Antidepressant Actions of Ketamine and Its Two Enantiomers

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Abstract The *N*-methyl-D-aspartate receptor antagonist ketamine has been widely used as an off-label medication to treat depression because it elicits rapid and robust antidepressant effects in treatment-resistant patients with depression. (*R*,*S*)-ketamine is a racemic mixture containing equal amounts of (*R*)-ketamine (or arketamine) and (*S*)-ketamine (or esketamine). On March 5, 2019, the United States Food and Drug Administration approved an (*S*)-ketamine nasal spray for treatment-resistant depression. In contrast, (*R*)-ketamine has been reported to have a greater potency and longer-lasting antidepressant effects than (*S*)-ketamine in rodent models of depression. However, the precise mechanisms underlying the robust antidepressant effects of ketamine enantiomers remain unknown. In this chapter, we discuss recent findings on the antidepressant actions of two enantiomers of ketamine.

Keywords Arketamine · Ketamine · Esketamine

1 Introduction

Ketamine is a noncompetitive *N*-methyl-D-aspartate receptor (NMDAR) antagonist that has drawn significant attention in recent decades from scientists all over the world because of its robust antidepressant effects (Cusin 2019; Duman 2018; Hashimoto 2016b, 2017, 2019). Ketamine was first synthesized at Parke-Davis (Detroit, MI, USA) by Calvin Lee Stevens in 1962, with a study of ketamine's

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dissociative anesthetics effects in the prison population quickly following in 1964 (Cohen et al. 2018; Domino 2010; Li and Vlisides 2016). Afterward, ketamine's anesthetic effects were subsequently confirmed by other investigators, and the drug began to be employed as an anesthetic in humans and animals in 1966 (Domino 2010; Stevenson 2005). In view of ketamine's unique pharmacological properties of pain relief and sedation (Gao et al. 2016), it was approved formally for use by the United States (US) Food and Drug Administration (FDA) in 1970 and was placed by the World Health Organization (WHO) in 1985 onto an essential medicines list as an intravenous anesthetic (Gowda et al. 2016; WHO 2011).

Berman et al. (2000) first conducted a placebo-controlled study of ketamine application in eight patients with major depressive disorder (MDD), who were given a dosage of 0.5 mg/kg over 40 min; their depressive symptoms significantly improved within 3 days, while feelings of perceptual disturbances or euphoria occurred in the same patients after treatment (Berman et al. 2000). More generally, in these individuals, the drug produced rapid-acting and sustained antidepressant effects although psychotomimetic effects were also reported after a single infusion of ketamine (Berman et al. 2000). Subsequent studies replicated the noted robust antidepressant effects of ketamine in treatment-resistant patients with MDD and bipolar disorder (BD) (Zarate et al. 2006; Newport et al. 2015; Kishimoto et al. 2016).

Despite ketamine's powerful antidepressant effects in humans, there are some potential drawbacks that cannot be neglected. When used as an anesthetic for anesthesia in surgical procedures, acute and chronic pain management, and critical care (Kurdi et al. 2014), side effects such as hallucinations, agitation, confusion, and psychotomimetic effects resembling schizophrenia can follow (Domino 2010; Gao et al. 2016; Krystal et al. 1994; Kurdi et al. 2014). For some patients, ketamine also brings about cognitive impairments (Molero et al. 2018; Szlachta et al. 2017), urinary tract inflammation (Sihra et al. 2018), liver enzyme abnormalities (Zhao et al. 2018), and other symptoms such as an increase in the heart rate or blood pressure (Sheth et al. 2018). Further, considering the effects reported during recreational usage or the euphoric "dissociated" state caused by higher doses, there exists a potential for abuse no matter what the drug's original intended purpose in a situation is (Heal et al. 2018; Ivan Ezquerra-Romano et al. 2018; Liao et al. 2017; Morgan

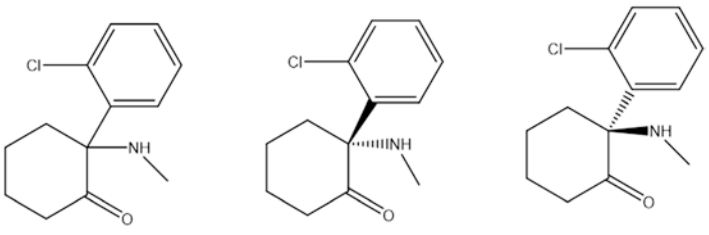

Fig. 1 Chemical structure of ketamine and its two enantiomers. The values in the parenthesis are the *K*i value for the NMDAR (Hashimoto 2019)

and Curran 2012; Tracy et al. 2017). At present, however, there are no superior antidepressants to ketamine that show robust antidepressant effects in patients with MDD (Duman 2018).

