine ( $EC_{50} = 8.2\text{--}15.6 \mu\text{M}$ ) on HCN1–HCN2

heteromeric channels and hyperpolarization-activated pacemaker currents ( $I_h$ ; Chen et al., 2009). This may be relevant to the anesthetic actions of ketamine, as ketamine-induced anesthesia was significantly suppressed in HCN knockout mice (Chen et al., 2009). Additionally, (*S*)-ketamine was found to be more potent at inhibiting these channels ( $EC_{50} = 4.1\text{--}7.4 \mu\text{M}$ ) compared with racemic ketamine ( $EC_{50} = 8.2\text{--}15.6 \mu\text{M}$ ; Chen et al., 2009), concordant with the greater anesthetic potency of (*S*)-ketamine. Indeed, it has been hypothesized that NMDAR inhibition is not the sole mechanism underlying the anesthetic properties of ketamine (Petrenko et al., 2014). Further studies are required to substantiate the exact role of HCN channel inhibition in this regard, and to replicate these findings.

In addition to a possible role in the anesthetic properties of ketamine, HCN1 channel inhibition may have a role in ketamine's antidepressant actions because reduced HCN1 activity in the hippocampus has been associated with antidepressant effects in rodents (Lewis et al., 2011; Kim et al., 2012; Han et al., 2017). Of interest, mice lacking the HCN1 gene did not manifest ketamine-induced reductions in immobility time in the forced-swim test following chronic oral corticosterone treatment (Li et al., 2014). Furthermore, following ketamine administration, these mice did not show increased sucrose preference or decreased latency to feed in the novelty-suppressed feeding test (Zhang et al., 2016). Unfortunately, these results cannot be unambiguously interpreted as evidence that HCN1 mediates the antidepressant effects of ketamine because HCN1 deletion by itself induced baseline behavioral changes compatible with reduced depressive-like behavior (e.g., decreased immobility in the forced-swim test). In addition, Zhang et al. (2016) suggested that reduction of HCN1 function by ketamine was secondary to inhibition of presynaptic NMDARs. The authors did not test the hypothesis that direct inhibition of HCN1 by ketamine, as was suggested by Petrenko et al. (2014), accounts for its antidepressant effects. There are currently no published data on the activity of ketamine's metabolites on the function of HCN1 channels or the involvement of these channels on the behavioral effects of these metabolites.

### C. GABA Uptake and GABA Receptors

The primary inhibitory neurotransmitter, GABA, activates both the ionotropic GABA receptor subtypes A and C (GABA<sub>A</sub> and GABA<sub>C</sub>) and the metabotropic GABA receptor subtype B (GABA<sub>B</sub>) in the brain (Jacob et al., 2008). Electrophysiological studies have revealed that high concentrations of ketamine potentiate GABAergic inhibitory postsynaptic currents in neurons of guinea pig olfactory cortical slices (300  $\mu\text{M}$ ; Scholfield, 1980) and of rat hippocampal slices (500  $\mu\text{M}$ ; Gage and Robertson, 1985). At high concentrations, ketamine potentiates GABA-activated GABA<sub>A</sub> receptors ectopically expressed

in *Xenopus* oocytes (365  $\mu\text{M}$ ; Lin et al., 1992) and HEK293 cells ( $>500 \mu\text{M}$ ;  $\text{EC}_{50} = 1.2 \text{ mM}$ ; Flood and Krasowski, 2000; but see Anis et al., 1983). There is also evidence for an inhibitory effect of ketamine on GABA uptake ( $K_i = 6.2 \pm 1.1$ ;  $\text{IC}_{50} = 50 \mu\text{M}$ ), as assessed by the [ $^3\text{H}$ ]GABA-binding assay in striatal synaptosomes of rats (Mantz et al., 1995), indicating that ketamine might cause an increase in extracellular GABA levels. Indeed, it was shown that intramuscular administration of ketamine to rats increases GABA content in the brain and in synaptosomal-enriched fractions of the brain (Wood and Hertz, 1980). However, the effect of ketamine on GABA uptake was not found at clinically relevant concentrations in mice ( $\text{IC}_{50} > 1000 \mu\text{M}$ ; Wood and Hertz, 1980).

The functional relevance of the actions of ketamine on GABA<sub>A</sub> receptors is not clear because ketamine concentrations required to modify the activity of these receptors are much higher than those achieved following ketamine administration in clinical settings for anesthetic, analgesic, anti-inflammatory, and antidepressant effects. Nevertheless, there is preclinical evidence for both agonist and antagonist properties of ketamine at GABA<sub>A</sub> receptors. For example, peripheral administration of subthreshold doses of ketamine (0.1 mg/kg, i.p.) combined with the GABA<sub>A</sub> receptor agonist muscimol (0.1 mg/kg, i.p.) induced a synergistic antidepressant behavioral response in the acute (30 minutes postinjection) forced-swim test in mice (Rosa et al., 2016). In contrast, direct infusion of muscimol into the infralimbic prefrontal cortex abolished the sustained (24 hours postinjection) antidepressant behavioral effects of ketamine in rats (Fuchikami et al., 2015), suggesting that the *in vivo* interaction between ketamine and GABA<sub>A</sub> receptors might be brain region specific. In addition, ketamine-associated delirium occurring at anesthetic doses (1–2 mg/kg, i.v. infusion) is effectively minimized via pretreatment with benzodiazepines (positive allosteric modulators of GABA<sub>A</sub> receptors; Dundee and Lilburn, 1978; Perumal et al., 2015). In contrast, Irifune et al. (2000) showed that both muscimol and the benzodiazepine receptor agonist diazepam augment ketamine-induced anesthesia, whereas the GABA<sub>A</sub> receptor antagonist bicuculline antagonizes ketamine-induced anesthesia in mice. Finally, at subanesthetic doses, ketamine does not bind to GABA<sub>A</sub> receptors in the human brain, as assessed by positron emission tomography (PET) scan imaging (Salmi et al., 2005), and does not alter GABA<sub>A</sub> receptor function at anesthetic-relevant concentrations (i.e., 10  $\mu\text{M}$ ) in HEK293 cells *in vitro* (Flood and Krasowski, 2000). These findings indicate that, at least at subanesthetic doses, ketamine itself might only indirectly affect GABA<sub>A</sub> receptor activity to exert any relevant behavioral effects. Indeed, it is postulated that ketamine-induced dissociation/psychotomimetic effects are due to NMDAR blockade on GABAergic inhibitory interneurons, an action that is presumed to disinhibit excitatory neurotransmission via

decreased GABA release, and to consequently reduce activation of the GABA<sub>A</sub> receptors in glutamatergic synapses (Moghaddam et al., 1997; Farber et al., 1998; Homayoun and Moghaddam, 2007; Hare et al., 2017; Wohleb et al., 2017).

#### D. Cholinergic Receptors

Ketamine is reported to bind to both muscarinic and nicotinic acetylcholine receptors (mAChRs and nAChRs, respectively). To date, five subtypes of mAChRs have been identified (M1–M5). These are metabotropic receptors that signal primarily, although not exclusively, through G<sub>ai/o</sub> (M1, M3, and M5) or G<sub>aq</sub> (Eglen, 2005). Binding of ketamine to the mAChR subtypes M1, M2, and M3 has been described. In particular, assessment of [ $^3\text{H}$ ]quinuclidinyl benzilate displacement revealed that (*S*)-ketamine has  $\sim$ twofold higher affinity than (*R*)-ketamine for mAChRs (Hustveit et al., 1995). In a subsequent study, Hirota et al. (2002) demonstrated that, with  $K_i$  values of approximately 45, 294, and 246  $\mu\text{M}$ , respectively, ketamine displaced [ $^3\text{H}$ ]N-methyl scopolamine binding to M1, M2, and M3 mAChRs ectopically expressed in Chinese hamster ovary (CHO) cells. However, the authors reported that ketamine had no significant effect on basal or methacholine-induced  $\text{Ca}^{2+}$  signals in M1-expressing CHO cells (Hirota et al., 2002). In contrast, Durieux (1995) reported that, at clinically relevant concentrations, ketamine inhibited M1 mAChR activation in *Xenopus* oocytes ( $\text{IC}_{50} = 5.7 \mu\text{M}$ ). The apparently discrepant results could be accounted for by the fact that receptors ectopically expressed in CHO cells and oocytes can have differential sensitivity (e.g., McIntyre et al., 2001). These findings suggest the need for additional studies to identify the exact effects of ketamine on mAChRs and the functional relevance of these effects.

In contrast to the metabotropic mAChRs, nAChRs are ionotropic receptors, which are nonselective cation channels activated by the neurotransmitter acetylcholine. These receptors are composed of five subunits. To date, 10  $\alpha$  ( $\alpha 1$ – $\alpha 10$ ) and four  $\beta$  ( $\beta 1$ – $\beta 4$ ) nAChR subunits have been cloned, and different combinations of these subunits give rise to a number of functional nAChR subtypes, which are expressed in neuronal and non-neuronal cells and have specific pharmacological, functional, and kinetic properties (Albuquerque et al., 2009).

Ketamine is reported to act as a noncompetitive, open-channel blocker of the  $\alpha 7$ ,  $\alpha 4\beta 2$ ,  $\alpha 4\beta 4$ , and  $\alpha 3\beta 4$  nAChR subtypes (Flood and Krasowski, 2000; Yamakura et al., 2000; Coates and Flood, 2001; Jozwiak et al., 2002; Pereira et al., 2002). Ketamine concentration dependently blocked acetylcholine (1 mM)-induced activation of  $\alpha 4\beta 4$  nAChRs ectopically expressed in *Xenopus* oocytes ( $\text{IC}_{50} = 0.24 \pm 0.03 \mu\text{M}$ ), with complete inhibition being achieved with 10  $\mu\text{M}$  ketamine (Flood and Krasowski, 2000). In addition, with  $\text{IC}_{50}$  values of

20 and 50  $\mu\text{M}$ , respectively, ketamine inhibited acetylcholine (1 mM)-induced activation of  $\alpha 7$  and  $\alpha 4\beta 2$  nAChRs ectopically expressed in oocytes (Coates and Flood, 2001). Moreover, Moaddel et al. (2013) showed that ketamine inhibits nicotine-induced  $\alpha 3\beta 4$  nAChR activation ( $\text{IC}_{50} = 3.1 \mu\text{M}$ ). Because ketamine concentrations up to  $\sim 10 \mu\text{M}$  are within the clinically relevant range, some nAChR subtypes may underlie the effects of ketamine in vivo.

Moaddel et al. (2013) also demonstrated that at 100 nM (*R,S*)-DHNK reduced the amplitude of acetylcholine-induced whole-cell currents in KX $\alpha 7$ R1 cells that ectopically express  $\alpha 7$  nAChRs by approximately 60%. At the same concentration, the metabolites (*2S,6S*)-HNK, (*2R,6R*)-HNK, and (*R,S*)-norketamine also reduced the amplitude of acetylcholine-induced  $\alpha 7$  nAChR currents by approximately 54%, 51%, and 45%, respectively (Moaddel et al., 2013). In this study, the authors reported that (*R,S*)-DHNK was not acting as a channel blocker at  $\alpha 7$  nAChRs, because its inhibitory effect was voltage independent. Moreover, (*R,S*)-DHNK did not bind at the agonist-binding site of the  $\alpha 7$  nAChRs, because it did not displace  $\alpha$ -bungarotoxin binding, suggesting that this metabolite might be acting as a negative allosteric modulator (Moaddel et al., 2013).

The  $\alpha 7$  nAChR antagonist activity of ketamine metabolites may have implications for the antidepressant action of ketamine. It is noteworthy in this context that blockade of  $\alpha 7$  nAChRs results in antidepressant effects in rodent models (Mineur and Picciotto, 2010; Philip et al., 2010). Thus, modulation of  $\alpha 7$  nAChR activity could also be one of the underlying mechanisms involved in ketamine's antidepressant actions, possibly through its metabolites. In support of this hypothesis, nAChR antagonists are already in clinical trials for the treatment of depression (Mineur and Picciotto, 2010; Philip et al., 2010).

Other nAChR subtypes are also sensitive to inhibition by therapeutically relevant concentrations of ketamine metabolites. Specifically, in KX $\alpha 3\beta 4$ R2 cells stably expressing rat  $\alpha 3\beta 4$  nAChRs, ketamine and (*R,S*)-norketamine were reported to inhibit the  $\alpha 3\beta 4$  nAChR with  $\text{IC}_{50}$  values of approximately 3.1 and 9.1  $\mu\text{M}$ , respectively, whereas DHNK, (*2S,6S*)-, or (*2R,6R*)-HNK did not have any significant effect on these receptors ( $\text{IC}_{50} > 200 \mu\text{M}$ ; Moaddel et al., 2013). Therefore, one cannot rule out the possibility that  $\alpha 3\beta 4$  nAChRs also contribute to the pharmacological effects of ketamine.

### E. Monoaminergic Receptors and Transporters

Dopamine (DA) and serotonin [5-hydroxytryptamine (5-HT)] receptors are metabotropic receptors, with the exception of the 5-HT receptor subtype 3, which is ionotropic. Five different subtypes of DA receptors ( $\text{D}_{1-5}\text{R}$ ) and seven subtypes of 5-HT receptors (5-HT $_{1-7}\text{R}$ ) have been characterized in the central nervous system (De Felice, 2017). Neurotransmitter transporters regulate DA and 5-HT uptake across the cellular/intracellular

membranes and play a key role in the regulation of dopaminergic and serotonergic neurotransmission.

Although there is some evidence that ketamine may act on DA receptors and transporters (see Table 3), there is also conflicting evidence indicating that ketamine does not directly alter dopaminergic signaling; also see Kokkinou et al. (2018). Ketamine was reported to have high affinity (0.06–1.0  $\mu\text{M}$ ) for  $\text{D}_2$  receptors ( $\text{D}_2\text{Rs}$ ; Kapur and Seeman, 2002; Seeman et al., 2005) and to act as a partial agonist at these receptors ( $\text{EC}_{50} = 0.9 \pm 0.4 \mu\text{M}$ ). This partial agonist activity at  $\text{D}_2\text{Rs}$  was suggested to contribute to the psychotomimetic effects of ketamine (Kapur and Seeman, 2002; Seeman et al., 2005). This is further supported by the finding that a ketamine-induced decrease in  $\text{D}_2\text{R}$  binding is significantly correlated with schizophrenia-related symptoms in humans, as measured by PET scanning (Breier et al., 1998).

There are several published studies reporting ketamine-induced decreases in striatal  $\text{D}_2\text{R}$  binding (an indirect measure of DA release) in humans. Specifically, subanesthetic doses of ketamine (i.v. bolus of ketamine; 0.12 mg/kg), followed by an i.v. infusion of 0.65 mg/kg ketamine over 60 minutes (0.29–0.45  $\mu\text{M}$ ; Breier et al., 1998), 0.5 mg/kg ketamine over 20 minutes (Smith et al., 1998), or 0.014 mg/kg per minute (*S*)-ketamine for 90 minutes (Vollenweider et al., 2000) decreased striatal  $\text{D}_2\text{R}$  binding. However, subsequent studies have failed to replicate these findings using single-photon emission computed tomography/PET techniques. In particular, when ketamine was administered as an i.v. bolus (0.12 mg/kg) followed by a constant 70-minute i.v. infusion (0.65 mg/kg per hour), resulting in an average plasma concentration of  $0.59 \pm 0.22 \mu\text{M}$  in healthy individuals, there was no change in  $\text{D}_2\text{R}$  availability in striatal regions of the brain (Kegeles et al., 2002). Similarly, i.v. infusion of ketamine (66-minute infusion yielding a stable plasma ketamine concentration of  $1.23 \pm 0.12 \mu\text{M}$ ) in healthy male volunteers did not alter striatal  $\text{D}_2\text{R}$  binding (Aalto et al., 2002). In accordance with the lack of direct effects of subanesthetic doses of ketamine on the dopamine  $\text{D}_2\text{R}$ , psychotomimetic effects of a 0.23 mg/kg bolus or 0.65 mg/kg per hour infusion of ketamine were not blocked by administration of a  $\text{D}_2\text{R}$  antagonist in humans (Krystal and D'Souza, 2001). In addition, ketamine was not found to modify electrically evoked accumbal DA release measured in real-time using fast-scan cyclic voltammetry in mice (Can et al., 2016). In contrast to the previously mentioned studies, it was also reported that ketamine lacks functional agonist and antagonist activity on all of the DA receptor subtypes at concentrations up to 10  $\mu\text{M}$  (Can et al., 2016).

Inhibition of the DA transporter by ketamine in HEK293 cells has also been reported ( $K_i = 62.9 \mu\text{M}$ ; Nishimura et al., 1998). However, this effect did not occur at concentrations up to 10  $\mu\text{M}$  (Can et al., 2016).

Because this effect was only observed at relatively high concentrations, its functional/clinical relevance remains to be determined.

Ketamine was also reported to bind to 5-HT<sub>2</sub> receptors with an affinity of  $15 \pm 5 \mu\text{M}$  (Kapur and Seeman, 2002). This finding might be relevant to the analgesic effects of the drug, because the 5-HT<sub>2B/2C</sub> receptor antagonist methysergide inhibited the analgesic effects of ketamine in rats (Crisp et al., 1991), implicating serotonergic signaling in the mechanisms of ketamine analgesia. Moreover, ketamine administration induced an increase in extracellular serotonin (5-HT) levels in the prefrontal cortex and dorsal raphe nucleus of mice (Pham et al., 2017b).

In nonhuman primates, ketamine administration was shown to significantly increase accumbal and ventral pallidum 5-HT<sub>1B</sub> receptor binding, an effect that was blocked by pretreatment with the  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo[f]quinoxaline-2,3-dione (NBQX; Yamanaka et al., 2014). This finding may suggest that this effect of ketamine is involved in its antidepressant actions because AMPA receptor activation is a convergent mechanism of ketamine's antidepressant actions, and NBQX administration abolishes ketamine's effects in several animal tests of antidepressant efficacy (Maeng et al., 2008; Autry et al., 2011; Koike et al., 2011; Walker et al., 2013; Fukumoto et al., 2014; Koike and Chaki, 2014; Zhou et al., 2014; Yang et al., 2015; Zanos et al., 2016; Zanos et al., 2018b,c). Antagonist actions of ketamine on 5-HT<sub>3</sub> receptors have been reported, but these occur at higher than clinically relevant concentrations ( $K_i > 90 \mu\text{M}$ ;  $IC_{50} > 100 \mu\text{M}$ ; Appadu and Lambert, 1996; Yamakura et al., 2000; Ho and Flood, 2004).

