(R)-ketamine as prophylactic and therapeutic drug for neurological disorders: Beyond depression

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ABSTRACT

Neurological disorders are the leading cause of disability and the second leading cause of death worldwide. The increasing social and economic burdens of neurological disorders are driven by global population growth and aging. Depression is a common psychiatric symptom in numerous neurological disorders. It is also a risk factor for Alzheimer’s disease (AD) and other dementias, Parkinson’s disease (PD), and stroke. The rapid-acting and sustained antidepressant actions of (R,S)-ketamine for severe depression was accidentally discovered. Interestingly, (R)-ketamine has greater potency and longer-lasting antidepressant-like effects than (S)-ketamine in rodents. Importantly, its side effects in rodents and humans are lower than those of (R,S)-ketamine and (S)-ketamine. Furthermore, (R)-ketamine could elicit beneficial actions in various rodent models of neurological disorders, including PD, multiple sclerosis (MS), and stroke. In this article, we review the potential of (R)-ketamine as a prophylactic or therapeutic drug for neurological disorders including AD and other dementias, PD, MS, and stroke.

1. Introduction

Neurological disorders are the leading cause of death and disability worldwide (Feigin et al., 2020). As the global population and aging increase, the social and economic burdens of neurological disorders also increase. Currently, several approved drugs could not improve some symptoms of neurological disorders; thus, new therapeutic drugs for neurological disorders should be developed (Grosso Jasutkar et al., 2022; LeWitt and Chaudhuri, 2020). Depression is the most common psychiatric symptom in patients with neurological disorders including Alzheimer’s disease (AD) and other dementias, Parkinson’s disease (PD), multiple sclerosis (MS), and stroke. Hence, depressive symptoms might play a role in the pathogenesis of these neurological disorders. According to a recent population-based longitudinal study of 1.7 million New Zealand citizens for 30 years, people with early-life mental disorders including psychotic disorder, substance use disorder, and mood disorder were highly at risk (relative risk = 4.24, hazard ratio = 6.49) for subsequent dementia (AD and other dementias) and early dementia onset (Richmond-Rakerd et al., 2022). Thus, depression might be a risk factor for AD and other dementias.

The rapid-onset and sustained antidepressant actions of (R,S)-ketamine, the N-methyl-D-aspartate receptor (NMDAR) antagonist, were only discovered by chance in depression research (Domino, 2010; Hashimoto, 2019, 2020a; Krystal et al., 2019; Wei et al., 2020; Zhang and Hashimoto, 2019). (R,S)-ketamine is a racemic mixture of (R)-ketamine (or esketamine) and (S)-ketamine (or esketamine), with (R)-ketamine showing more potent antidepressant-like actions in rodent models of depression (Hashimoto, 2019, 2020a; Wei et al., 2020; Yang et al., 2019). In addition to these antidepressant-like effects in several animal models, (R)-ketamine has beneficial effects in various animal models of neurological disorders.

Given the role of depression in neurological disorders, we hypothesize that (R)-ketamine has beneficial effects in patients with neurological disorder suffering from depression. In this review, we discuss the potential of (R)-ketamine in preventing and/or treating neurological disorders such as AD and other dementias, PD, MS, and stroke.

2. Brief history of ketamine and its enantiomers

The serendipitous discovery of the rapid-onset and sustained

Abbreviations: AD, Alzheimer’s disease; BDNF, Brain-derived neurotrophic factor; BMD, Bone mineral density; CPZ, Cuprizone; EAE, Experimental autoimmune encephalomyelitis; MS, Multiple sclerosis; PD, Parkinson’s disease; SSRI, Selective serotonin reuptake inhibitor.

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antidepressant effects of (R,S)-ketamine was a paradigm shift in depression research (Krystal et al., 2019). In drug-free patients with major depressive disorder (MDD), a single intravenous infusion of (R, S)-ketamine (0.5 mg/kg) caused rapid-acting antidepressant effects (Berman et al., 2000). Subsequent studies confirmed the robust antidepressant and anti-suicidal effects of intravenous (R,S)-ketamine (0.5 mg/kg) in treatment-resistant patients with MDD or bipolar disorder (Diazgranados et al., 2010; Fava et al., 2020; Su et al., 2017; Wilkinson et al., 2018; Zarate et al., 2006). Although safety data are limited, intravenous (R,S)-ketamine has been widely used as an off-label drug in the USA (Lengvenyte et al., 2022; O’Brien et al., 2022).

(R,S)-ketamine (Ki = 0.53 μM for NMDAR) is a mixture of equal amounts of (R)-ketamine (Ki = 1.4 μM for NMDAR) and (S)-ketamine (Ki = 0.30 μM for NMDAR) (Fig. 1) (Ebert et al., 1997). The USA and Europe approved the prescription of (S)-ketamine nasal spray (Johnson & Johnson) for treatment-resistant patients with MDD and people with high suicide risk, although several concerns about its efficacy and approval were raised (Fiorowitz and Moncrieff, 2021; Turner, 2019).