Ketamine is a racemic mixture containing equal amounts of (*R*)-ketamine (or arketamine) and (*S*)-ketamine (or esketamine) (Fig. 1) (Domino 2010). Different affinities and potencies of these two ketamine enantiomers exist. (*S*)-ketamine has about a three- to fourfold greater affinity for the NMDAR as compared with (*R*)-ketamine (Fig. 1). Conversely, (*S*)-ketamine holds approximately a three- to fourfold greater anesthetic potency and shows greater undesirable psychotomimetic side effects in comparison with (*R*)-ketamine (Domino 2010; Hashimoto 2016b, c). In prior research, (*R*)-ketamine showed a greater degree of potency and longer-lasting antidepressant effects than (*S*)-ketamine in several rodents model of depression (Fukumoto et al. 2017; Yang et al. 2015, 2018a; Zhang et al. 2014), and (*R*)-ketamine also did not present side effects on psychotomimetic actions or abuse liability in contrast with (*S*)-ketamine (Chang et al. 2019a; Yang et al. 2015). Third, (*R*)-ketamine is expected to constitute a safer choice than either (*R*,*S*)-ketamine or (*S*)-ketamine in consideration of its antidepressant actions (Chang et al. 2019a; Hashimoto 2016b, c). However, the precise molecular and cellular mechanisms underlying ketamine's antidepressant effects remain to be elucidated. To date, there is much debate ongoing about the molecular mechanisms underlying ketamine's antidepressant effects in humans and rodents alike. Therefore, it is necessary to summarize the current findings on ketamine's antidepressant effects to further the understanding of the neurobiology of ketamine's actions.

2 (*R*,*S*)-Ketamine's Antidepressant Effects

*2.1 Sumary of (*R,S*)-Ketamine's Antidepressant Effects*

Data from the WHO indicate that more than 300 million people of all ages are suffering from depression, which is the leading cause of disability worldwide, leading to a great expenditure of medical and health resources (WHO 2017). Currently available antidepressants have a delay period of approximately 3–4 weeks before they begin working, and about 30% of patients with depression are resistant entirely to these antidepressants (Zhang and Hashimoto 2019). Moreover, other NMDAR antagonists except ketamine have failed in clinical trials (Hashimoto 2019). Therefore, it is unlikely that NMDAR inhibition plays a key role in the antidepressant actions of ketamine.

(*R*,*S*)-Ketamine's antidepressant effects have been studied for almost 20 years after Berman et al.'s seminal report (Berman et al. 2000). In the following decade, most studies on patients with MDD have revealed promising prospects for the use of (*R*,*S*)-ketamine's antidepressant effects. Furthermore, clinical trials conducted on the subjects of ketamine's administration dosage, timing, route, curative effect,

tolerability, safety, and antisuicidal effects have also been investigated. Even its use in different types of depression, including treatment-resistant depression, posttraumatic stress disorder (PTSD), and bipolar depression, has been explored in more recent studies (Bobo et al. 2016; Liriano et al. 2019; Schwartz et al. 2016; Zhang and Hashimoto 2019). Further, several rodent models of depression [i.e., the learned helplessness (LH) model, chronic unpredictable mild stress (CUMS) model, and chronic social defeat stress (CSDS) model] have been established for the purpose of testing (*R*,*S*)-ketamine's antidepressant effects (Krishnan and Nestler 2011). In short, an array of research modalities including original investigations, clinical trials, systematic reviews, and meta-analyses have been used to study (*R*,*S*)-ketamine's antidepressant effects (Krishnan and Nestler 2011; Sanacora et al. 2017; Short et al. 2018; Singh et al. 2017; Veraart et al. 2018).

*2.2 (*R,S*)-Ketamine's Antidepressant Effects in Humans*

In clinical trials, interventional studies have been adopted for evaluating the beneficial effects of (*R*,*S*)-ketamine. A number of randomized single-/double-blind placebo-/drug-controlled studies have been performed by many researchers to observe the antidepressant effects of (*R*,*S*)-ketamine in patients with MDD, who were often infused with only a single intravenous dose of 0.5 mg/kg. Berman et al. (2000) first reported the double-blinded and placebo-controlled study of (*R*,*S*)-ketamine. Then, Zarate et al. (2006) replicated that a high number (71%) of participants showed significant improvements in depressive symptoms within 24 h of drug administration, and 25% of the study subjects showed antidepressant effects for at least 1 week after a single dose of ketamine as part a randomized, placebo-controlled, double-blind crossover study.

