Chapter 4
Rapid Antidepressant Activity of Ketamine Beyond NMDA Receptor

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Abstract Multiple lines of evidence suggest that *N*-methyl-D-aspartate (NMDA) receptor plays a key role in the pathophysiology of depression and therapeutic mechanisms of antidepressants. The NMDA receptor antagonist ketamine is one of the most attractive antidepressants because it can produce rapid and sustained effects in patients with treatment-resistant depression. Recent meta-analyses have shown that the antidepressant effect of ketamine is more potent than that of other NMDA receptor antagonists [e.g., memantine, traxoprodil (CP-101,606), lanicemine (AZD6765), and rapastinel (GLYX-13)] in patients with depression. Ketamine is a racemic mixture containing equal parts of (*R*)-ketamine and (*S*)-ketamine (esketamine). In comparison with (*R*)-ketamine, esketamine shows approximately fourfold greater potency at NMDA receptor. We recently reported that in comparison with esketamine, (*R*)-ketamine shows greater potency and longer-lasting antidepressant effects in animal models of depression. Therefore, it is unlikely that NMDA receptor has a major role in the longer-lasting antidepressant effects of (*R*)-ketamine, although antagonism at this receptor may promote its rapid antidepressant activity. Unlike esketamine, (*R*)-ketamine does not induce psychotomimetic side effects or have abuse potential in rodents. In this chapter, we discuss the role of NMDA receptor in the antidepressant activities of ketamine and its enantiomers.

Keywords Antidepressant • Brain-derived neurotrophic factor • Ketamine • Esketamine • (*R*)-ketamine

Abbreviations

AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BDNF	Brain-derived neurotrophic factor

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BPRS	Brief Psychiatric Rating Scale
CADSS	Clinician-Administered Dissociative States Scale
CNS	Central nervous system
FDA	Food Drug Administration
GLT-1	Glutamate transporter 1
mTORC1	Mammalian target of rapamycin complex 1
NMDA	*N*-methyl-D-aspartate
PCP	Phencyclidine
PV	Parvalbumin
TrkB	Tropomyosin receptor kinase B

4.1 Introduction

Glutamate (L-glutamic acid) is one of the major excitatory neurotransmitters in the mammalian central nervous system (CNS). Multiple lines of evidence suggest that glutamatergic neurotransmission via *N*-methyl-D-aspartate (NMDA) receptor plays a key role in the pathophysiology of depression and mechanisms of action of antidepressants [1–8].

In 2000, Burman et al. (Yale University) reported a rapid antidepressant effect of the NMDA receptor antagonist ketamine in patients with depression [9]. Subsequently, randomized, placebo-controlled studies demonstrated that ketamine produced rapid and sustained antidepressant effects in treatment-resistant patients with major depression and bipolar depression [10, 11]. Furthermore, ketamine showed antidepressant effects in electroconvulsive therapy (ECT)-resistant patients with depression [12]. These reports and many subsequent clinical studies make ketamine an attractive rapid-onset therapeutic drug for treatment-resistant depression, although its clinical application may be limited owing to its propensity of causing psychotomimetic effects [13–21].

In this chapter, I discuss the role of NMDA receptor in the antidepressant activities of ketamine.

4.2 History of Ketamine and Its Abuse Liability

Ketamine (formerly CI-581) was first synthesized in 1962 by Calvin L. Stevens (Wayne State University). After preclinical research, an intravenous subanesthetic dose of ketamine was introduced for testing in human prisoners in 1964. Edward F. Domino (Michigan University) and his wife Toni asserted that ketamine was "dissociative anesthesia" [22]. They demonstrated ketamine's short duration of action and low behavioral toxicity, which made it a more favorable choice compared with phencyclidine (PCP; formerly CI-395) as a dissociative anesthetic drug. Since its

Food and Drug Administration (FDA) approval in 1970, ketamine has been widely used as a dissociative anesthetic [22, 23].

During the late 1960s and early 1970s, many drugs were used by young people as part of "make love, not war" protests against the U.S. war in Vietnam. Ketamine is widely used in veterinary medicine, but sterile ketamine vials intended for veterinary use were diverted for recreational use [22]. Because of its lower potency and shorter duration of action, ketamine ("special K") is associated with less severe psychiatric problems than PCP ("angel dust") [24]. In some countries, ketamine is the most commonly abused drug, and the prevalence of health and social problems is associated with ketamine abuse [25]. Thus, ketamine is a scheduled drug, the use of which should be restricted because of its abuse liability.