Several studies suggest that increased 5-HT levels are necessary for the antidepressant-like effects of ketamine in rodents. For instance, pharmacological treatments that reduce 5-HT levels in the brain abolished ketamine's antidepressant behavioral effects in the forced-swim test (du Jardin et al., 2016; Pham et al., 2017b) and in the novelty-suppressed feeding test (Fukumoto et al., 2014) in rodents. In addition, higher extracellular 5-HT levels were positively correlated with ketamine's antidepressant activity in the forced-swim test in mice (Pham et al., 2017b). Whether these effects are due to a direct action of ketamine on 5-HT receptors is not clear and needs further investigation. Nevertheless, there are also conflicting data on the effects of ketamine on 5-HT receptors, because even at very high concentrations (1 mM) ketamine only slightly altered [<sup>3</sup>H]5-HT or [<sup>3</sup>H]spiroperidol binding to 5-HT<sub>1</sub> or 5-HT<sub>2</sub> receptors, respectively (Martin et al., 1982). It is thus possible that ketamine may interact with serotonin uptake as opposed to directly binding to serotonin receptors. Indeed, administration of antidepressant

doses of ketamine (1.5 mg/kg; 40-minute infusion) to nonhuman primates reduced serotonin transporter (SERT) activity (Yamamoto et al., 2013), an effect that was hypothesized to reflect direct binding of ketamine to SERTs to regulate 5-HT reuptake. However, in vitro work indicated that ketamine inhibits SERTs at concentrations ranging from 75 (Azzaro and Smith, 1977) to 162  $\mu\text{M}$  (Nishimura et al., 1998), which are not only above the antidepressant-relevant concentrations, but also well above the clinical anesthetic concentrations of ketamine. At antidepressant-relevant concentrations, ketamine does not have an agonist or antagonist effect on SERTs (Can et al., 2016). Therefore, in vivo evidence of ketamine-induced inhibition of serotonin reuptake (Martin et al., 1982) could be attributed to indirect interactions of ketamine with the serotonergic system, at least at subanesthetic concentrations.

Finally, although there is some evidence that ketamine acts as an uptake inhibitor at norepinephrine transporters (NETs;  $K_i = 66.8 \mu\text{M}$ ; Nishimura et al., 1998), the inhibition constant indicates that ketamine would not modulate NET function at clinically relevant concentrations (up to 10  $\mu\text{M}$ ). There is also a noted lack of functional activity of clinically relevant concentrations of ketamine (up to 10  $\mu\text{M}$ ) on NETs (Can et al., 2016).

To date, there is only one published study assessing the effect of ketamine's metabolites on monoaminergic receptors and transporters. At concentrations up to 10  $\mu\text{M}$  there was no agonist or antagonist activity of (*S*)-norketamine, (*R*)-norketamine, (*S*)-dehydronorketamine, (*R*)-dehydronorketamine, (2*S*,6*S*)-HNK, or (2*R*,6*R*)-HNK on D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub>, or D<sub>5</sub> receptors; DA transporter; NET; or SERT (Can et al., 2016). Although these findings suggest that direct effects of ketamine metabolites on DA receptors or monoaminergic transporters do not account for the antidepressant actions of ketamine, it cannot be ruled out that, at higher concentrations, ketamine's metabolites may interact with and directly or indirectly modify the activity of these receptors and transporters.

#### F. Opioid Receptors

Opioid receptors are expressed throughout the central nervous system as well as in peripheral tissues (Trescot et al., 2008). These receptors are G protein-coupled receptors and are classified into three subtypes ( $\mu$ -,  $\delta$ -, and  $\kappa$ -opioid receptors) (Kieffer and Gaveriaux-Ruff, 2002). A primary function of opioid receptor activation is inhibiting the transmission of nociceptive stimuli, resulting in analgesia (Trescot et al., 2008; Stein, 2016).

Ketamine was reported to activate human recombinant  $\mu$ -,  $\kappa$ -, and  $\delta$ -opioid receptors expressed in CHO cells ( $K_i = 42.1, 28.1, \text{ and } 272 \mu\text{M}$ , respectively; Hirota et al., 1999). (*S*)-ketamine was shown to have higher affinity compared with (*R*)-ketamine for binding to opioid receptors. In particular, (*S*)-ketamine's affinities

range from 11 to 29  $\mu\text{M}$  for the  $\mu$ -, 25–28  $\mu\text{M}$  for the  $\kappa$ -, and 130–205  $\mu\text{M}$  for the  $\delta$ -opioid receptors (Hustveit et al., 1995; Hirota et al., 1999; Nemeth et al., 2010). In contrast, (*R*)-ketamine has affinities ranging from 28 to 84  $\mu\text{M}$  for the  $\mu$ -, 60–100  $\mu\text{M}$  for the  $\kappa$ -, and 130–286  $\mu\text{M}$  for the  $\delta$ -opioid receptors (Hustveit et al., 1995; Hirota et al., 1999). Similar to these findings, (*S*)-ketamine ( $\text{IC}_{50} = 23.0 \pm 1.2 \mu\text{M}$ ) showed higher potency to bind and displace the non-specific opioid ligand [ $^3\text{H}$ ]dihydromorphine compared with the racemic ketamine ( $\text{IC}_{50} = 16.3 \pm 7.4 \mu\text{M}$ ) and (*R*)-ketamine ( $\text{IC}_{50} = 45.5 \pm 3.2 \mu\text{M}$ ; Finck and Ngai, 1982).

The actions of ketamine at opioid receptors are hypothesized to be involved in its analgesic effects (Finck et al., 1988; Pacheco Dda et al., 2014), and these findings are consistent with the higher potency of (*S*)-ketamine in measures of antinociception compared with (*R*)-ketamine (White et al., 1980; Oye et al., 1992; Mathisen et al., 1995). However, the exact roles of opioid receptors in mediating these effects are unclear.

Although the analgesic actions of ketamine are blocked by intracerebroventricular administration (i.e., direct brain exposure) of  $\mu$ - and  $\delta$ -, but not  $\kappa$ -opioid receptor antagonists in mice (Pacheco Dda et al., 2014), global opioid receptor inhibition achieved by systemic administration of naloxone does not prevent ketamine-induced analgesia in humans (Mikkelsen et al., 1999). These seemingly opposing findings indicate that ketamine might induce analgesia via an indirect interaction with the opioid system, or may exert an opioid receptor subtype-specific action. In support of such a subtype-specific effect, *in vivo* evidence indicates that ketamine might be a  $\kappa$ -opioid receptor agonist and a  $\mu$ -opioid receptor antagonist. Specifically, ketamine microinjection in the periaqueductal gray region, which contains  $\mu$ - but not  $\kappa$ -opioid receptors, did not exert antinociceptive effects, but blocked the effects of the  $\mu$ -opioid receptor agonist, morphine, in the same region (Smith et al., 1985). This could explain the failure of naloxone to block ketamine-induced analgesia and supports a subtype-specific role of opioid receptors in ketamine-induced analgesia. However, it should be noted that these findings are in opposition of the results of Pacheco Dda et al. (2014), as discussed above. Furthermore, it has been reported that sub-effective doses of ketamine only partially antagonize the cataleptic actions of morphine in rats (Hance et al., 1989); however, a combination of sub-effective doses of ketamine and morphine induced catalepsy in the same experimental settings (Hance et al., 1989). Altogether, these findings implicate the opioid system in ketamine's analgesic effects, but further studies are needed to clarify the exact mechanisms. Interactions between ketamine and the opioid system may be more relevant in chronic pain, in which ketamine reduces opioid tolerance. In particular, via acting on the downstream extracellular signal-regulated kinase

1/2 pathway, ketamine (10  $\mu\text{M}$ ) abolished  $\mu$ -opioid receptor-induced desensitization *in vitro* (Gupta et al., 2011).

Activation of  $\kappa$ -opioid receptors by ketamine ( $\text{EC}_{50} = 29 \mu\text{M}$ ) was reported to be involved in ketamine's effects on attention and visual perception in rats assessed in the five-choice serial reaction time task (Nemeth et al., 2010). Pretreatment with a selective  $\kappa$ -opioid receptor antagonist blocked the ability of ketamine (20 mg/kg) to impair attention and visual perception (Nemeth et al., 2010). In contrast, in healthy volunteers, inhibition of opioid receptors by naloxone augmented the dissociative and cognitive deficit effects induced by a subthreshold administration of ketamine (1-minute 0.23 mg/kg bolus, followed by a 60-minute 0.58 mg/kg ketamine infusion; Krystal et al., 2006), possibly indicating an antagonist activity of low doses of ketamine on the opioid receptors *in vivo*. Nevertheless, further work is needed to establish the exact role of opioid receptor modulation in mediating the side effects of ketamine. There are currently no published studies assessing the effects of ketamine's metabolites on opioid receptors. However, there is recent evidence indicating that (2*R*,6*R*;2*S*,6*S*)-HNK (at 10 and/or 30 mg/kg, *s.c.*) does not possess antinociceptive properties and does not alter opioid (morphine) tolerance in rats (Lilius et al., 2018a), indicating a possible lack of interactions between this metabolite and the opioid receptor system. Notably, norketamine, similar to ketamine, attenuates tolerance to morphine (Lilius et al., 2018b).

### G. Sigma Receptors

Another potential site of action of ketamine is the sigma receptor. Sigma receptors are classified into two different subtypes, sigma I and II receptors ( $\sigma_1\text{R}$  and  $\sigma_2\text{R}$ , respectively; Bowen et al., 1989). Although a third subtype has also been suggested to exist ( $\sigma_3\text{R}$ ), it has not been fully defined (Myers et al., 1994).

As illustrated in Table 3, ketamine binding has been described at both  $\sigma_1\text{R}$  and  $\sigma_2\text{R}$  (Smith et al., 1987; Hustveit et al., 1995; Robson et al., 2012). The first evidence of direct binding of ketamine to sigma receptors came from Klepstad et al. (1990), who demonstrated that (*R*)-ketamine has a potency of  $\text{IC}_{50} = \sim 15 \mu\text{M}$  to bind to sigma receptors, whereas (*S*)-ketamine has an  $\text{IC}_{50}$  of  $\sim 100 \mu\text{M}$ . Although these findings were qualitative and not absolutely quantitative due to the different brain regions used for the binding studies, Hustveit et al. (1995) confirmed these initial findings by showing that (*R*)-ketamine has an affinity of 19  $\mu\text{M}$  at sigma receptors, whereas (*S*)-ketamine shows  $\sim 15$ -fold lower binding affinity for these receptors (131  $\mu\text{M}$ ). Robson et al. (2012) reported that (*R,S*)-ketamine has a preferential affinity for the  $\sigma_2\text{R}$  ( $K_i = 26.3 \mu\text{M}$ ) compared with the  $\sigma_1\text{R}$  ( $K_i = 139.6 \mu\text{M}$ ). In support of such binding *in vivo*, studies in nonhuman primates showed competition binding between ketamine and [ $^{11}\text{C}$ ]SA5845, a sigma receptor PET tracer (Kortekaas et al., 2008).

Sigma receptors are promising targets for antidepressant treatment (Fishback et al., 2010), and activation of these receptors induces antidepressant behavioral responses in animals (Matsuno et al., 1996; Skuza and Rogoz, 2002; Wang et al., 2007; Lucas et al., 2008) and humans (Pande et al., 1999). As a result it could be postulated that the action of ketamine on sigma receptors is involved in the mechanisms underlying its antidepressant responses, consistent with (*R*)-ketamine's higher binding affinity for these receptors, and its more potent antidepressant effects compared with (*S*)-ketamine in rodent models (Zhang et al., 2014; Yang et al., 2015; Zanos et al., 2016; Fukumoto et al., 2017).

Although administration of  $\sigma_1$ R and  $\sigma_2$ R antagonists did not attenuate the antidepressant behavioral effects of ketamine in mice (Robson et al., 2012), administration of a  $\sigma_1$ R-selective antagonist blocked the potentiating effects of ketamine on nerve growth factor-induced neurite outgrowth, and thus, modulation of neuroplasticity-related pathways (Robson et al., 2012) that are involved in the antidepressant effects of the drug (see Kavalali and Monteggia (2012), Gerhard et al. (2016)). These findings may indicate that ketamine's actions on sigma receptors could be involved in the neuroplasticity-related effects of the drug, and thus indirectly involved in its antidepressant actions. There is currently no evidence of activity of ketamine's metabolites on sigma receptors.

#### H. Voltage-Gated Sodium Channels

Voltage-gated ion channels are among the first identified ion channels and are involved in the generation of action potentials (Hodgkin and Huxley, 1952). Local anesthetics typically induce concentration-dependent inhibition of sodium channel activity, via binding to sites within the channel pore (Becker and Reed, 2012). Whereas ketamine has been shown to act as a local anesthetic in veterinary practice and in human patients (Bion, 1984; Gomez de Segura et al., 1998; Hawksworth and Serpell, 1998; Kathirvel et al., 2000), there is currently conflicting evidence regarding the effects of ketamine on voltage-gated sodium channel activity.

In isolated guinea pig ventricular myocytes, ketamine at concentrations ranging from 30 to 300  $\mu$ M induced a concentration-, but not use-dependent tonic inhibition of sodium channel currents (16%–36% inhibition; Hara et al., 1998b). In contrast, both tonic ( $IC_{50} = 866.2 \pm 34.7 \mu$ M) and phasic ( $IC_{50} = 314.8 \mu$ M) blockade of sodium channels was induced by ketamine in rat dorsal root ganglion neurons (Zhou and Zhao, 2000). In addition, ketamine was reported to block voltage-gated sodium channels in *Xenopus* oocytes (tonic inhibition:  $IC_{50} = 800 \mu$ M; phasic inhibition:  $IC_{50} = 2.3$  mM; Wagner et al., 2001). Moreover, although Benoit (1995) demonstrated no inhibitory effect of ketamine on nodal sodium-channel currents of myelinated nerve fibers, others have reported up to 71.1% blockade of sodium channel

conductance by ketamine ( $ED_{50} = 1.1$  mM; Frenkel and Urban, 1992). A study assessing the effects of (*S*)- and (*R*)-ketamine on the activity of sodium channels showed that (*S*)-ketamine inhibits voltage-gated sodium channels with an apparent potency of  $240 \pm 60$  and  $59 \pm 10 \mu$ M in neuronal and skeletal muscle isoforms, respectively. The potency of (*R*)-ketamine to block sodium channels was lower ( $IC_{50} = 333 \pm 93$  and  $181 \pm 49 \mu$ M in neuronal and skeletal muscle isoforms, respectively; Haeseler et al., 2003) than that of (*S*)-ketamine. Similarly, Schnobel et al. (2005) showed stereoselective tonic block of voltage-gated sodium currents with (*S*)-ketamine being more potent than (*R*)-ketamine ( $IC_{50} = 128$  and  $269 \mu$ M, respectively). These findings predict that (*S*)-ketamine is a more effective local anesthetic than (*R*)-ketamine.

These discrepancies in the effects of ketamine on the activity of sodium channels might be due to differences in the cell populations and experimental procedures used. Overall, these findings support an inhibitory effect of ketamine on sodium channels, which is a characteristic of local anesthetics (Becker and Reed, 2012). These effects occur at concentrations well above circulating ketamine levels relevant for general anesthesia, but could possibly be relevant to local ketamine anesthesia.

#### I. L-Type Voltage-Dependent Calcium Channels

The L-type voltage-dependent calcium channel (VDCC) family consists of four different members referred to as  $Ca_v1.1$ – $Ca_v1.4$  (Catterall, 2011).  $Ca_v1.2$  is the main LTCC expressed in the mammalian brain (Bhat et al., 2012). Antagonism of L-type VDCCs by ketamine has been reported over a wide range of concentrations. In porcine tracheal smooth muscle cells, for example, ketamine blocked VDCCs with an  $IC_{50}$  of 1 mM (Yamakage et al., 1995). In rabbit portal vein smooth cells, 1 mM ketamine completely inhibited VDCC currents (Yamazaki et al., 1992). Finally, in bullfrog single atrial cells, ketamine inhibited VDCC currents with an  $IC_{50}$  of 9.2  $\mu$ M (Hatakeyama et al., 2001). This effect was not use-dependent, and ketamine did not act as an open channel blocker. Nonuse-dependent tonic inhibition of VDCCs was also reported in isolated guinea pig ventricular myocytes, in which 30–300  $\mu$ M induced a 26%–53% inhibition (Hara et al., 1998b). The discrepancies in the reported concentrations at which ketamine inhibits VDCCs may be due to differences in species, cell type, or experimental preparations (e.g., differences in bath solutions).

Despite evidence of VDCC inhibition by ketamine, an in vitro study showed that AMPA receptor activation and subsequent increases in brain-derived neurotrophic factor release and mechanistic target of rapamycin complex 1 activation—actions that are believed to underlie ketamine's antidepressant properties—require VDCC activation (Jourdi et al., 2009). Furthermore, ketamine's antidepressant effects in mice are blocked by

pretreatment with L-type calcium channel antagonists (Lepack et al., 2014). These findings are not in line with the inhibitory activity of ketamine at these channels, as previously described. However, it should be noted that these studies were performed in cells derived from peripheral tissues (e.g., heart, trachea) and that effects of ketamine on VDCCs in brain-derived cells at antidepressant-relevant concentrations have not been reported to our knowledge. In addition to the possible role of ketamine-induced inhibition of calcium channels in mediating the antidepressant actions of the drug, blockade of calcium channels has been also hypothesized to be involved in the psychoactive/psychotomimetic effects of ketamine (Lisek et al., 2016).

#### IV. Conclusions

Ketamine has been in clinical use as an anesthetic since the 1970s. However, novel use indications (e.g., chronic pain and depression) and mechanisms of action (e.g., HNK metabolites) are still emerging. Its use as an anesthetic, analgesic, anti-inflammatory, and antidepressant drug has reignited research to understand the neurobiological mechanisms underlying these effects of ketamine, as well as its metabolites, and several molecular and cellular targets have been identified to date.

Ketamine is typically used clinically (and in preclinical research) as the racemic mixture, (*R-S*)-ketamine. It is extensively and rapidly metabolized in vivo, resulting in the formation of norketamine and HKs, followed by production of the secondary metabolites, DHNK and the HNKs. Although ketamine, norketamine, and HNKs readily cross the blood-brain barrier, DHNK does not appear to reach pharmacologically active brain concentrations, at least in the mouse brain (Can et al., 2016). Ketamine, and to a lesser extent, norketamine, are noncompetitive antagonists of the NMDAR ion channel. DHNK and HNKs, however, appear to have much lower potency to inhibit the NMDAR, if at all (Morris et al., 2017; Suzuki et al., 2017; Zanos et al., 2017a).