A review of the ClinicalTrials.gov database found that about 160 applications from around the world for studying (*R*,*S*)-ketamine's antidepressant effect on patients with depression existed by the end of June 2019. Study subjects mainly included those with MDD with or without suicide ideation, treatment-resistant depression, BD, and PTSD. Studies chiefly involved a randomized single-blind or double-blind design and were placebo-controlled or midazolam-controlled interventions. Collectively, it seems that (*R*,*S*)-ketamine is viewed as a promising antidepressant for the treatment of severe depression. Systematic reviews and meta-analyses have also been adopted as investigational means by scientists for evaluating the impact of the antidepressant effect of (*R*,*S*)-ketamine. Such meta-analyses often include treatment-resistant patients with MDD or BD, and their data are mainly a collection of those from randomized controlled trials (RCTs) (Coyle and Laws 2015; Kishimoto et al. 2016; Newport et al. 2015; Serafini et al. 2014; Wilkinson et al. 2018).

(*R*,*S*)-Ketamine appears to exhibit rapid antidepressant and antisuicidal ideation effects in treatment-resistant patients with depression. Two midazolam-controlled randomized clinical trials conducted in depressed patients with low levels of suicidal

ideation (Grunebaum et al. 2018; Murrough et al. 2013a) demonstrated rapid reductions in suicidal ideation and depressive symptoms within 24 h after treatment with (*R*,*S*)-ketamine as compared with in the midazolam treatment group (Grunebaum et al. 2018; Murrough et al. 2013a). (*R,S*)-Ketamine has similarly demonstrated early emerging evidence of having antisuicidal effects in depressed patients with suicidal ideation in other research that last from 1 day to 1 week (Bartoli et al. 2017; Reinstatler and Youssef 2015; Wilkinson et al. 2018).

In special studies on treatment-resistant depression, (*R,S*)-ketamine has been proposed as an effective antidepressant, but there is a lack of long-term data on sustained depression remission in patients (Serafini et al. 2014; Papadimitropoulou et al. 2017). When considering bipolar depression, (*R,S*)-ketamine was found to be an effective antidepressant (Parsaik et al. 2015), but there is also limited evidence to support the maintenance of a response for up to 24 h following a single intravenous dose of ketamine in bipolar depression, and (*R,S*)-ketamine did not show a statistical advantage in remission of bipolar depression (McCloud et al. 2015). Therefore, more RCT studies are needed to verify (*R,S*)-ketamine's antidepressant effect in different types of depression.

*2.3 Routes of Administration of (*R,S*)-Ketamine*

An understanding of the route of administration of (*R*,*S*)-ketamine is required to confirm its antidepressant effects. There exist a number of studies on routes of administration of (*R*,*S*)-ketamine, including intravenous, intramuscular, intranasal, subcutaneous, oral, sublingual, transmucosal, and intrarectal, and the bioavailability of these forms of administration varies widely as determined by the absorption of pharmacokinetics although the intravenous route is the most commonly used in patients with depression at this time (Andrade 2017; Hashimoto 2019; Zanos et al. 2018; Zhang and Hashimoto 2019). The bioavailability of intranasal administration of (*R*,*S*)-ketamine is lower than that of either intravenous or intramuscular administration (Hashimoto 2019; Zhang and Hashimoto 2019). In an effort to assess the safety and efficacy of (*R*,*S*)-ketamine, Andrade (2017) suggested that the infusion of ketamine by the subcutaneous, intranasal, and oral routes is worth further study based on their clinical practicability. Retrospective data from 22 patients given oral ketamine at a dose of 50 mg per 3 days, which was titrated up by 25 mg per 3 days, showed that 30% of patients with treatment-resistant depression responded to the oral (*R*,*S*)-ketamine and approximately 70% patients had no improvement in mood symptoms (Al Shirawi et al. 2017). Rosenblat et al. (2019) published a systematic review involving a small number of clinical studies that suggested that oral ketamine could produce significant antidepressant effects, but the drug's antisuicidal effects and efficacy remain undetermined in patients with treatment-resistant depression. Andrade (2019) suggested that oral ketamine should be evaluated by higher-quality studies in the future. Elsewhere, intranasal administration of a single dose of 50 mg of (*R*,*S*)-ketamine in a 2014 randomized, double-blind crossover

study led to depressive symptoms being significantly improved in 44% of patients (8/18) after 24 h, with minimal psychosis and dissociation observed in the study (Lapidus et al. 2014). Thus, multiple routes other than the intravenous infusion of ketamine are under consideration in research.