4.3 Mechanism of Action of Ketamine

Lodge's group (Royal Veterinary College) reported for the first time that ketamine and PCP are selective NMDA receptor antagonists [24, 26]. The schizophrenia-like actions of PCP detected in Luby's study are well known [27]. Subsequently, ketamine caused schizophrenia-like symptoms in humans [22]. Thus, the psychosis caused by PCP and ketamine was the most closely related to schizophrenia [24, 27, 28]. In 1994, Krystal et al. (Yale University) reported that ketamine has positive and negative effects, including cognitive impairment, in healthy control subjects [29]. Taken together, these findings suggest the NMDA receptor hypofunction hypothesis in schizophrenia [30–34].

Ketamine is a racemic mixture of (*S*)-ketamine (esketamine) and (*R*)-ketamine (Fig. 4.1.). Esketamine (K_i = 0.30 μM for NMDA receptor) has approximately four-fold higher affinity for NMDA receptor relative to (*R*)-ketamine (K_i = 1.4 μM) (Fig. 4.1.) [35]. NMDA receptors are tetrameric combinations usually comprising two GluN1 and two GluN2 subunits, with four possible genes (A–D) encoding the latter.

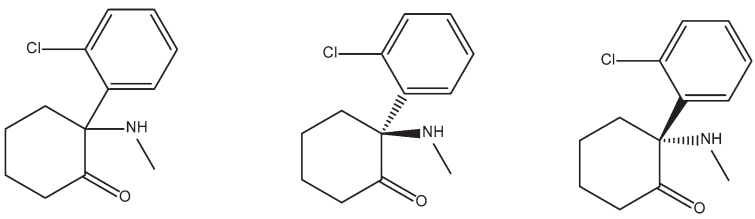

Fig. 4.1 Chemical structure of ketamine, ketamine enantiomers. The value in the parenthesis is the Ki value for NMDA receptor [35]

Esketamine was found to be approximately nine times less potent on GluN1/GluN2A than on GluN1/GluN2B-D [36].

Ketamine has several mechanisms of action besides NMDA receptor antagonism. Esketamine is two to three times more potent than (*R*)-ketamine at μ, κ, and δ opioid receptors [37, 38], although the opioid receptor antagonist naloxone did not block ketamine's action in humans [39]. Furthermore, ketamine has moderate affinity for the dopamine D_2 receptor [40, 41], although the affinity of the two enantiomers at D_2 receptors has not been investigated. (*R*)-ketamine has weak affinity for the sigma-1 receptor, at which only negligible binding of esketamine occurs [42]. However, the precise mechanisms of ketamine's activities are currently unknown.

4.4 Pharmacokinetic Profile of Ketamine

Because of its extensive first-pass metabolism, the oral bioavailability of ketamine is poor. Thus, it has been used via intravenous, intramuscular, and topical routes. Sublingual and nasal formulations of ketamine have also been developed [43]. Ketamine has short blood α and β $t_{1/2}$ of approximately 7 min and 2–4 h, respectively. Its metabolites (norketamine and dehydronorketamine) appear in venous blood approximately 10 and 30 min after administration. Ketamine is metabolized in the liver by CYP3A4 (major), CYP2B6 (minor), and CYP2C9 (minor) isoenzymes into norketamine (through N-demethylation) and finally dehydronorketamine (Fig. 4.2.). Esketamine and (*R*)-ketamine have similar pharmacokinetic profiles [22]. In addition, (*R*)-ketamine is not formed after the intravenous administration of esketamine in humans, indicating the lack of their interconversion [44, 45].

In human volunteers, intravenous esketamine (0.15 mg/kg) is more potent than (*R*)-ketamine (0.5 mg/kg) as an analgesic [46]. However, esketamine produced 1.6 times greater altered body image and changes in hearing, 2.5 times greater feelings of unreality, and 4 times more reduced visual acuity. Thus, it is likely that esketamine because of having greater potency at NMDA receptors has more unwanted psychiatric side effects than (*R*)-ketamine [22], supporting the hypothesis of NMDA receptor hypofunction in psychosis [30–34].