In addition to the NMDAR, we reviewed findings supporting ketamine's actions at a number of receptors and ion channels, including DA, 5-HT, opioid, cholinergic, sigma, and GABA<sub>A</sub> receptors, as well as monoamine transporters and HCN, sodium, and L-type VDCCs. Ketamine's well-characterized anesthetic effects are primarily attributed to NMDAR inhibition. However, there is evidence that HCN channel inhibition might also be involved in the anesthetic properties of ketamine. Similarly, evidence implicates NMDAR inhibition in the analgesic actions of ketamine, with the possibility of opioid receptors also playing a role.

##### A. (*R*)- and (*S*)-Ketamine as Antidepressants

Much attention has focused upon the NMDAR as the primary pharmacological target responsible for ketamine's antidepressant actions. However, in contrast to this

prediction, clinical studies have suggested no—or only modest—antidepressant efficacy of some alternative NMDAR antagonists. To date, these drugs lack the robust, rapid, or sustained antidepressant effectiveness of ketamine, and some (e.g., memantine) have been proven clinically ineffective in multiple studies (Newport et al., 2015). Moreover, Hashimoto and colleagues first reported superior and longer-lasting antidepressant actions of (*R*)-ketamine compared with (*S*)-ketamine in rodent models (Zhang et al., 2014; Yang et al., 2015; Fukumoto et al., 2017). These findings were also supported by Zanos et al. (2016), who showed that (*S*)-ketamine's antidepressant behavioral effects only become apparent at higher doses compared with (*R*)-ketamine. The increased potency of (*R*)-ketamine does not seem to be related to a U-shaped dose response of the drugs, as it has been shown more potent compared with (*S*)-ketamine with up to a 30-fold range of doses in multiple mouse tests of antidepressant efficacy (Zanos et al., 2016; Fukumoto et al., 2017). Administration of equal doses of (*R*)- and (*S*)-ketamine did not yield different levels of these enantiomers in the brains of rodents (Zanos et al., 2016; Fukumoto et al., 2017), indicating that increased antidepressant potency of (*R*)-ketamine in rodent models is not due to greater brain levels of the drug. These preclinical rodent data indicate that (*R*)-ketamine is a more potent antidepressant compared with the (*S*)-ketamine enantiomer (Zhang et al., 2014; Yang et al., 2015; Zanos et al., 2016; Fukumoto et al., 2017), suggesting that it is unlikely that ketamine exerts its antidepressant actions solely via inhibition of the NMDAR (Zanos et al., 2018a). Nevertheless, we note that preclinical rodent studies have also indicated rapid-acting antidepressant behavioral actions of (*S*)-ketamine in mice (Zhang et al., 2014; Yang et al., 2015; Zanos et al., 2016; Fukumoto et al., 2017).

The finding that ketamine exerts rapid antidepressant actions, within hours of administration, has focused extensive research efforts on understanding this phenomenon. This finding and elucidation of the relevant mechanisms involved have the potential to revolutionize the treatment of depression, considering that currently approved antidepressants take weeks or even months to exert their full antidepressant effects (Rush et al., 2006), and many patients suffering from major depressive disorders are resistant to classic antidepressant pharmacotherapies. Similar to racemic ketamine, clinical human studies in depressed patients have indicated that a 40-minute, i.v. infusion of (*S*)-ketamine exerts rapid antidepressant actions (within 2 hours of administration; Singh et al., 2016a). In addition, there are reported dose-dependent antidepressant actions of intranasally administered (*S*)-ketamine (dose of 28–84 mg, twice per week for a total of 2 weeks) in treatment-resistant depressed patients under oral classic antidepressant treatment (Daly et al., 2018). (*S*)-ketamine is currently in phase III clinical trials as an antidepressant (Andrade, 2017a).

If in human depression, as is the case in mouse models, (*R*)-ketamine has superior potency to (*S*)-ketamine, this would have advantages considering its fewer side effects due to less potent inhibition of the NMDAR (see section *N-Methyl-D-Aspartate Receptors*). However, there are currently no published clinical studies assessing the antidepressant efficacy of (*R*)-ketamine in depressed patients. Furthermore, there are no published clinical studies directly comparing the antidepressant actions of the (*S*)- and (*R*)-ketamine enantiomers, or comparing the actions of either enantiomer to the racemic mixture.

### B. Utility of Ketamine's Hydroxynorketamine Metabolites as Drug Treatments

It was reported that metabolism of ketamine is necessary for its full antidepressant actions in mice (Zanos et al., 2016). Specific HNK metabolites of ketamine, (*2S,6S*)-HNK, and (*2R,6R*)-HNK, derived from the metabolism of (*S*)-ketamine and (*R*)-ketamine, respectively, do not bind to or functionally inhibit the NMDAR at antidepressant-relevant concentrations (Morris et al., 2017; Suzuki et al., 2017; Zanos et al., 2017a), but do exert antidepressant behavioral effects similar to those observed following administration of ketamine itself (Zanos et al., 2016). These findings further challenge the NMDAR inhibition hypothesis of ketamine's antidepressant actions. In addition, (*2R,6R*)-HNK exerts antidepressant effects without the sensory dissociation, ataxia, and abuse liability of ketamine in animal tests (Zanos et al., 2016). Indeed, the psychoactive side effects of ketamine, including dissociation and changes in sensory perception, as well as its abuse potential, have been attributed to the NMDAR-inhibition effects of ketamine (Shaffer et al., 2014).

The recent findings that ketamine metabolites are involved in the antidepressant actions of ketamine suggest the possible use of these metabolites in the treatment of depression and open new paths for investigating their role in other brain disorders. As we discussed earlier, HNK metabolites may contribute to the clinical effects of subanesthetic doses of ketamine, perhaps due to their direct actions on nAChRs (Moaddel et al., 2013), indirect actions on D-serine (Singh et al., 2013, 2016c), or other targets that have not yet been identified. This work may provide a framework for a novel ketamine metabolite paradigm, which posits clinically relevant effects dependent upon metabolic conversion of ketamine, but it does not involve NMDAR inhibition (Singh et al., 2014). Nevertheless, future preclinical studies are needed to support the contention that NMDAR inhibition is not required for the effectiveness of ketamine's metabolites as fast-acting antidepressants and to identify the underlying mechanism of action of these metabolites. It also remains to be investigated whether ketamine metabolites have a role in the anti-inflammatory or analgesic actions of ketamine.

### C. Future Directions

Identification of the targets responsible for the different behavioral effects of ketamine, and potentially its metabolites, is critical for the development of novel pharmacotherapies that will lack the side effects of ketamine, including psychotomimetic effects, changes in sensory perception, and abuse potential. In addition to the recently completed studies in preclinical depression models (Zanos et al., 2016), studies of ketamine metabolites in animal models of pain, inflammation, depression, and suicidality (see Gould et al., 2017) are essential to better understand their therapeutic potential. Expanded clinical use of racemic ketamine, (*S*)-ketamine, (*R*)-ketamine, and potentially key metabolites [i.e., (*2R,6R*)-HNK] represents an important opportunity to define new therapies for unmet medical conditions and to better define pharmacology–phenotype relationships. Notably, clinical exploration of these agents is feasible given the historical safety knowledge surrounding racemic and enantio-pure forms of ketamine (and thus its metabolites) when given acutely. As such, investments in alternate routes of administration, dosing strategies, and drug combination assessments are not overly burdensome. Furthermore, the breadth of potential indications coupled to ketamine's multiple pharmacological targets offers an unprecedented window of insight into new mechanisms for future therapeutic interventions. Given these factors, it is clear that the comprehensive understanding of ketamine and ketamine metabolite pharmacology presents invaluable opportunities in both basic and translational research and clinical care.

#### Authorship Contributions

*Wrote or contributed to the writing of the manuscript:* Zanos, Moaddel, Morris, Riggs, Highland, Georgiou, Pereira, Albuquerque, Thomas, Zarate, Gould.

#### References

- Aalto S, Hirvonen J, Kajander J, Scheinin H, Nägren K, Vilkkumäki H, Gustafsson L, Syvälahti E, and Hietala J (2002) Ketamine does not decrease striatal dopamine D2 receptor binding in man. *Psychopharmacology (Berl)* **164**:401–406.
- Abel KM, Allin MP, Hemsley DR, and Geyer MA (2003) Low dose ketamine increases prepulse inhibition in healthy men. *Neuropharmacology* **44**:729–737.
- Adamowicz P and Kala M (2005) Urinary excretion rates of ketamine and norketamine following therapeutic ketamine administration: method and detection window considerations. *J Anal Toxicol* **29**:376–382.
- Adams JD Jr, Baillie TA, Trevor AJ, and Castagnoli N Jr (1981) Studies on the biotransformation of ketamine: 1-Identification of metabolites produced in vitro from rat liver microsomal preparations. *Biomed Mass Spectrom* **8**:527–538.
- Adams JD, Castagnoli N, and Trevor AJ (1978) Quantitative analysis of ketamine enantiomers. *Proc West Pharmacol Soc* **21**:471–472.
- Akin A, Esmoğlu A, Güler G, Demircioğlu R, Narin N, and Boyacı A (2005) Propofol and propofol-ketamine in pediatric patients undergoing cardiac catheterization. *Pediatr Cardiol* **26**:553–557.
- Albuquerque EX, Pereira EF, Alkondon M, and Rogers SW (2009) Mammalian nicotinic acetylcholine receptors: from structure to function. *Physiol Rev* **89**:73–120.
- Allaoua H and Chicheportiche R (1989) Anaesthetic properties of phencyclidine (PCP) and analogues may be related to their interaction with Na<sup>+</sup> channels. *Eur J Pharmacol* **163**:327–335.
- Allen HL and Iversen LL (1990) Phencyclidine, dizocilpine, and cerebrocortical neurons. *Science* **247**:221.
- Anand A, Charney DS, Oren DA, Berman RM, Hu XS, Cappiello A, and Krystal JH (2000) Attenuation of the neuropsychiatric effects of ketamine with lamotrigine: support for hyperglutamatergic effects of N-methyl-D-aspartate receptor antagonists. *Arch Gen Psychiatry* **57**:270–276.
- Andrade C (2017a) Ketamine for depression, 3: does chirality matter? *J Clin Psychiatry* **78**:e674–e677.



- Andrade C (2017b) Ketamine for depression, 4: in what dose, at what rate, by what route, for how long, and at what frequency? *J Clin Psychiatry* **78**: e852–e857.
- Anis NA, Berry SC, Burton NR, and Lodge D (1983) The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. *Br J Pharmacol* **79**:565–575.
- Appadu BL and Lambert DG (1996) Interaction of i.v. anaesthetic agents with 5-HT<sub>3</sub> receptors. *Br J Anaesth* **76**:271–273.
- Arditti J, Spadari M, de Haro L, Brun A, Bourdon JH, and Valli M (2002). Ketamine-dreams and realities. *Acta Clin Belg* **57** (Suppl 1):31–33.
- Arias HR, McCarty EA, Bayer EZ, Gallagher MJ, and Blanton MP (2002) Allosterically linked noncompetitive antagonist binding sites in the resting nicotinic acetylcholine receptor ion channel. *Arch Biochem Biophys* **403**:121–131.
- Auer RN (1996) Effect of age and sex on N-methyl-D-aspartate antagonist-induced neuronal necrosis in rats. *Stroke* **27**:743–746.
- Augustinack JC, Schneider A, Mandelkow EM, and Hyman BT (2002) Specific tau phosphorylation sites correlate with severity of neuronal cytopathology in Alzheimer's disease. *Acta Neuropathol* **103**:26–35.
- Autri AE, Adachi M, Nosyreva E, Na ES, Los MF, Cheng PF, Kavalali ET, and Monteggia LM (2011) NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. *Nature* **475**:91–95.
- Azevedo VM, Lauretti GR, Pereira NL, and Reis MP (2000) Transdermal ketamine as an adjuvant for postoperative analgesia after abdominal gynecological surgery using lidocaine epidural blockade. *Anesth Analg* **91**:1479–1482.
- Azzaro AJ and Smith DJ (1977) The inhibitory action of ketamine HC1 on [3H]5-hydroxytryptamine accumulation by rat brain synaptosomal-rich fractions: comparison with [3H]catecholamine and [3H] $\gamma$ -aminobutyric acid uptake. *Neuropharmacology* **16**:349–356.
- Backonja M, Arndt G, Gombar KA, Check B, and Zimmermann M (1994) Response of chronic neuropathic pain syndromes to ketamine: a preliminary study. *Pain* **56**: 51–57.
- Ballard ED, Ionescu DF, Vande Voort JL, Niciu MJ, Richards EM, Luckenbaugh DA, Brutsche NE, Ameli R, Furey ML, and Zarate CA Jr (2014) Improvement in suicidal ideation after ketamine infusion: relationship to reductions in depression and anxiety. *J Psychiatr Res* **58**:161–166.
- Ballard ED, Wills K, Lally N, Richards EM, Luckenbaugh DA, Walls T, Ameli R, Niciu MJ, Brutsche NE, Park L, et al. (2017) Anhedonia as a clinical correlate of suicidal thoughts in clinical ketamine trials. *J Affect Disord* **218**:195–200.
- Becker DE and Reed KL (2012) Local anesthetics: review of pharmacological considerations. *Anesth Prog* **59**:90–101, quiz 102–103.
- Beilin B, Rusabrov Y, Shapira Y, Roytblat L, Greenberg L, Yardeni IZ, and Bessler H (2007) Low-dose ketamine affects immune responses in humans during the early postoperative period. *Br J Anaesth* **99**:522–527.
- Benoit E (1995) Effects of intravenous anaesthetics on nerve axons. *Eur J Anaesthesiol* **12**:59–70.
- Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, and Krystal JH (2000) Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry* **47**:351–354.
- Bhat S, Dao DT, Terrillion CE, Arad M, Smith RJ, Soldatov NM, and Gould TD (2012) CACNA1C (Cav1.2) in the pathophysiology of psychiatric disease. *Prog Neurobiol* **99**:1–14.
- Bion JF (1984) Intrathecal ketamine for war surgery: a preliminary study under field conditions. *Anaesthesia* **39**:1023–1028.
- Blier P, Zigman D, and Blier J (2012) On the safety and benefits of repeated intravenous injections of ketamine for depression. *Biol Psychiatry* **72**:e11–e12.
- Bobo WV and Miller SC (2002) Ketamine as a preferred substance of abuse. *Am J Addict* **11**:332–334.
- Bokor G and Anderson PD (2014) Ketamine: an update on its abuse. *J Pharm Pract* **27**:582–586.
- Bolze S and Bouliou R (1998) HPLC determination of ketamine, norketamine, and dehydronorketamine in plasma with a high-purity reversed-phase sorbent. *Clin Chem* **44**:560–564.
- Bonanno FG (2002) Ketamine in war/tropical surgery (a final tribute to the racemic mixture). *Injury* **33**:323–327.
- Bonifazi A, Del Bello F, Mammoli V, Piergentili A, Petrelli R, Cimarelli C, Pelli M, Schepmann D, Wunsch B, Barocelli E, et al. (2015) Novel potent N-methyl-D-aspartate (NMDA) receptor antagonists or  $\sigma$ 1 receptor ligands based on properly substituted 1,4-dioxane ring. *J Med Chem* **58**:8601–8615.
- Bourke DL, Malit LA, and Smith TC (1987) Respiratory interactions of ketamine and morphine. *Anesthesiology* **66**:153–156.
- Bowdle TA, Radant AD, Cowley DS, Kharasch ED, Strassman RJ, and Roy-Byrne PP (1998) Psychedelic effects of ketamine in healthy volunteers: relationship to steady-state plasma concentrations. *Anesthesiology* **88**:82–88.
- Bowen WD, Hellewell SB, and McGarry KA (1989) Evidence for a multi-site model of the rat brain sigma receptor. *Eur J Pharmacol* **163**:309–318.
- Bree MM, Feller I, and Corssen G (1967) Safety and tolerance of repeated anesthesia with CI 581 (ketamine) in monkeys. *Anesth Analg* **46**:596–600.
- Breier A, Adler CM, Weisenfeld N, Su TP, Elman I, Picken L, Malhotra AK, and Pickar D (1998) Effects of NMDA antagonism on striatal dopamine release in healthy subjects: application of a novel PET approach. *Synapse* **29**:142–147.
- Bresink I, Danysz W, Parsons CG, and Mutschler E (1995) Different binding affinities of NMDA receptor channel blockers in various brain regions—indication of NMDA receptor heterogeneity. *Neuropharmacology* **34**:533–540.
- Can A, Zanos P, Moaddel R, Kang HJ, Dossou KSS, Wainer IW, Cheer JF, Frost DO, Huang X-P, and Gould TD (2016) Effects of ketamine and ketamine metabolites on evoked striatal dopamine release, dopamine receptors, and monoamine transporters. *J Pharmacol Exp Ther* **359**:159–170.
- Canuso CM, Singh JB, Fedgchin M, Alphas L, Lane R, Lim P, Pinter C, Hough D, Sanacora G, Manji H, et al. (2018) Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: results of a double-blind, randomized, placebo-controlled study. *Am J Psychiatry* DOI: 10.1176/appi.ajp.2018.17060720.
- Carliss RD, Radovsky A, Chengelis CP, O'Neill TP, and Shuey DL (2007) Oral administration of dextromethorphan does not produce neuronal vacuolation in the rat brain. *Neurotoxicology* **28**:813–818.
- Carr DB, Goudas LC, Denman WT, Brookoff D, Staats PS, Brennen L, Green G, Albin R, Hamilton D, Rogers MC, et al. (2004) Safety and efficacy of intranasal ketamine for the treatment of breakthrough pain in patients with chronic pain: a randomized, double-blind, placebo-controlled, crossover study. *Pain* **108**:17–27.
- Catterall WA (2011) Voltage-gated calcium channels. *Cold Spring Harb Perspect Biol* **3**:a003947.
- Cavalleri L, Merlo Pich E, Millan MJ, Chiamulera C, Kunath T, Spano PF, and Collo G (2017) Ketamine enhances structural plasticity in mouse mesencephalic and human iPSC-derived dopaminergic neurons via AMPAR-driven BDNF and mTOR signaling. *Molecular Psychiatry* **23**:812.
- Chang T and Glazko AJ (1972) A gas chromatographic assay for ketamine in human plasma. *Anesthesiology* **36**:401–404.
- Chang T and Glazko AJ (1974) Biotransformation and disposition of ketamine. *Int Anesthesiol Clin* **12**:157–177.
- Chen G, Ensor CR, and Bohner B (1966) The neuropharmacology of 2-(omicron-chlorophenyl)-2-methylaminocyclohexane hydrochloride. *J Pharmacol Exp Ther* **152**:332–339.
- Chen X, Shu S, and Bayliss DA (2009) HCN1 channel subunits are a molecular substrate for hypnotic actions of ketamine. *J Neurosci* **29**:600–609.
- Cheng PS, Fu CY, Lee CH, Liu C, and Chien CS (2007) GC-MS quantification of ketamine, norketamine, and dehydronorketamine in urine specimens and comparative study using ELISA as the preliminary test methodology. *J Chromatogr B Analyt Technol Biomed Life Sci* **852**:443–449.
- Cho JE, Shim JK, Choi YS, Kim DH, Hong SW, and Kwak YL (2009) Effect of low-dose ketamine on inflammatory response in off-pump coronary artery bypass graft surgery. *Br J Anaesth* **102**:23–28.
- Chong C, Schug SA, Page-Sharp M, Jenkins B, and Ilett KF (2009) Development of a sublingual/oral formulation of ketamine for use in neuropathic pain: preliminary findings from a three-way randomized, crossover study. *Clin Drug Investig* **29**:317–324.
- Chu PS, Ma WK, Wong SC, Chu RW, Cheng CH, Wong S, Tse JM, Lau FL, Yiu MK, and Man CW (2008) The destruction of the lower urinary tract by ketamine abuse: a new syndrome? *BJU Int* **102**:1616–1622.
- Clements JA and Nimmo WS (1981) Pharmacokinetics and analgesic effect of ketamine in man. *Br J Anaesth* **53**:27–30.
- Clements JA, Nimmo WS, and Grant IS (1982) Bioavailability, pharmacokinetics, and analgesic activity of ketamine in humans. *J Pharm Sci* **71**:539–542.
- Coates KM and Flood P (2001) Ketamine and its preservative, benzethonium chloride, both inhibit human recombinant  $\alpha$ 7 and  $\alpha$ 4 $\beta$ 2 neuronal nicotinic acetylcholine receptors in *Xenopus* oocytes. *Br J Pharmacol* **134**:871–879.
- Cohen ML, Chan SL, Way WL, and Trevor AJ (1973) Distribution in the brain and metabolism of ketamine in the rat after intravenous administration. *Anesthesiology* **39**: 370–376.
- Collier BB (1972) Ketamine and the conscious mind. *Anaesthesia* **27**:120–134.
- Corazza O, Assi S, and Schifano F (2013) From “Special K” to “Special M”: the evolution of the recreational use of ketamine and methoxetamine. *CNS Neurosci Ther* **19**:454–460.
- Corssen G and Domino EF (1966) Dissociative anesthesia: further pharmacologic studies and first clinical experience with the phencyclidine derivative CI-581. *Anesth Analg* **45**:29–40.
- Craven R (2007) Ketamine. *Anaesthesia* **62** (Suppl 1):48–53.
- Cremer J, Martin M, Redl H, Bahrami S, Abraham C, Graeter T, Haverich A, Schlag G, and Borst HG (1996) Systemic inflammatory response syndrome after cardiac operations. *Ann Thorac Surg* **61**:1714–1720.
- Crisp T, Perrotti JM, Smith DL, Stafinsky JL, and Smith DJ (1991) The local monoaminergic dependency of spinal ketamine. *Eur J Pharmacol* **194**:167–172.
- Cusin C, Ionescu DF, Pavone KJ, Akeju O, Cassano P, Taylor N, Eikermann M, Durham K, Swee MB, Chang T, et al. (2017) Ketamine augmentation for outpatients with treatment-resistant depression: preliminary evidence for two-step intravenous dose escalation. *Aust N Z J Psychiatry* **51**:55–64.
- Dachs RJ and Innes GM (1997) Intravenous ketamine sedation of pediatric patients in the emergency department. *Ann Emerg Med* **29**:146–150.
- Dalgarno PJ and Shewan D (1996) Illicit use of ketamine in Scotland. *J Psychoactive Drugs* **28**:191–199.
- Daly EJ, Singh JB, Fedgchin M, Cooper K, Lim P, Shelton RC, Thase ME, Winokur A, Van Nueten L, Manji H, et al. (2018) Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry* **75**:139–148.
- Dayton PG, Stiller RL, Cook DR, and Perel JM (1983) The binding of ketamine to plasma proteins: emphasis on human plasma. *Eur J Clin Pharmacol* **24**:825–831.
- De Felice LJ (2017) Monoamine transporters as ionotropic receptors. *Trends Neurosci* **40**:195–196.
- De Kock M, Lavand'homme P, and Waterloo H (2001) ‘Balanced analgesia’ in the perioperative period: is there a place for ketamine? *Pain* **92**:373–380.
- De Kock M, Loix S, and Lavand'homme P (2013) Ketamine and peripheral inflammation. *CNS Neurosci Ther* **19**:403–410.
- Delini-Stula A (1980) Drug-induced alterations in animal behavior as a tool for the evaluation of antidepressants: correlation with biochemical effects, in *Psychotropic Agents: Part I. Antipsychotics and Antidepressants* (Hoffmeister F and Stille G eds) pp 505–526, Springer, Berlin.
- Desta Z, Moaddel R, Ogburn ET, Xu C, Ramamoorthy A, Venkata SL, Sanghvi M, Goldberg ME, Torjman MC, and Wainer IW (2012) Stereoselective and regioselective hydroxylation of ketamine and norketamine. *Xenobiotica* **42**:1076–1087.
- Diazgranados N, Ibrahim L, Brutsche NE, Newberg A, Kronstein P, Khalife S, Kammerer WA, Quezado Z, Luckenbaugh DA, Salvadore G, et al. (2010a) A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Arch Gen Psychiatry* **67**:793–802.