2.4 (R,S)-Ketamine's Antidepressant Effects After Repeated Infusion

Repeated ketamine infusion is very important for maintenance therapy of patients with treatment-resistant depression (Murrough et al. 2013b; Strong and Kabbaj 2018). In a randomized controlled trial, the infusion of ketamine with three methods, including single, repeated, and maintenance, was performed to observe (*R*,*S*)-ketamine's antidepressant effects in treatment-resistant patients; results suggested that a single intravenous dose (0.5 mg/kg) over 40 min significantly improved depressive symptoms after 24 h of infusion. Elsewhere, six repeated infusions worked for a time in 59% of participants whose response criteria met the clinical needs, while these participants had no further benefit from weekly maintenance infusions based on the Montgomery–Åsberg Depression Rating Scale (MADRS) scores (Phillips et al. 2019). In addition, the efficiency of (*R*,*S*)-ketamine's antidepressant effects were also investigated in patients with PTSD treated by eight repeated ketamine infusions done over 4 weeks (Abdallah et al. 2019) and in those with unipolar and bipolar depressive disorder with current suicidal ideation treated by six repeated ketamine infusions performed during a 12-day period (Zhan et al. 2019; Zheng et al. 2018); these studies supported that the rapid and robust antidepressant effects of (*R*,*S*)-ketamine can be cumulative and sustained following repeated infusion. Despite ketamine's potential for abuse and psychotomimetic effects, it represents a new drug option for antidepressant treatment. Thus, further investigation of (*R*,*S*)-ketamine's antidepressant effects is necessary.

2.5 (R,S)-Ketamine's Antidepressant Effects in Rodents

Animal models of depression were adopted by researchers to investigate (*R*,*S*)-ketamine's antidepressant effects. Animal models of depression have previously been used for the development of new antidepressants (Fernando and Robbins 2011; Pittenger et al. 2007). In a shock-induced depression model, Chaturvedi et al. (1999) reported that the antidepressant effects of (*R*,*S*)-ketamine at a dose range of 2.5–10 mg/kg significantly increased ambulation and rearing in the open field test and attenuated the immobility time during the forced swimming test as compared with control mice who received shock. In a rat LH model, Koike et al. (2011) reported that (*R*,*S*)-ketamine (10 mg/kg) exerted rapid and sustained antidepressant

effects for at least 72 h after treatment, in which the number of escape failures significantly decreased in the LH paradigm and the immobility time during the tail suspension test was significantly reduced in comparison with in the vehicle-treated group. In a CUMS model of either mice or rats, (*R*,*S*)-ketamine at a single dose of 10 mg/kg elicited rapid-onset and long-lasting antidepressant effects as evaluated by the behavioral tests of forced swimming, tail suspension, and sucrose preference; even the ameliorated anhedonia lasted for 8 days in this model (Ma et al. 2013; Sun et al. 2016). Hollis and Kabbaj (2014) suggested in their research that CSDS model is a valuable research tool for investigating possible causes and treatments for human depression. In a CSDS model, as compared with the TrkB agonists 7,8-dihydroxyflavone and TrkB antagonist ANA-12, (*R*,*S*)-ketamine showed longer-lasting antidepressant effects for 7 days (Zhang et al. 2015). In contrast, however, Donahue et al. (2014) reported that a single administration of ketamine (10 mg/kg) showed a rapid antidepressant effect in a CSDS model, attenuating social avoidance in the social interaction test but having no effect on anhedonia in the intracranial self-stimulation test (Donahue et al. 2014).

In addition, inflammation-induced mice or rat depression models, such as those using lipopolysaccharides or complete Freund's adjuvant, can also be useful in observing (*R*,*S*)-ketamine's antidepressant effects, in that depression-like behaviors were often determined by forced swimming test; sucrose preference test; and the pro-inflammatory cytokine levels of interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (Ji et al. 2019; Remus and Dantzer 2016; Reus et al. 2017; Zhang et al. 2016). However, (*R*,*S*)-ketamine's potential psychotomimetic and other unwanted side effects have also been well-documented in these animal models, prompting behaviors such as hyperlocomotion, prepulse inhibition deficits, conditioned place preference, schizophrenia-like psychotic symptoms, and novel object recognition impairment (Becker et al. 2003; Chan et al. 2013; Chang et al. 2019a; Giorgetti et al. 2015; Imre et al. 2006; Lahti et al. 1995; Ma and Leung 2018; Yang et al. 2015; Zanos et al. 2017), which may pose a major barrier to further clinical study in patients with MDD.