(R)-ketamine could be a safer antidepressant than (R,S)-ketamine and (S)-ketamine (Hashimoto, 2019, 2020a; Wei et al., 2020; Yang et al., 2019; Zhang and Hashimoto, 2019). Interestingly, (R)-ketamine produced greater potency and longer-lasting antidepressant-like actions than (S)-ketamine in rodent models such as chronic social defeat stress and learned helplessness (Chang et al., 2019; Yang et al., 2015, 2017a; Zhang et al., 2014). The superior effect of (R)-ketamine compared with (S)-ketamine was also observed in other groups worldwide (Fukumoto et al., 2017; Rafał-Ulińska and Pałucha-Poniewiera, 2022; Zanos et al., 2016; Zhu et al., 2020). Collectively, (R)-ketamine could have greater potency and longer-lasting antidepressant-like actions than (S)-ketamine, although its affinity at NMDAR was less potent. An open-label pilot study in Brazil reported that (R)-ketamine (0.5 mg/kg, intravenous) exhibited a rapid-onset and sustained antidepressant effects in treatment-resistant patients with MDD (Leal et al., 2021). A phase 2 study of (R)-ketamine (or PCN-101) in treatment-resistant patients with MDD is currently underway by Perception Neuroscience, Inc. (New York, USA).

Behavioral and biological abnormalities in rodents (i.e., hyperactivity, prepulse inhibition, abuse liability, and parvalbumin immuno-reactivity in the prefrontal cortex) after (R)-ketamine injection were less than those after (S)-ketamine injection (Bonaventura et al., 2021; Chang et al., 2019; Tan and Hashimoto, 2020; Yang et al., 2015, 2016). A single injection of (S)-ketamine (0.5 mg/kg, intravenous), not (R)-ketamine (0.5 mg/kg, intravenous), reduced the binding availability of the dopamine D2/3 receptor in the striatum of a conscious monkey (Hashimoto et al., 2017), suggesting that (S)-ketamine can cause dopamine release in the striatum; such release is associated with the detrimental side effects of (S)-ketamine in humans. Importantly, the side effects (i.e., psychotomimetic and dissociative effects) of (R)-ketamine (0.5 mg/kg, intravenous) in treatment-resistant patients with MDD (Leal et al., 2021) were markedly lower than those of (S)-ketamine (0.2 and 0.4 mg/kg, intravenous) (Singh et al., 2016). Therefore, (R)-ketamine elicits fewer side effects in humans than (R,S)-ketamine and (S)-ketamine.

Furthermore, non-ketamine NMDAR antagonists/modulators do not produce ketamine-like robust antidepressant actions in patients with MDD (Kishimoto et al., 2016; Newport et al., 2015). Thus, NMDAR inhibition unlikely plays a major role in the antidepressant effects of (R, S)-ketamine in patients with MDD (Hashimoto, 2019, 2020a; Wei et al., 2022). However, the neurobiological mechanisms underlying the antidepressant actions of (R)-ketamine remain elusive. We reported review articles on the molecular mechanisms underlying the antidepressant action of (R,S)-ketamine and its enantiomers (Hashimoto, 2019, 2020a; Yang et al., 2019; Wei et al., 2020, 2022). Recent preclinical findings suggest that neurotrophic factors, including brain-derived neurotrophic factor (BDNF), participate in the rapid and sustained antidepressant effects of (R)-ketamine (Fig. 2) (Yang et al., 2015, 2018; Yao et al., 2022).

![Fig. 1. Chemical structure of (R,S)-ketamine and its two enantiomers. Ki values for NMDAR are presented in parenthesis (Ebert et al., 1997).](attachment:image1.png)

![Fig. 2. Mechanisms underlying beneficial effects of (R)-ketamine, (R)-ketamine can stimulate BDNF-TrkB signaling through ERK signaling, resulting in robust antidepressant, anti-inflammatory and neurotrophic actions. A slight modification from the previous reports (Wei et al., 2022; Yao et al., 2022). ERK: extracellular signal-regulated kinase, CREB: cAMP response element binding protein. Some materials of the figure have been designated using resources from Biorender.com.](attachment:image2.png)
patients with late-life depression (Lijffijt et al., 2022). Thus, (R)-ketamine may block or delay the onset of dementia in people with late-life depression (Fig. 3). A randomized, double-blind, placebo-controlled, follow-up study is necessary to ascertain the prophylactic effects of (R)-ketamine for dementia onset in older people with depression.

In addition to prodromal symptom, depression is very common symptom in AD patients. In early stage of AD, depression is characterized by somatic symptoms and can be differentiated from apathy by the sadness, depressive thought, and early morning awakening. In late stage, depressive symptoms include sleep-wake cycle reversal, aggressive behavior, and agitation (Agüera-Ortíz et al., 2021). Notably, depression might accelerate the progression of dementia regardless of the stage. Although the current antidepressants are effective in AD patients, their efficacy is less than that in cognitively healthy individuals (Agüera-Ortíz et al., 2021). Therefore, it is very important to treat depressive symptoms in patients with AD and other dementias. A case report showed that subcutaneous injection of (R,S)-ketamine improved depressive symptoms in a treatment-resistant depressed patients with AD (Rocha et al., 2021). Therefore, it is of great interest to investigate whether (R)-ketamine can improve depressive symptoms in AD patients.