- DiazGranados N, Ibrahim LA, Brutsche NE, Ameli R, Henter ID, Luckenbaugh DA, Machado-Vieira R, and Zarate CA Jr (2010b) Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. *J Clin Psychiatry* **71**: 1605–1611.
- Dinis-Oliveira RJ (2017) Metabolism and metabolomics of ketamine: a toxicological approach. *Forensic Sci Res* **2**:2–10.
- Domino EF (2010) Taming the ketamine tiger: 1965. *Anesthesiology* **113**:678–684.
- Domino EF, Chodoff P, and Corssen G (1965) Pharmacologic effects of Ci-581, a new dissociative anesthetic, in man. *Clin Pharmacol Ther* **6**:279–291.
- Downey D, Dutta A, McKie S, Dawson GR, Dourish CT, Craig K, Smith MA, McCarthy DJ, Harmer CJ, Goodwin GM, et al. (2016) Comparing the actions of lanicemine and ketamine in depression: key role of the anterior cingulate. *Eur Neuropsychopharmacol* **26**:994–1003.
- Dravid SM, Erreger K, Yuan H, Nicholson K, Le P, Lyuboslavsky P, Almonte A, Murray E, Mosely C, Barber J, et al. (2007) Subunit-specific mechanisms and proton sensitivity of NMDA receptor channel block. *J Physiol* **581**:107–128.
- Driesen NR, McCarthy G, Bhagwagar Z, Bloch MH, Calhoun VD, D'Souza DC, Georgieva R, He G, Leung HC, Ramani R, et al. (2013) The impact of NMDA receptor blockade on human working memory-related prefrontal function and connectivity. *Neuropsychopharmacology* **38**:2613–2622.
- du Jardin KG, Liebenberg N, Müller HK, Elfving B, Sanchez C, and Wegener G (2016) Differential interaction with the serotonin system by S-ketamine, vortioxetine, and fluoxetine in a genetic rat model of depression. *Psychopharmacology (Berl)* **233**:2813–2825.
- Dundee JW, Knox JW, Black GW, Moore J, Pandit SK, Bovill J, Clarke RS, Love SH, Elliott J, and Coppel DL (1970) Ketamine as an induction agent in anaesthetics. *Lancet* **1**:1370–1371.
- Dundee JW and Lilburn JK (1978) Ketamine-iorazepam: attenuation of psychic sequelae of ketamine by lorazepam. *Anaesthesia* **33**:312–314.
- Durieux ME (1995) Inhibition by ketamine of muscarinic acetylcholine receptor function. *Anesth Analg* **81**:57–62.
- Ebert B, Mikkelsen S, Thorkildsen C, and Borgbjerg FM (1997) Norketamine, the main metabolite of ketamine, is a non-competitive NMDA receptor antagonist in the rat cortex and spinal cord. *Eur J Pharmacol* **333**:99–104.
- Edginton AN, Schmitt W, Voith B, and Willmann S (2006) A mechanistic approach for the scaling of clearance in children. *Clin Pharmacokinet* **45**:683–704.
- Eglen RM (2005) Muscarinic receptor subtype pharmacology and physiology. *Prog Med Chem* **43**:105–136.
- Eide K, Stubhaug A, Oye I, and Breivik H (1995) Continuous subcutaneous administration of the N-methyl-D-aspartic acid (NMDA) receptor antagonist ketamine in the treatment of post-herpetic neuralgia. *Pain* **61**:221–228.
- Eide PK, Jørum E, Stubhaug A, Bremnes J, and Breivik H (1994) Relief of post-herpetic neuralgia with the N-methyl-D-aspartic acid receptor antagonist ketamine: a double-blind, cross-over comparison with morphine and placebo. *Pain* **58**: 347–354.
- Emmett C, Li H, Jiang X, Benz A, Boggiano J, Conyers S, Wozniak DF, Zorumski CF, Reichert DE, and Mennerick S (2016) A clickable analogue of ketamine retains NMDA receptor activity, psychoactivity, and accumulates in neurons. *Sci Rep* **6**: 38808.
- Erdemir H, Huber FC, and Corssen G (1970) Dissociative anesthesia with ketamine: a suitable adjunct to epidural anesthesia. *Anesth Analg* **49**:623–627.
- Fanta S, Kinnunen M, Backman JT, and Kalso E (2015) Population pharmacokinetics of S-ketamine and norketamine in healthy volunteers after intravenous and oral dosing. *Eur J Clin Pharmacol* **71**:441–447.
- Farber NB, Newcomer JW, and Olney JW (1998) The glutamate synapse in neuropsychiatric disorders: focus on schizophrenia and Alzheimer's disease. *Prog Brain Res* **116**:421–437.
- Felsler JM and Orban DJ (1982) Dystonic reaction after ketamine abuse. *Ann Emerg Med* **11**:673–675.
- Finck AD and Ngai SH (1982) Opiate receptor mediation of ketamine analgesia. *Anesthesiology* **56**:291–297.
- Finck AD, Samaniego E, and Ngai SH (1988) Morphine tolerance decreases the analgesic effects of ketamine in mice. *Anesthesiology* **68**:397–400.
- Fishback JA, Robson MJ, Xu YT, and Matsumoto RR (2010) Sigma receptors: potential targets for a new class of antidepressant drug. *Pharmacol Ther* **127**: 271–282.
- Fix AS, Horn JW, Wightman KA, Johnson CA, Long GG, Storts RW, Farber N, Wozniak DF, and Olney JW (1993) Neuronal vacuolization and necrosis induced by the noncompetitive N-methyl-D-aspartate (NMDA) antagonist MK(+)-801 (dizocilpine maleate): a light and electron microscopic evaluation of the rat retrosplenial cortex. *Exp Neurol* **123**:204–215.
- Flood P and Krasowski MD (2000) Intravenous anesthetics differentially modulate ligand-gated ion channels. *Anesthesiology* **92**:1418–1425.
- Franks NP and Lieb WR (1994) Molecular and cellular mechanisms of general anaesthesia. *Nature* **367**:607–614.
- Frenkel C and Urban BW (1992) Molecular actions of racemic ketamine on human CNS sodium channels. *Br J Anaesth* **69**:292–297.
- Fuchikami M, Thomas A, Liu R, Wohleb ES, Land BB, DiLeone RJ, Aghajanian GK, and Duman RS (2015) Optogenetic stimulation of infralimbic PFC re-produces ketamine's rapid and sustained antidepressant actions. *Proc Natl Acad Sci USA* **112**:8106–8111.
- Fukumoto K, Iijima M, and Chaki S (2014) Serotonin-1A receptor stimulation mediates effects of a metabotropic glutamate 2/3 receptor antagonist, 2S-2-amino-2-(1S,2S-2-carboxycycloprop-1-yl)-3-(xanth-9-yl)propanoic acid (LY341495), and an N-methyl-D-aspartate receptor antagonist, ketamine, in the novelty-suppressed feeding test. *Psychopharmacology (Berl)* **231**:2291–2298.
- Fukumoto K, Toki H, Iijima M, Hashihayata T, Yamaguchi JI, Hashimoto K, and Chaki S (2017) Antidepressant potential of (R)-ketamine in rodent models: comparison with (S)-ketamine. *J Pharmacol Exp Ther* **361**:9–16.
- Gage PW and Robertson B (1985) Prolongation of inhibitory postsynaptic currents by pentobarbitone, halothane and ketamine in CA1 pyramidal cells in rat hippocampus. *Br J Pharmacol* **85**:675–681.
- Gao M, Rejaei D, and Liu H (2016) Ketamine use in current clinical practice. *Acta Pharmacol Sin* **37**:865–872.
- Garfield JM, Garfield FB, Stone JG, Hopkins D, and Johns LA (1972) A comparison of psychologic responses to ketamine and thiopental–nitrous oxide–halothane anesthesia. *Anesthesiology* **36**:329–338.
- Geisslinger G, Hering W, Thomann P, Knoll R, Kamp HD, and Brune K (1993) Pharmacokinetics and pharmacodynamics of ketamine enantiomers in surgical patients using a stereoselective analytical method. *Br J Anaesth* **70**:666–671.
- Georg A and Friedl A (1991) Identification and characterization of two sigma-like binding sites in the mouse neuroblastoma × rat glioma hybrid cell line NG108-15. *J Pharmacol Exp Ther* **259**:479–483.
- George D, Gálvez V, Martin D, Kumar D, Leyden J, Hadzi-Pavlovic D, Harper S, Brodaty H, Glue P, Taylor R, et al. (2017) Pilot randomized controlled trial of titrated subcutaneous ketamine in older patients with treatment-resistant depression. *Am J Geriatr Psychiatry* **25**:1199–1209.
- Gerhard DM, Wohleb ES, and Duman RS (2016) Emerging treatment mechanisms for depression: focus on glutamate and synaptic plasticity. *Drug Discov Today* **21**: 454–464.
- Ghoneim MM, Hinrichs JV, Mewaldt SP, and Petersen RC (1985) Ketamine: behavioral effects of subanesthetic doses. *J Clin Psychopharmacol* **5**:70–77.
- Gill JR and Stajic M (2000) Ketamine in non-hospital and hospital deaths in New York city. *J Forensic Sci* **45**:655–658.
- Gilling KE, Jatzke C, Hechenberger M, and Parsons CG (2009) Potency, voltage-dependency, agonist concentration-dependency, blocking kinetics and partial untrapping of the uncompetitive N-methyl-D-aspartate (NMDA) channel blocker memantine at human NMDA (GluN1/GluN2A) receptors. *Neuropharmacology* **56**: 866–875.
- Goldberg ME, Torjman MC, Schwartzman RJ, Mager DE, and Wainer IW (2010) Pharmacodynamic profiles of ketamine (R)- and (S)- with 5-day inpatient infusion for the treatment of complex regional pain syndrome. *Pain Physician* **13**:379–387.
- Gómez de Segura IA, De Rossi R, Santos M, López San-Roman J, Tendillo FJ, and San-Roman F (1998) Epidural injection of ketamine for perineal analgesia in the horse. *Vet Surg* **27**:384–391.
- Gonzalez-Burgos G, Cho RY, and Lewis DA (2015) Alterations in cortical network oscillations and parvalbumin neurons in schizophrenia. *Biol Psychiatry* **77**: 1031–1040.
- Gorlin AW, Rosenfeld DM, and Ramakrishna H (2016) Intravenous sub-anesthetic ketamine for perioperative analgesia. *J Anaesthesiol Clin Pharmacol* **32**:160–167.
- Gould TD, Georgiou P, Brenner LA, Brundin L, Can A, Courtet P, Donaldson ZR, Dwivedi Y, Guillaume S, Gottesman II, et al. (2017) Animal models to improve our understanding and treatment of suicidal behavior. *Transl Psychiatry* **7**:e1092.
- Grant IS, Nimmo WS, and Clements JA (1981) Pharmacokinetics and analgesic effects of i.m. and oral ketamine. *Br J Anaesth* **53**:805–810.
- Grant IS, Nimmo WS, McNicol LR, and Clements JA (1983) Ketamine disposition in children and adults. *Br J Anaesth* **55**:1107–1111.
- Green CJ, Knight J, Precious S, and Simpkin S (1981) Ketamine alone and combined with diazepam or xylazine in laboratory animals: a 10 year experience. *Lab Anim* **15**:163–170.
- Green SM, Roback MG, Kennedy RM, and Krauss B (2011) Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. *Ann Emerg Med* **57**:449–461.
- Grott Zanicotti C, Perez D, and Glue P (2013) Case report: long-term mood response to repeat dose intramuscular ketamine in a depressed patient with advanced cancer. *J Palliat Med* **16**:719–720.
- Gupta A, Devi LA, and Gomes I (2011) Potentiation of  $\mu$ -opioid receptor-mediated signaling by ketamine. *J Neurochem* **119**:294–302.
- Haas DA and Harper DG (1992) Ketamine: a review of its pharmacologic properties and use in ambulatory anesthesia. *Anesth Prog* **39**:61–68.
- Haeseler G, Tetzlaff D, Bufler J, Dengler R, Münte S, Hecker H, and Leuwer M (2003) Blockade of voltage-operated neuronal and skeletal muscle sodium channels by S(+)- and R(-)-ketamine. *Anesth Analg* **96**:1019–1026.
- Hagelberg NM, Peltoniemi MA, Saari TI, Kurkinen KJ, Laine K, Neuvonen PJ, and Ollkka KT (2010) Clarithromycin, a potent inhibitor of CYP3A, greatly increases exposure to oral S-ketamine. *Eur J Pain* **14**:625–629.
- Han Y, Heuermann RJ, Lyman KA, Fisher D, Ismail QA, and Chetkovich DM (2017) HCN-channel dendritic targeting requires bipartite interaction with TRIP9b and regulates antidepressant-like behavioral effects. *Mol Psychiatry* **22**:458–465.
- Hance AJ, Winters WD, Quam DD, Benthuysen JL, and Cadd GG (1989) Catalepsy induced by combinations of ketamine and morphine: potentiation, antagonism, tolerance and cross-tolerance in the rat. *Neuropharmacology* **28**:109–116.
- Hansen G, Jensen SB, Chandresh L, and Hilden T (1988) The psychotropic effect of ketamine. *J Psychoactive Drugs* **20**:419–425.
- Hara K, Yanagihara N, Minami K, Ueno S, Toyohira Y, Sata T, Kawamura M, Brüss M, Bönisch H, Shigematsu A, et al. (1998a) Ketamine interacts with the noradrenaline transporter at a site partly overlapping the desipramine binding site. *Naunyn Schmiedeberg Arch Pharmacol* **358**:328–333.
- Hara Y, Chugun A, Nakaya H, and Kondo H (1998b) Tonic block of the sodium and calcium currents by ketamine in isolated guinea pig ventricular myocytes. *J Vet Med Sci* **60**:479–483.
- Hare BD, Ghosal S, and Duman RS (2017) Rapid acting antidepressants in chronic stress models: molecular and cellular mechanisms. *Chronic Stress (Thousand Oaks)* **1**: DOI: 10.1177/2470547017697317.
- Hargreaves RJ, Hill RG, and Iversen LL (1994) Neuroprotective NMDA antagonists: the controversy over their potential for adverse effects on cortical neuronal morphology. *Acta Neurochir Suppl (Wien)* **60**:15–19.