3 (*S*)-Ketamine's Antidepressant Effects

3.1 Summary of (S)-Ketamine's Antidepressant Effects

(*S*)-Ketamine is an isomer of (*R*,*S*)-ketamine, which was introduced for medical use in analgesia and anesthesia in the early 1990s (Esketamine 2006; Trimmel et al. 2018). The US FDA originally stated that the stereoisomers of (*R*,*S*)-ketamine had not received enough attention for its commercial development in 1992 (Luft and Mendes 2005). Now, (*S*)-ketamine has been brought into greater focus over (*R*,*S*)-ketamine for its antidepressant effects in patients with treatment-resistant depression, due to its incorporation into a nasal spray approved by the US FDA on March

5, 2019 (Canady 2019; US Food and Drug Administration 2019). The evaluation of the (*S*)-ketamine nasal spray was conducted by way of four phase III RCTs, including three short-term (4-week) clinical trials and a withdrawal maintenance-of-effect trial, where patients experienced many side effects including disassociation, dizziness, nausea, sedation, vertigo, anxiety, and lethargy (US Food and Drug Administration 2019). Therefore, there are many challenges in the study of (*S*)-ketamine, which cannot meet the needs of all patients with MDD, and even the antidepressant efficiency and the side effects of (*S*)-ketamine are still under discussion. On the other hand, the existing literature or studies concerning the use of (*S*)-ketamine in patients with MDD number far less than those on the topic of (*R*,*S*)-ketamine, but the latter is still not yet approved by FDA for treatment via any route of administration.

In a case report, Paslakis et al. (2010) reported their results obtained with using off-label oral (*S*)-ketamine (1.25 mg/kg) within 14 days: two patients with treatment-resistant depression showed rapid and sustained improvement in their psychopathology within the first week, while another two patients did not respond to the drug throughout the entire treatment period. In addition, several studies have concluded that (*S*)-ketamine produces similar antidepressant effects to those of (*R*,*S*)-ketamine (Paul et al. 2009) but is better-tolerated than (*R*,*S*)-ketamine, yet severe psychotomimetic effects with (*S*)-ketamine have also been reported (Correia-Melo et al. 2017; Paul et al. 2009). It is worth mentioning that a case series of repeated (*S*)-ketamine (0.25 mg/kg over 40 min) off-label use demonstrated an improvement in depressive symptoms in 50% of the patients following infusion within 1 or 2 weeks, although 25% of the patients suffered from dissociative symptoms (Segmiller et al. 2013). Another case series reported that the safety and efficacy of (*S*)-ketamine were well demonstrated in patients with treatment-resistant depression (TRD); still, the potential for associated psychotic symptoms can leave some patients out of consideration (Ajub and Lacerda 2018). Thus, additional case studies are needed to review the efficacy and psychosis effects of (*S*)-ketamine.

According to clinical trials records from ClinicalTrials.gov, about 18 applications for studying (*S*)-ketamine's antidepressant effect in patients with depression have been uploaded as of April 1, 2019. Some clinical trials have been completed, while others are currently recruiting patients. The route of administration in these clinical trials is mainly intranasal injection, for evaluating the efficacy and safety in patients with MDD or TRD. Therapeutic regimens in these clinical trials also include single and repeated administration. Singh et al. (2016) found in a double-blind, multicenter, randomized, placebo-controlled trial involving patients with TRD that 67% and 64% of the patients, respectively, responded to (*S*)-ketamine given at a single dose of 0.2 mg/kg or 0.4 mg/kg over 40 min within 1 day. Another clinical trial of a head-to-head study compared the antidepressant actions of (*S*)-ketamine and (*R*,*S*)-ketamine in 96 individuals with TRD given a single dose of (*S*)-ketamine (0.25 mg/kg) or (*R*,*S*)-ketamine (0.5 mg/kg) over 40 min (Correia-Melo et al. 2018). The authors considered their study as the best way to evaluate the efficacy and safety of (*S*)-ketamine and (*R*,*S*)-ketamine, as adverse psychotomimetic effects between the two compounds may be different (Correia-Melo et al.

2018). Clinical trials still need to provide more powerful evidence to assist the clinical application of (*S*)-ketamine in depression or TRD.