4.5 Antidepressant Effects of Ketamine Racemate

As mentioned in the introduction, Robert Burman et al. (Yale University) reported a rapid antidepressant effect in patients with depression [9]. Subsequently, randomized, placebo-controlled studies demonstrated that ketamine produced rapid antidepressant effects in patients with treatment-resistant and bipolar depression [10, 11]. A randomized, active placebo (midazolam) control study showed that ketamine had greater improvement in the depression score than the midazolam group 24 h after infusion [47]. Singh et al. [48] reported that two- and three-time weekly infusions

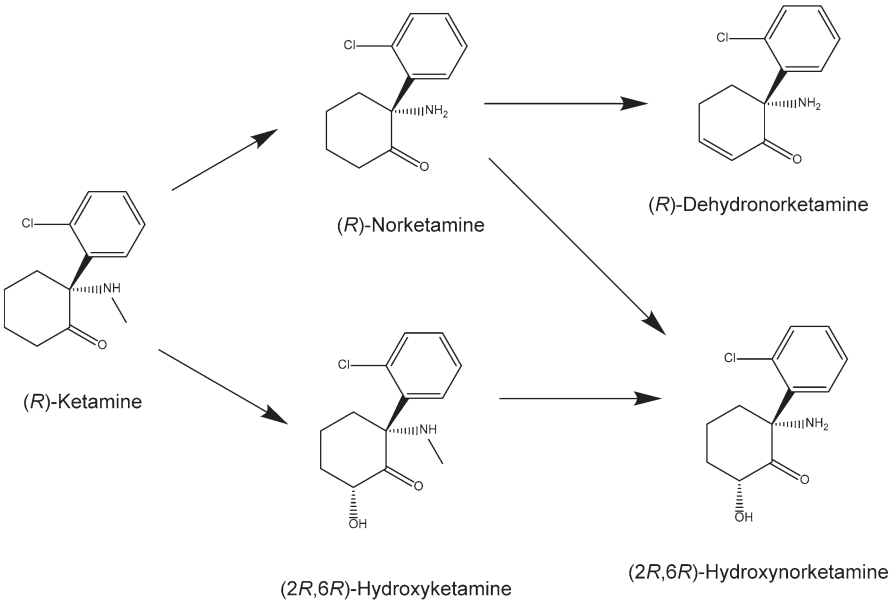

Fig. 4.2 Metabolism of (*R*)-ketamine to (*R*)-norketamine, (*R*)-dehydronorketamine, (2*R*,6*R*)-hydroxyketamine and (2*R*,6*R*)-hydroxynorketamine

of ketamine (0.5 mg/kg) maintained antidepressant efficacy over 15 days, although dissociative symptoms occurred transiently and were attenuated by repeated dosing. Recent meta-analyses have demonstrated that non-ketamine NMDA receptor antagonists [e.g., memantine, traxoprodil (CP-101,606), lanicemine (AZD6765), and rapastinel (GLYX-13)] have smaller effects than ketamine racemate, although the reason underlying this remains unclear [49, 50].

4.6 Mechanisms of Ketamine's Antidepressant Activity

Although ketamine's rapid-onset antidepressant activity is well known, the cellular and molecular mechanisms underlying this remain unclear [51–55]. The rapid antidepressant action of ketamine is currently thought to occur via the blockade of NMDA receptors located on inhibitory γ-aminobutylic acid (GABA)ergic neurons. This causes disinhibition of the pyramidal cells, resulting in a burst of glutamate transmission. Increased glutamate release activates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, resulting in depolarization and calcium influx. Depolarization of the cell induces the release of brain-derived neurotrophic factor (BDNF) and activation of the mammalian target of rapamycin complex 1 (mTORC1) signaling pathway. Finally, the stimulation of mTORC1 increases the synthesis of synaptic proteins, which results in increased number and function of spine

synapses [56–58]. A recent study showed that the antidepressant effect of ketamine via mTOR signaling is mediated by the inhibition of nitrergic Rheb degradation [59].

BDNF and its receptor, tropomyosin receptor kinase B (TrkB), play a role in the pathophysiology of depression and in the therapeutic mechanisms of antidepressants [60–63]. In preclinical models, we reported that regional differences in BDNF, its precursor proBDNF, and BDNF pro-peptide confer resilience to stress [64, 65]. Furthermore, TrkB agonist and antagonist showed a rapid antidepressant effect in inflammation [66, 67], social defeat stress [68], and learned helplessness [69] models of depression. It has been reported that BDNF plays a role in the antidepressant effect of ketamine because its antidepressant effects could be antagonized by TrkB antagonist [70, 71]. Taking these findings together, it is likely that BDNF–TrkB signaling plays a key role in the antidepressant effects of ketamine.