- Harris JA, Biersner RJ, Edwards D, and Bailey LW (1975) Attention, learning, and personality during ketamine emergence: a pilot study. *Anesth Analg* **54**:169–172.
- Harrison NL and Simmonds MA (1985) Quantitative studies on some antagonists of N-methyl D-aspartate in slices of rat cerebral cortex. *Br J Pharmacol* **84**:381–391.
- Hashimoto K (2014) Blood D-serine levels as a predictive biomarker for the rapid antidepressant effects of the NMDA receptor antagonist ketamine. *Psychopharmacology (Berl)* **231**:4081–4082.
- Hatakeyama N, Yamazaki M, Shibuya N, Yamamura S, and Momose Y (2001) Effects of ketamine on voltage-dependent calcium currents and membrane potentials in single bullfrog atrial cells. *J Anesth* **15**:149–153.
- Hawthornthwaite C and Serpell M (1998) Intrathecal anesthesia with ketamine. *Reg Anesth Pain Med* **23**:283–288.
- Henneberger C, Papouin T, Oliet SHR, and Rusakov DA (2010) Long-term potentiation depends on release of D-serine from astrocytes. *Nature* **463**:232–236.
- Hennein HA, Ebba H, Rodriguez JL, Merrick SH, Keith FM, Bronstein MH, Leung JM, Mangan DT, Greenfield LJ, and Rankin JS (1994) Relationship of the proinflammatory cytokines to myocardial ischemia and dysfunction after uncomplicated coronary revascularization. *J Thorac Cardiovasc Surg* **108**:626–635.
- Hetem LA, Danion JM, Diemunsch P, and Brandt C (2000) Effect of a subanesthetic dose of ketamine on memory and conscious awareness in healthy volunteers. *Psychopharmacology (Berl)* **152**:283–288.
- Hijazi Y and Bouliou R (2002) Contribution of CYP3A4, CYP2B6, and CYP2C9 isoforms to N-demethylation of ketamine in human liver microsomes. *Drug Metab Dispos* **30**:853–858.
- Himmelscher S and Pfenninger E (1998) The clinical use of S(+)-ketamine—a determination of its place. *Anesthesiol Intensivmed Notfallmed Schmerzther* **33**:764–770.
- Hiringer WK and Dick W (1984) Intramuscular ketamine analgesia in emergency patients. II. Clinical study of traumatized patients. *Anesthesiol* **33**:272–275.
- Hirota K, Hashimoto Y, and Lambert DG (2002) Interaction of intravenous anesthetics with recombinant human M1–M3 muscarinic receptors expressed in Chinese hamster ovary cells. *Anesth Analg* **95**:1607–1610.
- Hirota K and Lambert DG (2011) Ketamine: new uses for an old drug? *Br J Anaesth* **107**:123–126.
- Hirota K, Okawa H, Appadu BL, Grandy DK, Devi LA, and Lambert DG (1999) Stereoselective interaction of ketamine with recombinant mu, kappa, and delta opioid receptors expressed in Chinese hamster ovary cells. *Anesthesiol* **90**:174–182.
- Hirsiger S, Simmen HP, Werner CM, Wanner GA, and Rittirsch D (2012) Danger signals activating the immune response after trauma. *Mediators Inflamm* **2012**:315941.
- Ho KK and Flood P (2004) Single amino acid residue in the extracellular portion of transmembrane segment 2 in the nicotinic alpha7 acetylcholine receptor modulates sensitivity to ketamine. *Anesthesiol* **100**:657–662.
- Hodgkin AL and Huxley AF (1952) Currents carried by sodium and potassium ions through the membrane of the giant axon of Lolligo. *J Physiol* **116**:449–472.
- Homayoun H and Moghaddam B (2007) NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons. *J Neurosci* **27**:11496–11500.
- Honey GD, Honey RA, Sharar SR, Turner DC, Pomarol-Clotet E, Kumaran D, Simons JS, Hu X, Rugg MD, Bullmore ET, et al. (2005) Impairment of specific episodic memory processes by sub-psychotic doses of ketamine: the effects of levels of processing at encoding and of the subsequent retrieval task. *Psychopharmacology (Berl)* **181**:445–457.
- Hornik CP, Gonzalez D, van den Anker J, Atz AM, Yoge R, Poindexter BB, Ng KC, Delmore P, Harper BL, Melloni C, et al. (2018) Population pharmacokinetics of intramuscular and intravenous ketamine in children. *J Clin Pharmacol* **54**: DOI: 10.1002/jcph.1116.
- Hu YD, Xiang YT, Fang JX, Zu S, Sha S, Shi H, Ungvari GS, Correll CU, Chiu HF, Xue Y, et al. (2016) Single i.v. ketamine augmentation of newly initiated escitalopram for major depression: results from a randomized, placebo-controlled 4-week study. *Psychol Med* **46**:623–635.
- Huang HC and Jiang ZF (2009) Accumulated amyloid-beta peptide and hyperphosphorylated tau protein: relationship and links in Alzheimer's disease. *J Alzheimers Dis* **16**:15–27.
- Huettner JE and Bean BP (1988) Block of N-methyl-D-aspartate-activated current by the anticonvulsant MK-801: selective binding to open channels. *Proc Natl Acad Sci USA* **85**:1307–1311.
- Huge V, Lauchart M, Magerl W, Schelling G, Beyer A, Thieme D, and Azad SC (2010) Effects of low-dose intranasal (S)-ketamine in patients with neuropathic pain. *Eur J Pain* **14**:387–394.
- Hustveit O, Maurset A, and Oye I (1995) Interaction of the chiral forms of ketamine with opioid, phencyclidine, sigma and muscarinic receptors. *Pharmacol Toxicol* **77**:355–359.
- Ibrahim L, Diazgranados N, Franco-Chaves J, Brutsche N, Henter ID, Kronstein P, Moaddel R, Wainer I, Luckenbaugh DA, Manji HK, et al. (2012) Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs add-on riluzole: results from a 4-week, double-blind, placebo-controlled study. *Neuropsychopharmacology* **37**:1526–1533.
- Ivdall J, Ahlgren I, Aronsen KR, and Stenberg P (1979) Ketamine infusions: pharmacokinetics and clinical effects. *Br J Anaesth* **51**:1167–1173.
- Ivdall J, Holasek J, and Stenberg P (1983) Rectal ketamine for induction of anaesthesia in children. *Anaesthesia* **38**:60–64.
- Ihmsen H, Geisslinger G, and Schüttler J (2001) Stereoselective pharmacokinetics of ketamine: R(-)-ketamine inhibits the elimination of S(+)-ketamine. *Clin Pharmacol Ther* **70**:431–438.
- Ionescu DF, Luckenbaugh DA, Niciu MJ, Richards EM, and Zarate CA Jr (2015) A single infusion of ketamine improves depression scores in patients with anxious bipolar depression. *Bipolar Disord* **17**:438–443.
- Irifune M, Sato T, Kamata Y, Nishikawa T, Dohi T, and Kawahara M (2000) Evidence for GABA(A) receptor agonistic properties of ketamine: convulsive and anesthetic behavioral models in mice. *Anesth Analg* **91**:230–236.
- Izumi Y and Zorumski CF (2014) Metaplastic effects of subanesthetic ketamine on CA1 hippocampal function. *Neuropharmacology* **86**:273–281.
- Jacob TC, Moss SJ, and Jurd R (2008) GABA(A) receptor trafficking and its role in the dynamic modulation of neuronal inhibition. *Nat Rev Neurosci* **9**:331–343.
- Jahr CE (1992) High probability opening of NMDA receptor channels by L-glutamate. *Science* **255**:470–472.
- Jansen K (1989) Near death experience and the NMDA receptor. *BMJ* **298**:1708.
- Jansen KL (2000) A review of the nonmedical use of ketamine: use, users and consequences. *J Psychoactive Drugs* **32**:419–433.
- Jansen KL and Darracot-Cankovic R (2001) The nonmedical use of ketamine, part two: a review of problem use and dependence. *J Psychoactive Drugs* **33**:151–158.
- Jevtovic-Todorovic V, Wozniak DF, Benshoff ND, and Olney JW (2001) A comparative evaluation of the neurotoxic properties of ketamine and nitrous oxide. *Brain Res* **895**:264–267.
- Johansson J, Sjöberg J, Nordgren M, Sandström E, Sjöberg F, and Zetterström H (2013) Prehospital analgesia using nasal administration of S-ketamine—a case series. *Scand J Trauma Resusc Emerg Med* **21**:38.
- Jourdi H, Hsu YT, Zhou M, Qin Q, Bi X, and Baudry M (2009) Positive AMPA receptor modulation rapidly stimulates BDNF release and increases dendritic mRNA translation. *J Neurosci* **29**:8688–8697.
- Jozwiak K, Haginaka J, Moaddel R, and Wainer IW (2002) Displacement and non-linear chromatographic techniques in the investigation of interaction of non-competitive inhibitors with an immobilized alpha3beta4 nicotinic acetylcholine receptor liquid chromatographic stationary phase. *Anal Chem* **74**:4618–4624.
- Kadriu B, Gold PW, Luckenbaugh DA, Lener MS, Ballard ED, Niciu MJ, Henter ID, Park LT, De Sousa RT, Yuan P, et al. (2017) Acute ketamine administration corrects abnormal inflammatory bone markers in major depressive disorder. *Mol Psychiatry* [published ahead of print].
- Kang H, Park P, Bortolotto ZA, Brandt SD, Colestock T, Wallach J, Collingridge GL, and Lodge D (2017) Ephrenidine: a new psychoactive agent with ketamine-like NMDA receptor antagonist properties. *Neuropharmacology* **112**:144–149.
- Kapur S and Seeman P (2001) Ketamine has equal affinity for NMDA receptors and the high-affinity state of the dopamine D2 receptor. *Biol Psychiatry* **49**:954–957.
- Kapur S and Seeman P (2002) NMDA receptor antagonists ketamine and PCP have direct effects on the dopamine D(2) and serotonin 5-HT(2) receptors—implications for models of schizophrenia. *Mol Psychiatry* **7**:837–844.
- Karch SB and Drummer OH (2015) Dissociative anesthetics, in *Karch's Pathology of Drug Abuse*, 5th ed, pp 697–754, CRS Press, Boca Raton, FL.
- Kathirvel S, Sadhasivam S, Saxena A, Kannan TR, and Ganjoo P (2000) Effects of intrathecal ketamine added to bupivacaine for spinal anaesthesia. *Anaesthesia* **55**:899–904.
- Kavalali ET and Monteggia LM (2012) Synaptic mechanisms underlying rapid antidepressant action of ketamine. *Am J Psychiatry* **169**:1150–1156.
- Kawasaki C, Kawasaki T, Ogata M, Nandate K, and Shigematsu A (2001) Ketamine isomers suppress superantigen-induced proinflammatory cytokine production in human whole blood. *Can J Anaesth* **48**:819–823.
- Kawasaki T, Ogata M, Kawasaki C, Ogata J, Inoue Y, and Shigematsu A (1999) Ketamine suppresses proinflammatory cytokine production in human whole blood in vitro. *Anesth Analg* **89**:665–669.
- Ke X, Ding Y, Xu K, He H, Wang D, Deng X, Zhang X, Zhou Y, Zhou C, Liu Y, et al. (2018) The profile of cognitive impairments in chronic ketamine users. *Psychiatry Res* **266**:124–131.
- Kegeles LS, Martinez D, Kochan LD, Hwang DR, Huang Y, Mawlawi O, Suckow RF, Van Heertum RL, and Laruelle M (2002) NMDA antagonist effects on striatal dopamine release: positron emission tomography studies in humans. *Synapse* **43**:19–29.
- Keita H, Lechary JB, Henzel D, Desmonts JM, and Mantz J (1996) Is inhibition of dopamine uptake relevant to the hypnotic action of i.v. anaesthetics? *Br J Anaesth* **77**:254–256.
- Kennedy RM, Porter FL, Miller JP, and Jaffe DM (1998) Comparison of fentanyl/midazolam with ketamine/midazolam for pediatric orthopedic emergencies. *Pediatrics* **102**:956–963.
- Kharasch ED and Labroo R (1992) Metabolism of ketamine stereoisomers by human liver microsomes. *Anesthesiol* **77**:1201–1207.
- Khorramzadeh E and Lotfy AO (1973) The use of ketamine in psychiatry. *Psychosomatics* **14**:344–346.
- Kieffer BL and Gavériaux-Ruff C (2002) Exploring the opioid system by gene knockout. *Prog Neurobiol* **66**:285–306.
- Kim CS, Chang PY, and Johnston D (2012) Enhancement of dorsal hippocampal activity by knockdown of HCN1 channels leads to anxiolytic- and antidepressant-like behaviors. *Neuron* **75**:503–516.
- Kishimoto T, Chawla JM, Hagi K, Zarate CA, Kane JM, Bauer M, and Correll CU (2016) Single-dose infusion ketamine and non-ketamine N-methyl-D-aspartate receptor antagonists for unipolar and bipolar depression: a meta-analysis of efficacy, safety and time trajectories. *Psychol Med* **46**:1459–1472.
- Klepstad P, Maurset A, Moberg ER, and Oye I (1990) Evidence of a role for NMDA receptors in pain perception. *Eur J Pharmacol* **187**:513–518.
- Kohrs R and Durieux ME (1998) Ketamine: teaching an old drug new tricks. *Anesth Analg* **87**:1186–1193.
- Koike H and Chaki S (2014) Requirement of AMPA receptor stimulation for the sustained antidepressant activity of ketamine and LY341495 during the forced swim test in rats. *Behav Brain Res* **271**:111–115.
- Koike H, Iijima M, and Chaki S (2011) Involvement of AMPA receptor in both the rapid and sustained antidepressant-like effects of ketamine in animal models of depression. *Behav Brain Res* **224**:107–111.
- Kokkinou M, Ashok AH, and Howes OD (2018) The effects of ketamine on dopaminergic function: meta-analysis and review of the implications for neuropsychiatric disorders. *Mol Psychiatry* **23**:59–69.
- Kornhuber J, Mack-Burkhardt F, Kornhuber ME, and Riederer P (1989) [3H]MK-801 binding sites in post-mortem human frontal cortex. *Eur J Pharmacol* **162**:483–490.