Other research on (*S*)-ketamine's antidepressant effects mainly involves combination therapy. Bartova et al. (2015) investigated combined intravenous therapy of (*S*)-ketamine and oral tranylcypromine in two patients with multi-treatment-resistant depression, showing a confusing outcome of evident antisuicidal effects but no detailed improvement in antidepressant effectiveness. Electroconvulsive therapy (ECT) plus (*S*)-ketamine has also been applied in three patients with TRD. Kallmunzer et al. (2016) reported that all subjects showed remission in terms of suicidal ideation and no serious side effects during treatment. In contrast, another clinical trial suggested that (*S*)-ketamine (0.4 mg/kg in a bolus) as adjuvant therapy with propofol made no contribution to the enhanced role of ECT in patients with resistance to antidepressants, even going as far as to cause adverse effects like posttreatment disorientation and restlessness (Jarventausta et al. 2013). Although ECT can help to remedy depression, there is still a lack of clear evidence (Read et al. 2019). Therefore, there is no valid data to prove the combination of (*S*)-ketamine and ECT is beneficial, especially given that the antidepressant effects of (*R*,*S*)-ketamine are more potent than those of ECT (Muller et al. 2016).

In humans, the idea of using (*S*)-ketamine as an antidepressant is relatively new and its intranasal treatment modality has recently been receiving a lot of attention. However, many challenges need to be faced in future study. For instance, how about its optimal dose and route of administration? How to solve its side effects during treatment? How long does it sustain antidepressant effects? More importantly, how does it work as an antidepressant? These questions remain without an answer at this time.

3.2 (S)-Ketamine's Antidepressant Effects in Rodents

Animal experiments aimed at elucidating (*S*)-ketamine's antidepressant effect and its underlying mechanisms have also been conducted although no definitive answer was achieved. The current findings point out that (*S*)-ketamine works in a very complicated way, in that it can bind to multiple receptors in an organism, such as NMDAR, opioid receptors, monoamine receptors, adenosine receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPAR) receptors, metabotropic glutamate receptors, L-type calcium channels, and other purinergic receptors (Kohrs and Durieux 1998; Trimmel et al. 2018). The prevailing view is that (*S*)-ketamine's antidepressant effect is related with the noncompetitive inhibition of NMDAR through binding to the phencyclidine (PCP) sites (Sinner and Graf 2008), due to its three- to fourfold higher affinity in comparison with (*R*)-ketamine (Domino 2010; Kohrs and Durieux 1998). Yet, (*S*)-ketamine dominates in the areas of anesthetic potency and undesirable psychotomimetic side effects over (*R*)-ketamine, in that seeing illusions, hearing and vision changes, and proprioception are related to

(*S*)-ketamine, while feelings of relaxation are connected with the actions of (*R*)-ketamine (Zanos et al. 2018).

Treccani et al. (2019) suggested that a single dose of (*S*)-ketamine (15 mg/kg) can induce acute antidepressant action in a rat model of depression, concluding first that dendritic spine density rapidly (<1 h) increases in brain structural changes and also that balancing the relationship between cofilin activity, homer3 levels, and the NMDAR subunits GluN2A and GluN2B plays a key role in the antidepressant effect. However, Ide et al. (2017), upon investigating the role of GluN2D in the antidepressant effects of ketamine enantiomers, suggested that such did not play a key role in the sustained antidepressant effects of (*R*,*S*)-ketamine and (*S*)-ketamine but rather in those of (*R*)-ketamine. Recent studies have indicated that (*S*)-ketamine elicits its acute and sustained antidepressant-like actions via a 5-hydroxytryptamine (5HT) receptor-dependent mechanism, which is confirmed via the forced swimming test by comparing the vortioxetine, fluoxetine, and (*S*)-ketamine in the serotonin system or by using the 5-HT_{1B} receptor agonist CP94253 in a genetic rat model (du Jardin et al. 2016, 2017).

Other studies of note regarding the mechanisms of (*S*)-ketamine's antidepressant actions are as follows. In a rat depression model of maternal deprivation, it was suggested that a single dose of (*S*)-ketamine showed long-term antidepressant effects through acting against neural damage induced by oxidative stress (Reus et al. 2015). In a long-term corticosterone infusion rat model of depression, it was suggested that (*S*)-ketamine decreased depressive-like behaviors for at least 4 weeks, but not in a manner related with rapid maturity of the new hippocampal neurons (Soumier et al. 2016). In a rat hippocampus study, Ardalan et al. (2017) put forward the notion that a single injection (15 mg/kg) of (*S*)-ketamine improved the immobility behavior during the modified forced swim test within 24 h after treatment, proving that astrocyte plasticity in the hippocampus has a bearing on the (*S*)-ketamine antidepressant effect in a rat genetic animal model of depression.