The protein p11 (also known as S100A10), a member of the S100 EF-hand protein family, is widely expressed in several brain regions that are implicated in the pathophysiology of depression, including the hippocampus and frontal cortex. Accumulating evidence suggests a key role of p11 in the pathophysiology of depression [72]. For example, a recent study showed that hippocampal p11 played a key role in the sustained antidepressant effect of ketamine in a chronic unpredictable mild stress model of depression [73].

Growing evidence suggests that downregulated clearance of glutamate and signaling pathways involving BDNF–TrkB signaling play a role in the morphological changes within the hippocampus of patients with depression. A recent study showed that the regulation of glutamate transporter 1 (GLT-1) on astrocytes, responsible for 90 % of glutamate reuptake from the synapse, through BDNF–TrkB signaling is involved in ketamine's antidepressant activity [74].

Panos Zanos et al. (University of Maryland) recently reported that the metabolism of ketamine to (2*S*,6*S*; 2*R*,6*R*)-hydroxynorketamine (Fig. 4.2.) is essential for its antidepressant effects [75]. These antidepressant activities are independent of NMDA receptor inhibition but involve early and sustained activation of AMPA receptors. This study suggests a novel mechanism underlying the antidepressant properties of ketamine; this mechanism is important for the development of next-generation, rapid-acting antidepressants. In contrast, we recently reported that a bilateral infusion of (*R*)-ketamine into the medial prefrontal cortex caused antidepressant effects in the rat learned helplessness model [76], indicating that a direct antidepressant action of (*R*)-ketamine itself. Very recently, we reported that (*R*)-ketamine showed greater potency and longer lasting antidepressant effects than its metabolite (2*R*,6*R*)-hydroxynorketamine in inflammation and social defeat stress models [77].

4.7 Antidepressant Effects of Esketamine

Many scientists believe that NMDA receptor antagonism plays a key role in the mechanisms of ketamine's antidepressant activity. Considering the high affinity of esketamine at NMDA receptor [approximately four times more potent than

(*R*)-ketamine], the company Johnson & Johnson has been developing a method for the intranasal administration of esketamine as a treatment for depression. Intranasal esketamine received the breakthrough treatment designation from the US FDA. In addition, Singh et al. [78] reported a rapid-onset antidepressant effect of intravenous esketamine infusion in treatment-resistant patients with depression, although the Brief Psychiatric Rating Scale (BPRS) score and the Clinician-administered Dissociative States Scale (CADSS) score peaked 40 min after esketamine infusion (0.20 or 0.40 mg/kg for 40 min). It is also likely that the potency of the antidepressant effect of intranasal ketamine administration is lower than that of the effect of intravenous ketamine infusion [79].

4.8 Antidepressant Effects of *R*-Ketamine

Because non-ketamine NMDA receptor antagonists have smaller effects than ketamine [49, 50], we hypothesized that NMDA receptor may not play a key role in the antidepressant effects of ketamine. Given the different affinities of the two ketamine enantiomers for NMDA receptor (Fig. 4.1.) [22, 35], we compared the antidepressant effects and side effect profiles of these two enantiomers in rodents.

We found that (*R*)-ketamine showed greater potency and longer-lasting antidepressant effects than esketamine in animal models of depression, including neonatal dexamethasone exposure, repeated social defeat stress, and learned helplessness [80, 81]. Therefore, it is unlikely that NMDA receptor has a major role in the long-lasting antidepressant effects of (*R*)-ketamine, although antagonism at this receptor may promote its rapid antidepressant activity [81]. Our findings have been replicated by a recent study [75]. Unlike esketamine, (*R*)-ketamine does not induce psychotomimetic side effects or abuse potential in rodents [81, 82]. Furthermore, we reported that a single dose of esketamine (10 mg/kg) but not (*R*)-ketamine (10 mg/kg) resulted in the loss of parvalbumin (PV) immunoreactivity in mouse brain regions, such as the prefrontal cortex [81], suggesting that the loss of PV-positive cells is associated with ketamine-induced psychotomimetic effects.