- Kortekaas R, Maguire RP, van Waarde A, Leenders KL, and Elsinga PH (2008) Despite irreversible binding, PET tracer [<sup>11</sup>C]-SA5845 is suitable for imaging of drug competition at sigma receptors: the cases of ketamine and haloperidol. *Neurochem Int* **53**:45–50.
- Kotermanski SE and Johnson JW (2009) Mg<sup>2+</sup> imparts NMDA receptor subtype selectivity to the Alzheimer's drug memantine. *J Neurosci* **29**:2774–2779.
- Kotermanski SE, Wood JT, and Johnson JW (2009) Memantine binding to a superficial site on NMDA receptors contributes to partial trapping. *J Physiol* **587**:4589–4604.
- Krystal JH and D'Souza DC (2001) Comment on "ketamine has equal affinity for NMDA receptors and the high-affinity state of the dopamine D(2) receptor." *Biol Psychiatry* **50**:555–556.
- Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB Jr, and Charney DS (1994) Subanesthetic effects of the non-competitive NMDA antagonist, ketamine, in humans: psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry* **51**:199–214.
- Krystal JH, Madonick S, Perry E, Gueorguieva R, Brush L, Wray Y, Belger A, and D'Souza DC (2006) Potentiation of low dose ketamine effects by naltrexone: potential implications for the pharmacotherapy of alcoholism. *Neuropsychopharmacology* **31**:1793–1800.
- Kuroda K, Suzumura K, Shirakawa T, Hiraishi T, Nakahara Y, Fushiki H, Honda S, Naraoka H, Miyoshi S, and Aoki Y (2015) Investigation of mechanisms for MK-801-induced neurotoxicity utilizing metabolomic approach. *Toxicol Sci* **146**:344–353.
- Lahti AC, Weiler MA, Tamara Michaelidis BA, Parwani A, and Tamminga CA (2001) Effects of ketamine in normal and schizophrenic volunteers. *Neuropsychopharmacology* **25**:455–467.
- Lai R, Katalinic N, Glue P, Somogyi AA, Mitchell PB, Leyden J, Harper S, and Loo CK (2014) Pilot dose-response trial of i.v. ketamine in treatment-resistant depression. *World J Biol Psychiatry* **15**:579–584.
- Lally N, Nugent AC, Luckenbaugh DA, Ameli R, Roiser JP, and Zarate CA (2014) Anti-anhedonic effect of ketamine and its neural correlates in treatment-resistant bipolar depression. *Transl Psychiatry* **4**:e469.
- Lally N, Nugent AC, Luckenbaugh DA, Nicu MJ, Roiser JP, and Zarate CA Jr (2015) Neural correlates of change in major depressive disorder anhedonia following open-label ketamine. *J Psychopharmacol* **29**:596–607.
- Lankveld DP, Bull S, Van Dijk P, Fink-Gremmels J, and Hellebrekers LJ (2005) Ketamine inhibits LPS-induced tumour necrosis factor-alpha and interleukin-6 in an equine macrophage cell line. *Vet Res* **36**:257–262.
- Lapidus KA, Levitch CF, Perez AM, Brallier JW, Parides MK, Soleimani L, Feder A, Iosifescu DV, Charney DS, and Murrough JW (2014) A randomized controlled trial of intranasal ketamine in major depressive disorder. *Biol Psychiatry* **76**:970–976.
- Larsen B, Hoff G, Wilhelm W, Buchinger H, Wanner G, and Bauer M (1998) Effect of intravenous anesthetics on spontaneous and endotoxin-stimulated cytokine response in cultured human whole blood. *Anesthesiology* **89**:1218–1227.
- Laskowski K, Stirling A, McKay WP, and Lim HJ (2011) A systematic review of intravenous ketamine for postoperative analgesia. *Can J Anaesth* **58**:911–923.
- Lauretti GR, Lima IC, Reis MP, Prado WA, and Pereira NL (1999) Oral ketamine and transdermal nitroglycerin as analgesic adjuvants to oral morphine therapy for cancer pain management. *Anesthesiology* **90**:1528–1533.
- Lepack AE, Fuchikami M, Dwyer JM, Banasr M, and Duman RS (2014) BDNF release is required for the behavioral actions of ketamine. *Int J Neuropsychopharmacol* **18**: DOI: 10.1093/ijnp/ppy033.
- Lerma J, Zukin RS, and Bennett MV (1991) Interaction of Mg<sup>2+</sup> and phencyclidine in use-dependent block of NMDA channels. *Neurosci Lett* **123**:187–191.
- Leung LY and Baillie TA (1986) Comparative pharmacology in the rat of ketamine and its two principal metabolites, norketamine and (Z)-6-hydroxynorketamine. *J Med Chem* **29**:2396–2399.
- Lewis AS, Vaidya SP, Blaiss CA, Liu Z, Stoub TR, Brager DH, Chen X, Bender RA, Estep CM, Popov AB, et al. (2011) Deletion of the hyperpolarization-activated cyclic nucleotide-gated channel auxiliary subunit TRIP8b impairs hippocampal Ih localization and function and promotes antidepressant behavior in mice. *J Neurosci* **31**:7424–7440.
- Li CT, Chen MH, Lin WC, Hong CJ, Yang BH, Liu RS, Tu PC, and Su TP (2016) The effects of low-dose ketamine on the prefrontal cortex and amygdala in treatment-resistant depression: a randomized controlled study. *Hum Brain Mapp* **37**:1080–1090.
- Li CY, Chou TC, Wong CS, Ho ST, Wu CC, Yen MH, and Ding YA (1997) Ketamine inhibits nitric oxide synthase in lipopolysaccharide-treated rat alveolar macrophages. *Can J Anaesth* **44**:989–995.
- Li J, Chen FF, Chen XD, and Zhou C (2014) Inhibition of HCN1 channels by ketamine accounts for its antidepressant actions. *Sichuan Da Xue Xue Bao Yi Xue Ban* **45**:888–892, 932.
- Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, Li XY, Aghajanian G, and Duman RS (2010) mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science* **329**:959–964.
- Li Q, Shi L, Lu G, Yu HL, Yeung FK, Wong NK, Sun L, Liu K, Yew D, Pan F, et al. (2017) Chronic ketamine exposure causes white matter microstructural abnormalities in adolescent cynomolgus monkeys. *Front Neurosci* **11**:285.
- Liao Y, Tang J, Ma M, Wu Z, Yang M, Wang X, Liu T, Chen X, Fletcher PC, and Hao W (2010) Frontal white matter abnormalities following chronic ketamine use: a diffusion tensor imaging study. *Brain* **133**:2115–2122.
- Lilium T, Kangas E, Niemi M, Rauhala P, and Kalso E (2018a) Ketamine and norketamine attenuate oxycodone tolerance markedly less than that of morphine: from behaviour to drug availability. *Br J Anaesth* **120**:818–826.
- Lilium TO, Viisanen H, Jokinen V, Niemi M, Kalso EA, and Rauhala PV (2018b) Interactions of (2S,6S;2R,6R)-Hydroxynorketamine, a Secondary Metabolite of (R,S)-Ketamine, with Morphine. *Basic Clin Pharmacol Toxicol* **122**:481–488.
- Lim DK (2003) Ketamine associated psychedelic effects and dependence. *Singapore Med J* **44**:31–34.
- Lin HR and Lua AC (2004) Detection of acid-labile conjugates of ketamine and its metabolites in urine samples collected from pub participants. *J Anal Toxicol* **28**:181–186.
- Lin LH, Chen LL, Zirrollo JA, and Harris RA (1992) General anesthetics potentiate gamma-aminobutyric acid actions on gamma-aminobutyric acid receptors expressed by *Xenopus* oocytes: lack of involvement of intracellular calcium. *J Pharmacol Exp Ther* **263**:569–578.
- Lisek M, Boczek T, Ferenc B, and Zylinska L (2016) Regional brain dysregulation of Ca(2+)-handling systems in ketamine-induced rat model of experimental psychosis. *Cell Tissue Res* **363**:609–620.
- Little B, Chang T, Chucot L, Dill WA, Enrile LL, Glazko AJ, Jassani M, Kretschmer H, and Sweet AY (1972) Study of ketamine as an obstetric anesthetic agent. *Am J Obstet Gynecol* **113**:247–260.
- Littlewood CL, Cash D, Dixon AL, Dix SL, White CT, O'Neill MJ, Tricklebank M, and Williams SCR (2006) Using the BOLD MR signal to differentiate the stereoisomers of ketamine in the rat. *NeuroImage* **32**:1733–1746.
- Lockhart CH and Nelson WL (1974) The relationship of ketamine requirement to age in pediatric patients. *Anesthesiology* **40**:507–508.
- Lodge D, Anis NA, and Burton NR (1982) Effects of optical isomers of ketamine on excitation of cat and rat spinal neurons by amino acids and acetylcholine. *Neurosci Lett* **29**:281–286.
- Lodge DJ, Behrens MM, and Grace AA (2009) A loss of parvalbumin-containing interneurons is associated with diminished oscillatory activity in an animal model of schizophrenia. *J Neurosci* **29**:2344–2354.
- Loix S, De Kock M, and Henin P (2011) The anti-inflammatory effects of ketamine: state of the art. *Acta Anaesthesiol Belg* **62**:47–58.
- Loo CK, Gálvez V, O'Keefe E, Mitchell PB, Hadzi-Pavlovic D, Leyden J, Harper S, Somogyi AA, Lai R, Weickert CS, et al. (2016) Placebo-controlled pilot trial testing dose titration and intravenous, intramuscular and subcutaneous routes for ketamine in depression. *Acta Psychiatr Scand* **134**:48–56.
- Lucas G, Rymar VV, Sadikot AF, and Debonnel G (2008) Further evidence for an antidepressant potential of the selective sigma1 agonist SA 4503: electrophysiological, morphological and behavioural studies. *Int J Neuropsychopharmacol* **11**:485–495.
- Lüthi A and McCormick DA (1998) H-current: properties of a neuronal and network pacemaker. *Neuron* **21**:9–12.
- Lynch DR, Lawrence JJ, Lenz S, Aneqawa NJ, Dichter M, and Pritchett DB (1995) Pharmacological characterization of heterodimeric NMDA receptors composed of NR 1a and 2B subunits: differences with receptors formed from NR 1a and 2A. *J Neurochem* **64**:1462–1468.
- Ma M, Ren Q, Fujita Y, Yang C, Dong C, Ohgi Y, Futamura T, and Hashimoto K (2017) Alterations in amino acid levels in mouse brain regions after adjunctive treatment of brexpiprazole with fluoxetine: comparison with (R)-ketamine. *Psychopharmacology (Berl)* **234**:3165–3173.
- MacDonald JF, Bartlett MC, Mody I, Pahapill P, Reynolds JN, Salter MW, Schneiderman JH, and Pennefather PS (1991) Actions of ketamine, phencyclidine and MK-801 on NMDA receptor currents in cultured mouse hippocampal neurons. *J Physiol* **432**:483–508.
- MacDonald JF, Miljkovic Z, and Pennefather P (1987) Use-dependent block of excitatory amino acid currents in cultured neurons by ketamine. *J Neurophysiol* **58**:251–266.
- Maeng S, Zarate CA Jr, Du J, Schloesser RJ, McCammon J, Chen G, and Manji HK (2008) Cellular mechanisms underlying the antidepressant effects of ketamine: role of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors. *Biol Psychiatry* **63**:349–352.
- Malaquin JM (1984) Ketamine via rectal route for the induction of pediatric anesthesia. *Cah Anesthesiol* **32**:373–374.
- Malhotra AK, Pinals DA, Adler CM, Elman I, Clifton A, Pickar D, and Breier A (1997) Ketamine-induced exacerbation of psychotic symptoms and cognitive impairment in neuroleptic-free schizophrenics. *Neuropsychopharmacology* **17**:141–150.
- Malhotra AK, Pinals DA, Weingartner H, Sirocco K, Missar CD, Pickar D, and Breier A (1996) NMDA receptor function and human cognition: the effects of ketamine in healthy volunteers. *Neuropsychopharmacology* **14**:301–307.
- Malinovsky JM, Servin F, Cozian A, Lepage JY, and Pinaud M (1996) Ketamine and norketamine plasma concentrations after i.v., nasal and rectal administration in children. *Br J Anaesth* **77**:203–207.
- Mantz J, Lecharny JB, Loudenbach V, Henzel D, Peytavin G, and Desmonts JM (1995) Anesthetics affect the uptake but not the depolarization-evoked release of GABA in rat striatal synaptosomes. *Anesthesiology* **82**:502–511.
- Marchetti F, Coutaux A, Bellanger A, Magneux C, Bourgeois P, and Mion G (2015) Efficacy and safety of oral ketamine for the relief of intractable chronic pain: a retrospective 5-year study of 51 patients. *Eur J Pain* **19**:984–993.
- Marietta MP, Way WL, Castagnoli N Jr, and Trevor AJ (1977) On the pharmacology of the ketamine enantiomorphs in the rat. *J Pharmacol Exp Ther* **202**:157–165.
- Martin DC, Adams RJ, and Watkins CA (1988) Inhibition of synaptosomal serotonin uptake by Ketalar. *Res Commun Chem Pathol Pharmacol* **62**:129–132.
- Martin DC, Introna RP, and Aronstam RS (1990) Inhibition of neuronal 5-HT uptake by ketamine, but not halothane, involves disruption of substrate recognition by the transporter. *Neurosci Lett* **112**:99–103.
- Martin LL, Bouchal RL, and Smith DJ (1982) Ketamine inhibits serotonin uptake in vivo. *Neuropharmacology* **21**:113–118.
- Mason K, Cottrell AM, Corrigan AG, Gillatt DA, and Mitchelmore AE (2010) Ketamine-associated lower urinary tract destruction: a new radiological challenge. *Clin Radiol* **65**:795–800.
- Mathew SJ, Murrough JW, aan het Rot M, Collins KA, Reich DL, and Charney DS (2010) Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression: a pilot randomized, placebo-controlled continuation trial. *Int J Neuropsychopharmacol* **13**:71–82.

- Mathisen LC, Skjelbred P, Skoglund LA, and Oye I (1995) Effect of ketamine, an NMDA receptor inhibitor, in acute and chronic orofacial pain. *Pain* **61**:215–220.
- Matsuno K, Kobayashi T, Tanaka MK, and Mita S (1996) Sigma 1 receptor subtype is involved in the relief of behavioral despair in the mouse forced swimming test. *Eur J Pharmacol* **312**:267–271.
- McCarthy DA, Chen G, Kaump DH, and Ensor C (1965) General anesthetic and other pharmacological properties of 2-(O-chlorophenyl)-2-methylamino cyclohexanone HCl (Ci-581). *J New Drugs* **5**:21–33.
- McGuinness SK, Wasiak J, Cleland H, Symons J, Hogan L, Hucker T, and Mahar PD (2011) A systematic review of ketamine as an analgesic agent in adult burn injuries. *Pain Med* **12**:1551–1558.
- McIntyre P, McLatchie LM, Chambers A, Phillips E, Clarke M, Savidge J, Toms C, Peacock M, Shah K, Winter J, et al. (2001) Pharmacological differences between the human and rat vanilloid receptor 1 (VR1). *Br J Pharmacol* **132**:1084–1094.
- Meng E, Wu S-T, Cha T-L, Sun G-H, Yu D-S, and Chang S-Y (2013) A murderer of young bladders: ketamine-associated cystitis. *Urol Sci* **24**:113–116.
- Mikkelsen S, Ilkjaer S, Brennum J, Borgbjerg FM, and Dahl JB (1999) The effect of naloxone on ketamine-induced effects on hyperalgesia and ketamine-induced side effects in humans. *Anesthesiology* **90**:1539–1545.
- Miller OH, Yang L, Wang CC, Hargroder EA, Zhang Y, Delpire E, and Hall BJ (2014) GluN2B-containing NMDA receptors regulate depression-like behavior and are critical for the rapid antidepressant actions of ketamine. *eLife* **3**:e03581.
- Mineur YS and Picciotto MR (2010) Nicotine receptors and depression: revisiting and revising the cholinergic hypothesis. *Trends Pharmacol Sci* **31**:580–586.
- Mion G and Villevieille T (2013) Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). *CNS Neurosci Ther* **19**:370–380.
- Miyasaka M and Domino EF (1968) Neural mechanisms of ketamine-induced anesthesia. *Int J Neuropharmacol* **7**:557–573.
- Moaddel R, Abdрахманова G, Kozak J, Jozwiak K, Toll L, Jimenez L, Rosenberg A, Tran T, Xiao Y, Zarate CA, et al. (2013) Sub-anesthetic concentrations of (R,S)-ketamine metabolites inhibit acetylcholine-evoked currents in  $\alpha 7$  nicotinic acetylcholine receptors. *Eur J Pharmacol* **698**:228–234.
- Moaddel R, Luckenbaugh DA, Xie Y, Villaseñor A, Brutsche NE, Machado-Vieira R, Ramamoorthy A, Lorenzo MP, Garcia A, Bernier M, et al. (2015a) D-serine plasma concentration is a potential biomarker of (R,S)-ketamine antidepressant response in subjects with treatment-resistant depression. *Psychopharmacology (Berl)* **232**:399–409.
- Moaddel R, Sanghvi M, Dossou KS, Ramamoorthy A, Green C, Bupp J, Swezey R, O'Loughlin K, and Wainer IW (2015b) The distribution and clearance of (2S,6S)-hydroxynorketamine, an active ketamine metabolite, in Wistar rats. *Pharmacol Res Perspect* **3**:e00157.
- Moaddel R, Sanghvi M, Ramamoorthy A, Jozwiak K, Singh N, Green C, O'Loughlin K, Torjman M, and Wainer IW (2016) Subchronic administration of (R,S)-ketamine induces ketamine ring hydroxylation in Wistar rats. *J Pharm Biomed Anal* **127**:3–8.
- Moaddel R, Venkata SL, Tanga MJ, Bupp JE, Green CE, Iyer L, Furimsky A, Goldberg ME, Torjman MC, and Wainer IW (2010) A parallel chiral-achiral liquid chromatographic method for the determination of the stereoisomers of ketamine and ketamine metabolites in the plasma and urine of patients with complex regional pain syndrome. *Talanta* **82**:1892–1904.
- Moghaddam B, Adams B, Verma A, and Daly D (1997) Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. *J Neurosci* **17**:2921–2927.
- Morgan CJ and Curran HV; Independent Scientific Committee on Drugs (2012) Ketamine use: a review. *Addiction* **107**:27–38.
- Morgan CJ, Mofeez A, Brandner B, Bromley L, and Curran HV (2004) Acute effects of ketamine on memory systems and psychotic symptoms in healthy volunteers. *Neuropsychopharmacology* **29**:208–218.
- Morgan CJ, Rossell SL, Pepper F, Smart J, Blackburn J, Brandner B, and Curran HV (2006) Semantic priming after ketamine acutely in healthy volunteers and following chronic self-administration in substance users. *Biol Psychiatry* **59**:265–272.
- Morris PJ, Moaddel R, Zanos P, Moore CE, Gould T, Zarate CA Jr, and Thomas CJ (2017) Synthesis and N-methyl-D-aspartate (NMDA) receptor activity of ketamine metabolites. *Org Lett* **19**:4572–4575.
- Mössner LD, Schmitz A, Theurillat R, Thormann W, and Mevissen M (2011) Inhibition of cytochrome P450 enzymes involved in ketamine metabolism by use of liver microsomes and specific cytochrome P450 enzymes from horses, dogs, and humans. *Am J Vet Res* **72**:1505–1513.
- Muetzelfeldt L, Kamboj SK, Rees H, Taylor J, Morgan CJ, and Curran HV (2008) Journey through the K-hole: phenomenological aspects of ketamine use. *Drug Alcohol Depend* **95**:219–229.
- Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CE, Perez AM, Iqbal S, Pillemer S, Foulkes A, Shah A, et al. (2013a) Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *Am J Psychiatry* **170**:1134–1142.
- Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, aan het Rot M, Collins KA, Mathew SJ, Charney DS, and Iosifescu DV (2013b) Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. *Biol Psychiatry* **74**:250–256.
- Murrough JW, Soleimani L, DeWilde KE, Collins KA, Lapidus KA, Iacoviello BM, Lener M, Kautz M, Kim J, Stern JB, et al. (2015) Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial. *Psychol Med* **45**:3571–3580.
- Myers AM, Charifson PS, Owens CE, Kula NS, McPhail AT, Baldessarini RJ, Booth RG, and Wyrick SD (1994) Conformational analysis, pharmacophore identification, and comparative molecular field analysis of ligands for the neuromodulatory sigma 3 receptor. *J Med Chem* **37**:4109–4117.
- Nemeth CL, Paine TA, Rittiner JE, Béguin C, Carroll FI, Roth BL, Cohen BM, and Carlezon WA Jr (2010) Role of kappa-opioid receptors in the effects of salvinorin A and ketamine on attention in rats. *Psychopharmacology (Berl)* **210**:263–274.
- Newcomer JW, Farber NB, Jevtovic-Todorovic V, Selke G, Melson AK, Hershey T, Craft S, and Olney JW (1999) Ketamine-induced NMDA receptor hypofunction as a model of memory impairment and psychosis. *Neuropsychopharmacology* **20**:106–118.
- Newport DJ, Carpenter LL, McDonald WM, Potash JB, Tohen M, and Nemeroff CB; APA Council of Research Task Force on Novel Biomarkers and Treatments (2015) Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. *Am J Psychiatry* **172**:950–966.
- Newton K and Dixit VM (2012) Signaling in innate immunity and inflammation. *Cold Spring Harb Perspect Biol* **4**: DOI: 10.1101/cshperspect.a006049.
- Nishimura M, Sato K, Okada T, Yoshiya I, Schloss P, Shimada S, and Tohyama M (1998) Ketamine inhibits monoamine transporters expressed in human embryonic kidney 293 cells. *Anesthesiology* **88**:768–774.
- Oka Y, Murata A, Nishijima J, Yasuda T, Hiraoka N, Ohmachi Y, Kitagawa K, Yasuda T, Toda H, Tanaka N, et al. (1992) Circulating interleukin 6 as a useful marker for predicting postoperative complications. *Cytokine* **4**:298–304.
- Olney JW, Labruyere J, and Price MT (1989) Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. *Science* **244**:1360–1362.
- Olney JW, Labruyere J, Wang G, Wozniak DF, Price MT, and Sesma MA (1991) NMDA antagonist neurotoxicity: mechanism and prevention. *Science* **254**:1515–1518.
- Orser BA, Pennefather PS, and MacDonald JF (1997) Multiple mechanisms of ketamine blockade of N-methyl-D-aspartate receptors. *Anesthesiology* **86**:903–917.
- Oye I, Paulsen O, and Maurset A (1992) Effects of ketamine on sensory perception: evidence for a role of N-methyl-D-aspartate receptors. *J Pharmacol Exp Ther* **260**:1209–1213.
- Pacheco Dda F, Romero TR, and Duarte ID (2014) Central antinociception induced by ketamine is mediated by endogenous opioids and  $\mu$ - and  $\delta$ -opioid receptors. *Brain Res* **1562**:69–75.
- Pal HR, Berry N, Kumar R, and Ray R (2002) Ketamine dependence. *Anaesth Intensive Care* **30**:382–384.
- Pande AC, Genève J, Scherrer B, Smith F, Leadbetter RA, and de Meynard C (1999) A placebo-controlled trial of igmesine in the treatment of major depression. *Eur Neuropsychopharmacol* **9**:138.
- Paoletti P, Bellone C, and Zhou Q (2013) NMDA receptor subunit diversity: impact on receptor properties, synaptic plasticity and disease. *Nat Rev Neurosci* **14**:383–400.
- Park M, Newman LE, Gold PW, Luckenbaugh DA, Yuan P, Machado-Vieira R, and Zarate CA Jr (2017) Change in cytokine levels is not associated with rapid antidepressant response to ketamine in treatment-resistant depression. *J Psychiatr Res* **84**:113–118.
- Parsons CG, Panchenko VA, Pinchenko VO, Tsyndrenko AY, and Krishtal OA (1996) Comparative patch-clamp studies with freshly dissociated rat hippocampal and striatal neurons on the NMDA receptor antagonistic effects of amantadine and memantine. *Eur J Neurosci* **8**:446–454.
- Parsons CG, Quack G, Bresink I, Baran L, Przegalinski E, Kostowski W, Krzascik P, Hartmann S, and Danysz W (1995) Comparison of the potency, kinetics and voltage-dependency of a series of uncompetitive NMDA receptor antagonists in vitro with anticonvulsive and motor impairment activity in vivo. *Neuropharmacology* **34**:1239–1258.
- Paul RK, Singh NS, Khadeer M, Moaddel R, Sanghvi M, Green CE, O'Loughlin K, Torjman MC, Bernier M, and Wainer IW (2014) (R,S)-Ketamine metabolites (R,S)-norketamine and (2S,6S)-hydroxynorketamine increase the mammalian target of rapamycin function. *Anesthesiology* **121**:149–159.
- Peltoniemi MA, Hagelberg NM, Olkkola KT, and Saari TI (2016) Ketamine: a review of clinical pharmacokinetics and pharmacodynamics in anesthesia and pain therapy. *Clin Pharmacokinet* **55**:1059–1077.
- Peltoniemi MA, Saari TI, Hagelberg NM, Laine K, Kurkinen KJ, Neuvonen PJ, and Olkkola KT (2012) Rifampicin has a profound effect on the pharmacokinetics of oral S-ketamine and less on intravenous S-ketamine. *Basic Clin Pharmacol Toxicol* **111**:325–332.
- Pereira EF, Hilmas C, Santos MD, Alkondon M, Maelicke A, and Albuquerque EX (2002) Unconventional ligands and modulators of nicotinic receptors. *J Neurobiol* **53**:479–500.
- Perumal DK, Adhimoolam M, Selvaraj N, Lazarus SP, and Mohammed MA (2015) Midazolam premedication for ketamine-induced emergence phenomenon: a prospective observational study. *J Res Pharm Pract* **4**:89–93.
- Petrenko AB, Yamakura T, Sakimura K, and Baba H (2014) Defining the role of NMDA receptors in anesthesia: are we there yet? *Eur J Pharmacol* **723**:29–37.
- Pfenninger EG, Durieux ME, and Himmelseher S (2002) Cognitive impairment after small-dose ketamine isomers in comparison to equianalgesic racemic ketamine in human volunteers. *Anesthesiology* **96**:357–366.
- Pham TH, Defaix C, Xu X, Deng SX, Fabresse N, Alvarez JC, Landry DW, Brachman RA, Denny CA, and Gardier AM (2017a) Common neurotransmission recruited in (R,S)-ketamine and (2R,6R)-hydroxynorketamine-induced sustained antidepressant-like effects. *Biol Psychiatry* [published ahead of print].
- Pham TH, Mendez-David I, Defaix C, Guiard BP, Tritschler L, David DJ, and Gardier AM (2017b) Ketamine treatment involves medial prefrontal cortex serotonin to induce a rapid antidepressant-like activity in BALB/c mice. *Neuropharmacology* **112**:198–209.
- Phelps LE, Brutsche N, Moral JR, Luckenbaugh DA, Manji HK, and Zarate CA Jr (2009) Family history of alcohol dependence and initial antidepressant response to an N-methyl-D-aspartate antagonist. *Biol Psychiatry* **65**:181–184.
- Philip NS, Carpenter LL, Tyrka AR, and Price LH (2010) Nicotinic acetylcholine receptors and depression: a review of the preclinical and clinical literature. *Psychopharmacology (Berl)* **212**:1–12.
- Pomarov-Clotet E, Honey GD, Murray GK, Corlett PR, Absalom AR, Lee M, McKenna PJ, Bullmore ET, and Fletcher PC (2006) Psychological effects of ketamine in healthy volunteers: phenomenological study. *Br J Psychiatry* **189**:173–179.
- Porter RH and Greenamyre JT (1995) Regional variations in the pharmacology of NMDA receptor channel blockers: implications for therapeutic potential. *J Neurochem* **64**:614–623.