4 (*R*)-Ketamine's Antidepressant Effects

*4.1 Summary of the Differences Between (*R*)-Ketamine and (*S*)-Ketamine*

With the deepening and development of research, the focus on antidepressant effects will be quickly shifted toward (*R*)-ketamine, because its advantages are becoming more and more obvious. As compared with (*S*)-ketamine, (*R*)-ketamine has been proven to be more potent and have longer-lasting antidepressant effects and was deemed to be free of psychotomimetic side effects in many studies on rodent models of depression (Chang et al. 2019a; Fukumoto et al. 2017; Yang et al. 2015, 2016b; Zhang et al. 2014), signifying that (*R*)-ketamine will be one of the most promising antidepressants.

(*R*)-Ketamine is an isomer of (*R*,*S*)-ketamine. (*R*)-ketamine is a left-handed molecule, while (*S*)-ketamine is a right-handed molecule, per the carbon connections in either one or the other direction of nonsuperimposable mirror images, prompting a difference in the body metabolism (Calvey 1995; Kharasch and Labroo 1992). As compared with (*S*)-ketamine, (*R*)-ketamine has a lower affinity to the PCP binding site of the NMDAR, with a lower anesthetic potency (Thomson et al. 1985; White et al. 1985; Zeilhofer et al. 1992). In addition, (*R*)-ketamine could also weakly bind to the sigma receptor sites, without (*S*)-ketamine binding to these sites (Vollenweider et al. 1997). Research on the side effects of the two isomers showed that (*R*)-ketamine produces a feeling of relaxation or "well-being," while (*S*)-ketamine is mainly responsible for psychotomimetic effects, such as dissociations in hearing, vision, and proprioception (Hashimoto 2019; Vollenweider et al. 1997; Zanos et al. 2018). Moreover, Marietta et al. (1977) reported acute toxic effects of racemic ketamine and its two isomers at the dose of 40 mg/kg in male Sprague-Dawley rats based on median lethal dose values, indicating that (*R*)-ketamine is more secure than (*R,S*)-ketamine and (*S*)-ketamine, and its potential advantage is not a fatal drug according to the high dose and with less posthypnotic stimulation.

4.2 Different Antidepressant Effects Between (R)-Ketamine and (S)-Ketamine

Our group reported that (*R*)-ketamine has a greater potency and longer-lasting antidepressant roles than (*S*)-ketamine in rodent models of depression (Yang et al. 2015; Zhang et al. 2014). In addition, it was suggested that ketamine's side effects (e.g., psychotomimetic behaviors, neurotoxicity, abuse potential) may be associated with (*S*)-ketamine but not (*R*)-ketamine (Chang et al. 2019a; Hashimoto 2016a, b, c). Subsequently, different kinds of depression models with comparative objects and their relevant behavioral tests were employed to evaluate and identify the advantages of (*R*)-ketamine's antidepressant effects. Fukumoto et al. (2017) reported that (*R*)-ketamine can elicit longer-lasting antidepressant effects than (*S*)-ketamine in forced swimming and tail suspension tests, and (*R*)-ketamine showed a sustained antidepressant effect in a treatment-refractory model while (*S*)-ketamine did not. Moreover, Fukumoto et al. (2017) also suggested that (*R*)-ketamine's antidepressant effects may be related with AMPAR by testing the rats of a repeated corticosterone treatment model with an AMPAR antagonist, NBQX (Fukumoto et al. 2017). In a conscious positron-emission tomography study, a single infusion of (*S*)-ketamine but not (*R*)-ketamine caused dopamine release, indicating that (*S*)-ketamine-induced dopamine release may be associated with acute psychotomimetic and dissociative effects in humans (Hashimoto et al. 2017).

In addition, further research on the molecular mechanisms revealed more data about the differences between (*R*)-ketamine and (*S*)-ketamine. Specifically, the extracellular-signal-regulated kinase signaling pathway may play a role in

(*R*)-ketamine's antidepressant effects, while the mammalian target of rapamycin signaling pathway plays a role in the antidepressant effects of (*S*)-ketamine (Yang et al. 2018a). Nevertheless, glutamate is the primary excitatory neurotransmitter in the human brain in physiology (Jewett and Thapa 2019) and its participation in the role of ketamine's antidepressant effects should not be neglected in the following study, although we still cannot explain the real difference between (*R,S*)-ketamine and its two isomers (Zanos and Gould 2018). Even more important, the causes for the differences in antidepressant effects between (*R*)-ketamine and (*S*)-ketamine may be related with the gut microbiota–brain axis (Qu et al. 2017; Yang et al. 2017). As compared with (*S*)-ketamine, (*R*)-ketamine significantly attenuated the decrease in the levels of *Mollicutes* of susceptible mice in a CSDS model, and (*R*)-ketamine presented a stronger advantage than (*S*)-ketamine in reducing the levels of *Butyricimonas* (Yang et al. 2017).