A recent study using [^{11}C]raclopride and positron emission tomography showed a marked reduction of dopamine $D_{2/3}$ receptor binding in the monkey striatum after a single infusion of esketamine (0.5 mg/kg, 40 min) but not (*R*)-ketamine (0.5 mg/kg, 40 min) [83]. Singh et al. [78] reported a rapid-onset antidepressant effect of esketamine in patients with treatment-resistant depression, although the BPRS and CADSS scores peaked 40 min after esketamine infusion (0.20 or 0.40 mg/kg for 40 min). Considering the role of dopamine release in psychosis, it is likely that the marked release of dopamine from presynaptic terminals in the striatum is associated with the psychotomimetic side effects in humans after an infusion of ketamine or esketamine. It is well known that psychosis induced by NMDA receptor antagonists such as ketamine and PCP could be associated with NMDA receptor antagonism [24, 30], suggesting that the psychotomimetic effects of ketamine and esketamine are associated with their antagonism at NMDA receptor.

Studies using repeated ketamine (or esketamine) infusions resulted in significant antidepressant effects with an extended median time to recurrence of depressive symptoms in a 4-week open-label study [13], an 18-day open-label study [84], a 12-month, naturalistic, three-patient case series [85], a four-open-label-injection study [78], and a double-blind placebo-controlled study [48]. However, psychotomimetic side effects were shown after each infusion of ketamine or esketamine [13, 48, 84]. There were no differences in dissociative, psychotomimetic, or high feelings between responders and non-responders [84], suggesting that ketamine's antidepressant effects are not associated with psychotomimetic effects. We recently reported that repeated, intermittent administration of esketamine (10 mg/kg, once per week for 8 weeks) but not (*R*)-ketamine led to loss of PV immunoreactivity in the prefrontal cortex of mouse brain [86]. Because such loss of PV immunoreactivity in the prefrontal cortex may be associated with psychosis and γ-oscillation deficits in schizophrenia [87, 88], repeated administration of esketamine or ketamine may have long-lasting detrimental side effects in the prefrontal cortex of humans. Thus, it seems that the loss of PV immunoreactivity in the prefrontal cortex is associated with NMDA receptor antagonism. Taking these findings together, it is likely that the repeated intermittent use of (*R*)-ketamine is safer than that of esketamine or ketamine in the treatment of depression [14, 17, 18].

Rapastinel (formerly GLYX-13), a partial agonist at glycine site of the NMDA receptor, shows antidepressant-like effects without ketamine-like side effects in animal models [89]. A recent double-blind, placebo-controlled study demonstrated that a single intravenous (i.v.) infusion of rapastinel (5 or 10 mg/kg) produced rapid and sustained antidepressant effects in depressed patients who had not responded to another antidepressant, and that this drug did not elicit psychotomimetic or other significant side effects [90]. The Phase III study of rapastinel (Allergan) received the Breakthrough Therapy designation from the U.S. FDA for adjunctive treatment of major depression. Very recently, we reported that (*R*)-ketamine is a longer-lasting antidepressant compared with rapastinel in social defeat stress model of depression [91].

These findings suggest that in comparison with esketamine and rapastinel, (*R*)-ketamine shows greater potency and longer-lasting antidepressant effects in animal models of depression. (*R*)-ketamine has fewer psychotomimetic side effects and lower abuse potential than esketamine. However, further detailed studies on the precise molecular and cellular mechanisms of (*R*)-ketamine's antidepressant effect are needed.

4.9 Conclusions and Perspectives

There is an urgent need for rapid-onset antidepressants for treatment-resistant depression. A number of clinical studies have demonstrated that ketamine has rapid-onset and sustained antidepressant effects in patients with treatment-resistant depression, although psychotomimetic effects of ketamine infusion have also been

identified. Although ketamine has not yet been approved for use in depression, it has been widely used as an off-label approach in US. Because preclinical data suggests that repeated infusions of ketamine leads to detrimental side effects on the brain, careful screening, management, and follow-up of depressed patients who have received repeated ketamine therapy will be necessary.

In conclusion, the use of (*R*)-ketamine for treatment-resistant depression should provide a new therapeutic approach by reducing the detrimental side effects of racemate ketamine [14, 17, 18, 92] since possible advantages and disadvantages in the potential clinical use of racemate ketamine are pointed [93, 94].

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Conflict of Interest Dr. Hashimoto is an inventor on a filed patent application on "The use of (*R*)-ketamine in the treatment of psychiatric diseases" by Chiba University. Dr. Hashimoto has received research support from Dainippon Sumitomo, Mochida, Otsuka, and Taisho.

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