- Portmann S, Kwan HY, Theurillat R, Schmitz A, Mevissen M, and Thormann W (2010) Enantioselective capillary electrophoresis for identification and characterization of human cytochrome P450 enzymes which metabolize ketamine and norketamine in vitro. *J Chromatogr A* **1217**:7942–7948.
- Price RB, Nock MK, Charney DS, and Mathew SJ (2009) Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. *Biol Psychiatry* **66**:522–526.
- Rao LK, Flaker AM, Friedel CC, and Kharasch ED (2016) Role of cytochrome P4502B6 polymorphisms in ketamine metabolism and clearance. *Anesthesiology* **125**:1103–1112.
- Rasmussen KG, Lineberry TW, Galardy CW, Kung S, Lapid MI, Palmer BA, Ritter MJ, Schak KM, Sola CL, Hanson AJ, et al. (2013) Serial infusions of low-dose ketamine for major depression. *J Psychopharmacol* **27**:444–450.
- Reich DL and Silvey G (1989) Ketamine: an update on the first twenty-five years of clinical experience. *Can J Anaesth* **36**:186–197.
- Reid C, Hattori R, and Middleton P (2011) Case report: prehospital use of intranasal ketamine for paediatric burn injury. *Emerg Med J* **28**:328–329.
- Remérand F, Le Tendre C, Baud A, Couvret C, Pourrat X, Favard L, Laffon M, and Fusciardi J (2009) The early and delayed analgesic effects of ketamine after total hip arthroplasty: a prospective, randomized, controlled, double-blind study. *Anesth Analg* **109**:1963–1971.
- Reynolds IJ and Miller RJ (1989) Ifenprodil is a novel type of N-methyl-D-aspartate receptor antagonist: interaction with polyamines. *Mol Pharmacol* **36**:758–765.
- Riva-Posse P, Reiff CM, Edwards JA, Job GP, Galendez GC, Garlow SJ, Saah TC, Dunlop BW, and McDonald WM (2018) Blood pressure safety of subanesthetic ketamine for depression: a report on 684 infusions. *J Affect Disord* DOI: 10.1016/j.jad.2018.02.025 [published ahead of print].
- Robson MJ, Elliott M, Seminerio MJ, and Matsumoto RR (2012) Evaluation of sigma ( $\sigma$ ) receptors in the antidepressant-like effects of ketamine in vitro and in vivo. *Eur Neuropsychopharmacol* **22**:308–317.
- Rolan P, Lim S, Sunderland V, Liu Y, and Molnar V (2014) The absolute bioavailability of racemic ketamine from a novel sublingual formulation. *Br J Clin Pharmacol* **77**:1011–1016.
- Rosa PB, Neis VB, Ribeiro CM, Moretti M, and Rodrigues AL (2016) Antidepressant-like effects of ascorbic acid and ketamine involve modulation of GABA<sub>A</sub> and GABAB receptors. *Pharmacol Rep* **68**:996–1001.
- Roytblat L, Korotkoruchko A, Katz J, Glazer M, Greemberg L, and Fisher A (1993) Postoperative pain: the effect of low-dose ketamine in addition to general anesthesia. *Anesth Analg* **77**:1161–1165.
- Roytblat L, Talmor D, Rachinsky M, Greemberg L, Pekar A, Appelbaum A, Gurman GM, Shapira Y, and Dudvenani A (1998) Ketamine attenuates the interleukin-6 response after cardiopulmonary bypass. *Anesth Analg* **87**:266–271.
- Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederrehe G, Thase ME, Lavori PW, Lebowitz BD, et al. (2006) Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR\*D report. *Am J Psychiatry* **163**:1905–1917.
- Russabrov E, Davies JM, Bessler H, Greemberg L, Roytblat L, Yardeni I-Z, Artru AA, and Shapira Y (2008) Effect of ketamine on inflammatory and immune responses after short-duration surgery in obese patients. *Open Anesthesiol J* **2**:40–45.
- Ryder S, Way WL, and Trevor AJ (1978) Comparative pharmacology of the optical isomers of ketamine in mice. *Eur J Pharmacol* **49**:15–23.
- Sage M and Laird SM (1972) Ketamine anaesthesia for burns surgery. *Postgrad Med J* **48**:156–161.
- Salat K, Siwek A, Starowicz G, Librowski T, Nowak G, Drabik U, Gajdosz R, and Popik P (2015) Antidepressant-like effects of ketamine, norketamine and dehydronorketamine in forced swim test: role of activity at NMDA receptor. *Neuropharmacology* **99**:301–307.
- Salmi E, Långsjö JW, Aalto S, Nägren K, Metsähonkala L, Kaisti KK, Korpi ER, Hietala J, and Scheinin H (2005) Subanesthetic ketamine does not affect 11C-flumazenil binding in humans. *Anesth Analg* **101**:722–725.
- Schoebel R, Wolff M, Peters SC, Bräu ME, Scholz A, Hempelmann G, Olschewski H, and Olschewski A (2005) Ketamine impairs excitability in superficial dorsal horn neurons by blocking sodium and voltage-gated potassium currents. *Br J Pharmacol* **146**:826–833.
- Schoffeld CN (1980) Potentiation of inhibition by general anaesthetics in neurones of the olfactory cortex in vitro. *Pflugers Arch* **383**:249–255.
- Schüttler J, Stanski DR, White PF, Trevor AJ, Horai Y, Verotta D, and Sheiner LB (1987) Pharmacodynamic modeling of the EEG effects of ketamine and its enantiomers in man. *J Pharmacokinetic Biopharm* **15**:241–253.
- Seeman P and Kapur S (2003) Anesthetics inhibit high-affinity states of dopamine D2 and other G-linked receptors. *Synapse* **50**:35–40.
- Seeman P, Ko F, and Tallericco T (2005) Dopamine receptor contribution to the action of PCP, LSD and ketamine psychotomimetics. *Mol Psychiatry* **10**:877–883.
- Segmiller F, Rütther T, Linhardt A, Padberg F, Berger M, Pogarell O, Möller HJ, Kohler C, and Schüle C (2013) Repeated S-ketamine infusions in therapy resistant depression: a case series. *J Clin Pharmacol* **53**:996–998.
- Sekerici C, Dönmez A, Ateş Y, and Okten F (1996) Oral ketamine premedication in children (placebo controlled double-blind study). *Eur J Anaesthesiol* **13**:606–611.
- Selye H (1976) Forty years of stress research: principal remaining problems and misconceptions. *Can Med Assoc J* **115**:53–56.
- Shaffer CL, Osgood SM, Smith DL, Liu J, and Trapa PE (2014) Enhancing ketamine translational pharmacology via receptor occupancy normalization. *Neuropharmacology* **86**:174–180.
- Shah MM (2014) Cortical HCN channels: function, trafficking and plasticity. *J Physiol* **592**:2711–2719.
- Shahani R, Streutker C, Dickson B, and Stewart RJ (2007) Ketamine-associated ulcerative cystitis: a new clinical entity. *Urology* **69**:810–812.
- Sharif NA, Nunes JL, and Whiting RL (1991) Pharmacological characterization of the N-methyl-D-aspartate (NMDA) receptor-channel in rodent and dog brain and rat spinal cord using [<sup>3</sup>H]MK-801 binding. *Neurochem Res* **16**:563–569.
- Shimada T, Yamazaki H, Mimura M, Inui Y, and Guengerich FP (1994) Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. *J Pharmacol Exp Ther* **270**:414–423.
- Shimaoka M, Iida T, Ohara A, Taenaka N, Mashimo T, Honda T, and Yoshiya I (1996) Ketamine inhibits nitric oxide production in mouse-activated macrophage-like cells. *Br J Anaesth* **77**:238–242.
- Shirayama Y and Hashimoto K (2018) Lack of antidepressant effects of (2R,6R)-hydroxynorketamine in a rat learned helplessness model: comparison with (R)-ketamine. *Int J Neuropsychopharmacol* **21**:84–88.
- Short B, Fong J, Galvez V, Shelker W, and Loo CK (2018) Side-effects associated with ketamine use in depression: a systematic review. *Lancet Psychiatry* **5**:65–78.
- Siegel RK (1978) Phencyclidine and ketamine intoxication: a study of four populations of recreational users. *NIDA Res Monogr* **21**:119–147.
- Singh JB, Fedgchin M, Daly E, Xi L, Melman C, De Bruecker G, Tadic A, Sienaert P, Wiegand F, Manji H, et al. (2016a) Intravenous esketamine in adult treatment-resistant depression: a double-blind, double-randomization, placebo-controlled study. *Biol Psychiatry* **80**:424–431.
- Singh JB, Fedgchin M, Daly EJ, De Boer P, Cooper K, Lim P, Pinter C, Murrough JW, Sanacora G, Shelton RC, et al. (2016b) A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. *Am J Psychiatry* **173**:816–826.
- Singh NS, Bernier M, Camandola S, Khadeer MA, Moaddel R, Mattson MP, and Wainer IW (2015) Enantioselective inhibition of d-serine transport by (S)-ketamine. *Br J Pharmacol* DOI: 10.1111/bph.13239 [published ahead of print].
- Singh NS, Paul RK, Ramamoorthy A, Torjman MC, Moaddel R, Bernier M, and Wainer IW (2013) Nicotinic acetylcholine receptor antagonists alter the function and expression of serine racemase in PC-12 and 1321N1 cells. *Cell Signal* **25**:2634–2645.
- Singh NS, Rutkowska E, Plazinska A, Khadeer M, Moaddel R, Jozwiak K, Bernier M, and Wainer IW (2016c) Ketamine metabolites enantioselectively decrease intracellular D-serine concentrations in PC-12 cells. *PLoS One* **11**:e0149499.
- Singh NS, Zarate CA Jr, Moaddel R, Bernier M, and Wainer IW (2014) What is hydroxynorketamine and what can it bring to neurotherapeutics? *Expert Rev Neurother* **14**:1239–1242.
- Sinner B and Graf BM (2008) Ketamine. *Handb Exp Pharmacol* **14**:313–333.
- Skeldon SC and Goldenberg SL (2014) Urological complications of illicit drug use. *Nat Rev Urol* **11**:169–177.
- Skuza G and Rogóž Z (2002) A potential antidepressant activity of SA4503, a selective sigma 1 receptor agonist. *Behav Pharmacol* **13**:537–543.
- Smith DJ, Bouchal RL, deSanctis CA, Monroe PJ, Amedro JB, Perrotti JM, and Crisp T (1987) Properties of the interaction between ketamine and opiate binding sites in vivo and in vitro. *Neuropharmacology* **26**:1253–1260.
- Smith DJ, Perrotti JM, Mansell AL, and Monroe PJ (1985) Ketamine analgesia is not related to an opiate action in the periaqueductal gray region of the rat brain. *Pain* **21**:253–265.
- Smith GS, Schloesser R, Brodie JD, Dewey SL, Logan J, Vitkun SA, Simkowitz P, Hurley A, Cooper T, Volkow ND, et al. (1998) Glutamate modulation of dopamine measured in vivo with positron emission tomography (PET) and 11C-raclopride in normal human subjects. *Neuropharmacology* **18**:18–25.
- Sofia RD and Harakal JJ (1975) Evaluation of ketamine HCl for anti-depressant activity. *Arch Int Pharmacodyn Ther* **214**:68–74.
- Stein C (2016) Opioid receptors. *Annu Rev Med* **67**:433–451.
- Stewart CE (2001) Ketamine as a street drug. *Emerg Med Serv* **30**:30, 32, 34 passim.
- Strayer RJ and Nelson LS (2008) Adverse events associated with ketamine for procedural sedation in adults. *Am J Emerg Med* **26**:985–1028.
- Stubhaug A, Breivik H, Eide PK, Kreunen M, and Foss A (1997) Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. *Acta Anaesthesiol Scand* **41**:1124–1132.
- Sun L, Li Q, Li Q, Zhang Y, Liu D, Jiang H, Pan F, and Yew DT (2014) Chronic ketamine exposure induces permanent impairment of brain functions in adolescent cynomolgus monkeys. *Addict Biol* **19**:185–194.
- Sun W and Wessinger WD (2004) Characterization of the non-competitive antagonist binding site of the NMDA receptor in dark Agouti rats. *Life Sci* **75**:1405–1415.
- Sussman DR (1974) A comparative evaluation of ketamine anesthesia in children and adults. *Anesthesiology* **40**:459–464.
- Suzuki K, Nosyreva E, Hunt KW, Kavalali ET, and Monteggia LM (2017) Effects of a ketamine metabolite on synaptic NMDAR function. *Nature* **546**:E1–E3.
- Suzuki M, Haraguti S, Sugimoto K, Kikutani T, Shimada Y, and Sakamoto A (2006) Low-dose intravenous ketamine potentiates epidural analgesia after thoracotomy. *Anesthesiology* **105**:111–119.
- Szymkowitz SM, Finnegan N, and Dale RM (2013) A 12-month naturalistic observation of three patients receiving repeat intravenous ketamine infusions for their treatment-resistant depression. *J Affect Disord* **147**:416–420.
- Takeyama K, Yoshikawa M, Oka T, Kawaguchi M, Suzuki T, and Hashimoto A (2006) Ketamine enhances the expression of serine racemase and D-amino acid oxidase mRNAs in rat brain. *Eur J Pharmacol* **540**:82–86.
- Tanaka M, Sato M, Saito A, and Nishikawa T (2000) Reevaluation of rectal ketamine premedication in children: comparison with rectal midazolam. *Anesthesiology* **93**:1217–1224.
- Temme L, Schepmann D, Schreiber JA, Frehland B, and Wünsch B (2018) Comparative pharmacological study of common NMDA receptor open channel blockers regarding their affinity and functional activity toward GluN2A and GluN2B NMDA receptors. *ChemMedChem* **13**:446–452.
- Thomson AM, West DC, and Lodge D (1985) An N-methylaspartate receptor-mediated synapse in rat cerebral cortex: a site of action of ketamine? *Nature* **313**:479–481.
- Traber DL and Wilson RD (1969) Involvement of the sympathetic nervous system in the pressor response to ketamine. *Anesth Analg* **48**:248–252.