*4.3 (*R*)-Ketamine's Antidepressant Effects*

(*R*)-ketamine has its own special features of antidepressant effects from the current study. As compared with the NMDAR partial agonist rapastinel, (*R*)-ketamine had longer-lasting antidepressant effects and significantly changed the brain-derived neurotrophic factor–TrkB signaling in a CSDS model (Yang et al. 2016a). Recent Ph3 data of rapastinel were negative (Hashimoto 2019).

In the light of the complex physiology and particularity that of NMDAR for regulating the electroneurographic signal in depression by voltage-gated ion channel influx, including calcium, sodium, and potassium (Cui et al. 2018; Yang et al. 2018b). Tian et al. (2018b) reported that the low-voltage-sensitive, T-type calcium channel blocker ethosuximide did not produce rapid or sustained antidepressant effects in a CSDS model, although (*R*)-ketamine showed rapid and sustained antidepressant effects in the same model (Tian et al. 2018b). Furthermore, Xiong et al. (2019) reported that the Kir4.1 inhibitors quinacrine and sertraline did not improve the depression-like behaviors during the tail suspension test and forced swimming test in a CSDS model, while (*R*)-ketamine produced rapid and sustained antidepressant effects in this model (Xiong et al. 2019).

Treatment with the 5-HT inhibitor para-chlorophenylalanine methyl ester hydrochloride also did not impact the antidepressant effects of (*R*)-ketamine in s CSDS model (Zhang et al. 2018). Furthermore, dopamine D_1 receptors may not play a major role in the antidepressant actions of (*R*)-ketamine, because pretreatment with the dopamine D_1 receptor antagonist SCH-23390 did not block the antidepressant effects of (*R*)-ketamine in the CSDS model (Chang et al. 2019b).

Given the role of gamma-aminobutyric acid receptors in depression (Zanos et al. 2017), both (*R*)-ketamine and MRK-016 (full inverse $GABA_A$ agonist) displayed rapid antidepressant effects, while only (*R*)-ketamine produced a longer-lasting antidepressant effect in a CSDS model (Xiong et al. 2018).

In addition, (*R*)-ketamine's antidepressant effects had regional differences in rat brains. A single bilateral infusion of (*R*)-ketamine was injected into the brain in a rat LH model of depression, showing that the infralimbic cortex of the medial prefrontal cortex (mPFC), dentate gyrus, and CA3 subregions of the hippocampus are related with (*R*)-ketamine's antidepressant effects as compared with other injection site areas including the mPFC subregion PrL, subregions of the shell and core in NAc, and BLA and CeA subregions of the amygdala, which had nothing to do with the antidepressant effects of (*R*)-ketamine (Shirayama and Hashimoto 2017). No toxicity was shown in the brain after repeated, intermittent administration with (*R*)-ketamine, with no loss in parvalbumin immunoreactivity in the brain region of mPFC and hippocampus observed, which was the opposite finding to those of (*S*)-ketamine (Yang et al. 2016b). Additionally, another interesting finding regarding neuropathological changes revealed that the neuronal injury marker heat shock protein HSP-70 was expressed in the rat retrosplenial cortex not because of (*R*)-ketamine but instead due to (*R*,*S*)-ketamine and (*S*)-ketamine (Tian et al. 2018a).

Based on the above findings, (*R*)-ketamine shows the rapid-acting and long-lasting antidepressant effects in rodents although its precise mechanism underlying these effects is still uncertain. A clinical trial of (*R*)-ketamine in humans is currently underway (Hashimoto 2019).

5 Conclusion

The discovery of the robust antidepressant actions of (*R*,*S*)-ketamine in depressed patients is serendipitous (Krystal et al. 2019). However, (*R*,*S*)-ketamine has not been approved by the US FDA for antidepressant treatment in clinical application because of a lack of patent. An (*S*)-ketamine nasal spray was approved by the FDA on March 5, 2019, although its side effects are known and it must be administrated under supervision in a certified doctor's office or outpatient clinic after treatment. It seems that antidepressant effects of (*S*)-ketamine in patients with MDD are less potent than those related with (*R*,*S*)-ketamine in clinical studies. Although there is no clinical trial of (*R*)-ketamine in patients with MDD, many preclinical data show its more potent antidepressant effects without side effects, suggesting that (*R*)-ketamine could be a safer antidepressant alternative to (*R*,*S*)-ketamine and (*S*)-ketamine. Due to its lower adverse side effects, we are looking forward to seeing more data on (*R*)-ketamine's antidepressant effects in patients with MDD and other psychiatric disorders.

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