- Traber DL, Wilson RD, and Priano LL (1970) The effect of beta-adrenergic blockade on the cardiopulmonary response to ketamine. *Anesth Analg* **49**:604–613.
- Trescott AM, Datta S, Lee M, and Hansen H (2008) Opioid pharmacology. *Pain Physician* **11**:S133–S153.
- Tsai TH, Cha TL, Lin CM, Tsao CW, Tang SH, Chuang FP, Wu ST, Sun GH, Yu DS, and Chang SY (2009) Ketamine-associated bladder dysfunction. *Int J Urol* **16**: 826–829.
- Tsze DS, Steele DW, Machan JT, Akhlaghi F, and Linakis JG (2012) Intranasal ketamine for procedural sedation in pediatric laceration repair: a preliminary report. *Pediatr Emerg Care* **28**:767–770.
- Turfus SC, Parkin MC, Cowan DA, Halket JM, Smith NW, Braithwaite RA, Elliott SP, Steventon GB, and Kicman AT (2009) Use of human microsomes and deuterated substrates: an alternative approach for the identification of novel metabolites of ketamine by mass spectrometry. *Drug Metab Dispos* **37**: 1769–1778.
- Valentine GW, Mason GF, Gomez R, Fasula M, Watzl J, Pittman B, Krystal JH, and Sanacora G (2011) The antidepressant effect of ketamine is not associated with changes in occipital amino acid neurotransmitter content as measured by [(1)H]-MRS. *Psychiatry Res* **191**:122–127.
- Vickers BA, Lee W, and Hunsberger J (2017) A case report: subanesthetic ketamine infusion for treatment of cancer-related pain produces urinary urge incontinence. *A A Case Rep* **8**:219–221.
- Virtue RW, Alanis JM, Mori M, Lafargue RT, Vogel JH, and Metcalf DR (1967) An anesthetic agent: 2-ortho-chlorophenyl, 2-methylamino cyclohexanone HCl (CI-581). *Anesthesiology* **28**:823–833.
- Vollenweider FX, Leenders KL, Oye I, Hell D, and Angst J (1997) Differential psychopathology and patterns of cerebral glucose utilisation produced by (S)- and (R)-ketamine in healthy volunteers using positron emission tomography (PET). *Eur Neuropsychopharmacol* **7**:25–38.
- Vollenweider FX, Vontobel P, Oye I, Hell D, and Leenders KL (2000) Effects of (S)-ketamine on striatal dopamine: a [<sup>11</sup>C]raclopride PET study of a model psychosis in humans. *J Psychiatry Res* **34**:35–43.
- Vyklicky V, Korinek M, Smejkalova T, Balik A, Krausova B, Kaniakova M, Lichnerova K, Cerny J, Krusek J, Dittert I, et al. (2014) Structure, function, and pharmacology of NMDA receptor channels. *Physiol Res* **63** (Suppl 1): S191–S203.
- Wagner LE II, Gingrich KJ, Kulli JC, and Yang J (2001) Ketamine blockade of voltage-gated sodium channels: evidence for a shared receptor site with local anesthetics. *Anesthesiology* **95**:1406–1413.
- Wahl-Schott C and Biel M (2009) HCN channels: structure, cellular regulation and physiological function. *Cell Mol Life Sci* **66**:470–494.
- Walker AK, Budac DP, Bisulco S, Lee AW, Smith RA, Beenders B, Kelley KW, and Dantzer R (2013) NMDA receptor blockade by ketamine abrogates lipopolysaccharide-induced depressive-like behavior in C57BL/6J mice. *Neuropsychopharmacology* **38**:1609–1616.
- Wallach J, Kang H, Colestock T, Morris H, Bortolotto ZA, Collingridge GL, Lodge D, Halberstadt AL, Brandt SD, and Adejare A (2016) Pharmacological investigations of the dissociative 'legal highs' diphenidine, methoxphenidine and analogues. *PLoS One* **11**:e0157021.
- Wan LB, Levitch CF, Perez AM, Brallier JW, Iosifescu DV, Chang LC, Foulkes A, Mathew SJ, Charney DS, and Murrough JW (2015) Ketamine safety and tolerability in clinical trials for treatment-resistant depression. *J Clin Psychiatry* **76**: 247–252.
- Wang C, Zheng D, Xu J, Lam W, and Yew DT (2013) Brain damages in ketamine addicts as revealed by magnetic resonance imaging. *Front Neuroanat* **7**:23.
- Wang J, Mack AL, Coop A, and Matsumoto RR (2007) Novel sigma (sigma) receptor agonists produce antidepressant-like effects in mice. *Eur Neuropsychopharmacol* **17**:708–716.
- Watanabe M, Yoshikawa M, Takeyama K, Hashimoto A, Kobayashi H, and Suzuki T (2010) Subchronic administration of ketamine decreases the mRNA expression of serine racemase in rat brain. *Tokai J Exp Clin Med* **35**:137–143.
- Weber F, Wulf H, Gruber M, and Biallas R (2004) S-ketamine and s-norketamine plasma concentrations after nasal and i.v. administration in anesthetized children. *Paediatr Anaesth* **14**:983–988.
- Wei IH, Chen KT, Tsai MH, Wu CH, Lane HY, and Huang CC (2017) Acute amino acid d-serine administration, similar to ketamine, produces antidepressant-like effects through identical mechanisms. *J Agric Food Chem* **65**:10792–10803.
- Weiner AL, Vieira L, McKay CA, and Bayer MJ (2000) Ketamine abusers presenting to the emergency department: a case series. *J Emerg Med* **18**:447–451.
- Weisman H (1971) Anesthesia for pediatric ophthalmology. *Ann Ophthalmol* **3**:229–232.
- Weksler N, Ovadia L, Muati G, and Stav A (1993) Nasal ketamine for paediatric premedication. *Can J Anaesth* **40**:119–121.
- White PF, Ham J, Way WL, and Trevor AJ (1980) Pharmacology of ketamine isomers in surgical patients. *Anesthesiology* **52**:231–239.
- White PF, Schüttler J, Shafer A, Stanski DR, Horai Y, and Trevor AJ (1985) Comparative pharmacology of the ketamine isomers: studies in volunteers. *Br J Anaesth* **57**:197–203.
- White PF, Way WL, and Trevor AJ (1982) Ketamine—its pharmacology and therapeutic uses. *Anesthesiology* **56**:119–136.
- Wieber J, Gugler R, Hengstmann JH, and Dengler HJ (1975) Pharmacokinetics of ketamine in man. *Anaesthetist* **24**:260–263.
- Wilkins LK, Girard TA, and Cheyne JA (2012) Anomalous bodily-self experiences among recreational ketamine users. *Cogn Neuropsychiatry* **17**:415–430.
- Wohleb ES, Gerhard D, Thomas A, and Duman RS (2017) Molecular and cellular mechanisms of rapid-acting antidepressants ketamine and scopolamine. *Curr Neuropharmacol* **15**:11–20.
- Wolff K and Winstock AR (2006) Ketamine: from medicine to misuse. *CNS Drugs* **20**: 199–218.
- Wolosker H, Dumin E, Balan L, and Foltyn VN (2008) D-amino acids in the brain: D-serine in neurotransmission and neurodegeneration. *FEBS J* **275**:3514–3526.
- Wong EH, Kemp JA, Priestley T, Knight AR, Woodruff GN, and Iversen LL (1986) The anticonvulsant MK-801 is a potent N-methyl-D-aspartate antagonist. *Proc Natl Acad Sci USA* **83**:7104–7108.
- Wong EH, Knight AR, and Woodruff GN (1988) [<sup>3</sup>H]MK-801 labels a site on the N-methyl-D-aspartate receptor channel complex in rat brain membranes. *J Neurochem* **50**:274–281.
- Wood JD and Hertz L (1980) Ketamine-induced changes in the GABA system of mouse brain. *Neuropharmacology* **19**:805–808.
- Woolf TF and Adams JD (1987) Biotransformation of ketamine, (Z)-6-hydroxyketamine, and (E)-6-hydroxyketamine by rat, rabbit, and human liver microsomal preparations. *Xenobiotica* **17**:839–847.
- Wray NH, Schappi JM, Singh H, Senese NB, and Rasenick MM (2018) NMDAR-independent, cAMP-dependent antidepressant actions of ketamine. *Mol Psychiatry* DOI: 10.1038/s41380-018-0083-8 [published ahead of print].
- Wu YN and Johnson SW (1996) Pharmacological characterization of inward current evoked by N-methyl-D-aspartate in dopamine neurons in the rat brain slice. *J Pharmacol Exp Ther* **279**:457–463.
- Yamakage M, Hirshman CA, and Croxton TL (1995) Inhibitory effects of thiopental, ketamine, and propofol on voltage-dependent Ca<sup>2+</sup> channels in porcine tracheal smooth muscle cells. *Anesthesiology* **83**:1274–1282.
- Yamakura T, Chavez-Noriega LE, and Harris RA (2000) Subunit-dependent inhibition of human neuronal nicotinic acetylcholine receptors and other ligand-gated ion channels by dissociative anesthetics ketamine and dizocilpine. *Anesthesiology* **92**:1144–1153.
- Yamakura T, Mori H, Masaki H, Shimoji K, and Mishina M (1993) Different sensitivities of NMDA receptor channel subtypes to non-competitive antagonists. *Neuroreport* **4**:687–690.
- Yamakura T and Shimoji K (1999) Subunit- and site-specific pharmacology of the NMDA receptor channel. *Prog Neurobiol* **59**:279–298.
- Yamamoto S, Ohba H, Nishiyama S, Harada N, Kakiuchi T, Tsukada H, and Domino EF (2013) Subanesthetic doses of ketamine transiently decrease serotonin transporter activity: a PET study in conscious monkeys. *Neuropsychopharmacology* **38**: 2666–2674.
- Yamanaka H, Yokoyama C, Mizuma H, Kurai S, Finnema SJ, Halldin C, Doi H, and Onoe H (2014) A possible mechanism of the nucleus accumbens and ventral pallidum 5-HT1B receptors underlying the antidepressant action of ketamine: a PET study with macaques. *Transl Psychiatry* **4**:e342.
- Yamazaki M, Ito Y, Kuze S, Shibuya N, and Momose Y (1992) Effects of ketamine on voltage-dependent Ca<sup>2+</sup> currents in single smooth muscle cells from rabbit portal vein. *Pharmacology* **45**:162–169.
- Yanagihara Y, Kariya S, Ohtani M, Uchino K, Aoyama T, Yamamura Y, and Iga T (2001) Involvement of CYP2B6 in n-demethylation of ketamine in human liver microsomes. *Drug Metab Dispos* **29**:887–890.
- Yanagihara Y, Ohtani M, Kariya S, Uchino K, Hiraishi T, Ashizawa N, Aoyama T, Yamamura Y, Yamada Y, and Iga T (2003) Plasma concentration profiles of ketamine and norketamine after administration of various ketamine preparations to healthy Japanese volunteers. *Biopharm Drug Dispos* **24**:37–43.
- Yang C, Han M, Zhang JC, Ren Q, and Hashimoto K (2016) Loss of parvalbumin-immunoreactivity in mouse brain regions after repeated intermittent administration of esketamine, but not R-ketamine. *Psychiatry Res* **239**:281–283.
- Yang C, Qu Y, Abe M, Nozawa D, Chaki S, and Hashimoto K (2017) (R)-Ketamine shows greater potency and longer lasting antidepressant effects than its metabolite (2R,6R)-hydroxynorketamine. *Biol Psychiatry* **82**:e43–e44.
- Yang C, Shirayama Y, Zhang JC, Ren Q, Yao W, Ma M, Dong C, and Hashimoto K (2015) R-ketamine: a rapid-onset and sustained antidepressant without psychotomimetic side effects. *Transl Psychiatry* **5**:e632.
- Yang J, Li W, Duan M, Zhou Z, Lin N, Wang Z, Sun J, and Xu J (2005) Large dose ketamine inhibits lipopolysaccharide-induced acute lung injury in rats. *Inflamm Res* **54**:133–137.
- Yao N, Skiteva O, Zhang X, Svenningsson P, and Chergui K (2017) Ketamine and its metabolite (2R,6R)-hydroxynorketamine induce lasting alterations in glutamatergic synaptic plasticity in the mesolimbic circuit. *Mol Psychiatry* DOI: 10.1038/mp.2017.239 [published ahead of print].
- Yeung LY, Wai MS, Fan M, Mak YT, Lam WP, Li Z, Lu G, and Yew DT (2010) Hyperphosphorylated tau in the brains of mice and monkeys with long-term administration of ketamine. *Toxicol Lett* **193**:189–193.
- Zanos P and Gould TD (2018a) Intracellular signaling pathways involved in (S)- and (R)-ketamine antidepressant actions. *Biol Psychiatry* **83**:2–4.
- Zanos P, Thompson SM, Duman RS, Zarate CA Jr, and Gould TD (2018b) Convergent mechanisms underlying rapid antidepressant action. *CNS Drugs* **32**:197–227.
- Zanos P and Gould TD (2018c) Mechanisms of ketamine action as an antidepressant. *Mol Psychiatry* **23**:801–811.
- Zanos P, Moaddel R, Morris PJ, Georgiou P, Fischell J, Elmer GI, Alkondon M, Yuan P, Pribut HJ, Singh NS, et al. (2016) NMDAR inhibition-independent antidepressant actions of ketamine metabolites. *Nature* **533**:481–486.
- Zanos P, Moaddel R, Morris PJ, Georgiou P, Fischell J, Elmer GI, Alkondon M, Yuan P, Pribut HJ, Singh NS, et al. (2017a) Zanos et al. reply. *Nature* DOI: 10.1038/nature22085.
- Zanos P, Moaddel R, Morris PJ, Georgiou P, Fischell J, Elmer GI, Alkondon M, Yuan P, Pribut HJ, Singh NS, et al. (2017b) Zanos et al. reply. *Nature* **546**:E4–E5.
- Zanos P, Moaddel R, Morris PJ, Wainer IW, Albuquerque EX, Thompson SM, Thomas CJ, Zarate CA Jr, and Gould TD (2017c) Reply to: antidepressant actions of ketamine versus hydroxynorketamine. *Biol Psychiatry* **81**:e69–e71.
- Zarate CA Jr, Brutsche N, Laje G, Luckenbaugh DA, Venkata SL, Ramamoorthy A, Moaddel R, and Wainer IW (2012a) Relationship of ketamine's plasma metabolites with response, diagnosis, and side effects in major depression. *Biol Psychiatry* **72**:331–338.
- Zarate CA Jr, Brutsche NE, Ibrahim L, Franco-Chaves J, Diazgranados N, Cravchik A, Selter J, Marquardt CA, Liberty V, and Luckenbaugh DA (2012b) Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. *Biol Psychiatry* **71**:939–946.

- Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, and Manji HK (2006) A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry* **63**:856–864.
- Zeilhofer HU, Swandulla D, Geisslinger G, and Brune K (1992) Differential effects of ketamine enantiomers on NMDA receptor currents in cultured neurons. *Eur J Pharmacol* **213**:155–158.
- Zhang C, Tang WK, Liang HJ, Ungvari GS, and Lin SK (2018) Other drug use does not impact cognitive impairments in chronic ketamine users. *Drug Alcohol Depend* **186**:1–8.
- Zhang JC, Li SX, and Hashimoto K (2014) R (-)-ketamine shows greater potency and longer lasting antidepressant effects than S (+)-ketamine. *Pharmacol Biochem Behav* **116**:137–141.
- Zhang K, Xu T, Yuan Z, Wei Z, Yamaki VN, Huang M, Haganir RL, and Cai X (2016) Essential roles of AMPA receptor GluA1 phosphorylation and presynaptic HCN channels in fast-acting antidepressant responses of ketamine. *Sci Signal* **9**:ra123.
- Zhao X, Venkata SL, Moaddel R, Luckenbaugh DA, Brutsche NE, Ibrahim L, Zarate CA Jr, Mager DE, and Wainer IW (2012) Simultaneous population pharmacokinetic modelling of ketamine and three major metabolites in patients with treatment-resistant bipolar depression. *Br J Clin Pharmacol* **74**:304–314.
- Zhao Y and Sun L (2008) Antidepressants modulate the in vitro inhibitory effects of propofol and ketamine on norepinephrine and serotonin transporter function. *J Clin Neurosci* **15**:1264–1269.
- Zhou W, Wang N, Yang C, Li XM, Zhou ZQ, and Yang JJ (2014) Ketamine-induced antidepressant effects are associated with AMPA receptors-mediated upregulation of mTOR and BDNF in rat hippocampus and prefrontal cortex. *Eur Psychiatry* **29**:419–423.
- Zhou ZS and Zhao ZQ (2000) Ketamine blockage of both tetrodotoxin (TTX)-sensitive and TTX-resistant sodium channels of rat dorsal root ganglion neurons. *Brain Res Bull* **52**:427–433.



# **Correction to “Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms”**

In the above article [Zanos Z, Moaddel R, Morris PJ, Riggs LM, Highland JN, Georgiou P, Pereira EFR, Albuquerque EX, Thomas CJ, Zarate CA, and Gould TD (2018) *Pharmacol Rev* 70(3):621–660; doi: <https://doi.org/10.1124/pr.117.015198>], was originally published under copyright by The American Society for Pharmacology and Experimental Therapeutics. The paper is U.S. Government work not protected by U.S. copyright. The article has been corrected to display the correct copyright in the HTML and PDF versions.

The compositor regrets this error and any inconvenience it has caused.