3. AD and other dementias

AD, which is the most common cause of dementia in older adults, is a progressive neurological disorder that slowly destroys one’s memory and thinking skills. An analysis for the Global Burden of Disease Study 2019 estimated that global cases of dementia would increase in number from 57.4 million in 2019–152.8 million in 2050, with more women than men (GBD, 2019 Dementia Forecasting Collaborators, 2022).

Late-life depression might increase the risk for incident dementia such as AD and vascular dementia (Risko et al., 2021). A meta-analysis of a community-based cohort study showed that late-life depression is associated with a significant risk of developing AD and vascular dementia (Diniz et al., 2013). According to two recent meta-analyses, late-life depression is strongly associated with all kinds of dementia (Yu et al., 2020; Zhao et al., 2022). Evidence-based factors on AD prevention include cognitive activity, education, high body mass index in late-life, hyperhomocysteinemia, depression, stress, diabetes, head trauma, hypertension in midlife, and orthostatic hypotension (Yu et al., 2020). Two interventions such as physical exercise and total homocysteine-lowering treatment are promising. In contrast, estrogen replacement therapy is not recommended since it was associated with an increase in the risk of dementia. In addition, acetylcholinesterase inhibitors should not be used for AD prevention in cognitively impaired individuals since the risk is larger than the benefit (Yu et al., 2020). These data strongly suggest that late-life depression must be treated to prevent the onset of dementia in older people (Fig. 3).

A recent Bayesian adaptive randomization trial showed that (R,S)-ketamine (0.5 mg/kg, intravenous) was effective in treatment-resistant patients with late-life depression (Lijffijt et al., 2022). Thus, (R,S)-ketamine may have beneficial effects in treatment-resistant patients with late-life depression and even AD since the current antidepressants are infective in these patients (Lijffijt et al., 2022; Modeiros da Frota Ribeiro and Riva-Posse, 2017; Mohammad Shehata et al., 2022; Pericaud et al., 2022). Considering that (R)-ketamine is a safer antidepressant than (R,S)-ketamine and (S)-ketamine (Hashimoto et al., 2019; 2020a; 2022; Wei et al., 2022), (R)-ketamine might also be an effective prophylactic drug by blocking or delaying the onset of dementia in people with late-life depression (Fig. 3).
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Symptoms of MS can lead to a major economic burden on the patients, childcare, and self-care (Rajachandrakumar and Finlayson, 2021). Pretreatment with ANA-12 (TrkB inhibitor) significantly blocked the protective effects of (R)-ketamine in the levodopa-induced dyskinesia model (Bartlett et al., 2020) and patients with PD (n = 5) experiencing levodopa-induced dyskinesia (Sherman et al., 2016). Therefore, (R,S)-ketamine is a potential therapeutic drug for these patients. On March 23, 2022, PhamTher Holding announced that dyskinesia was reduced in patients with PD after (R, S)-ketamine treatment, as measured by the United Dyskinesia Rating Scale during the study period compared with the pretreatment baseline (www.phamther.com). However, the enantiomers of (R,S)-ketamine that contribute to the beneficial effects of (R,S)-ketamine on levodopa-induced dyskinesia in patients with PD are yet to be determined.

Collectively, (R)-ketamine possibly has a protective effect against dopaminergic neurotoxicity in the brain compared with (S)-ketamine (Fujita et al., 2020; Wei et al., 2022). Apart from being an antidepressant, repeated intermittent administration of (R)-ketamine might block or delay the progression of PD symptoms. A future randomized, placebo-controlled study is needed to investigate whether (R)-ketamine could affect the progression of symptoms in patients with PD. In addition, (R)-ketamine may be used to treat the depressive symptoms in patients with PD.

5. MS

MS, a progressive and chronic demyelinating disease with autoimmune processes, causes limitations in one’s ability to fully engage in various daily activities, such as employment, home maintenance, childcare, and self-care (Rajachandrakumar and Finlayson, 2021). Symptoms of MS can lead to a major economic burden on the patients, their families and caregivers, employers, and the healthcare system (Dahham et al., 2021; Nicholas et al., 2021). Given the social and economic burden caused by MS, developing prophylactic or therapeutic drugs that block or delay the disease progression and severity of MS is necessary. Depression has been observed in numerous patients with MS, with a lifetime prevalence of approximately 50% (Feinstein, 2011; Jones et al., 2021; Wang, 2021). In addition, suicide rate in people with MS is approximately twice that of the general population (Feinstein and Pavlivan, 2017). Unfortunately, single, gold-standard treatment for depression and suicide ideation in patients with MS remains unestablished (Jones et al., 2021).

Experimental autoimmune encephalomyelitis (EAE) is the most commonly used rodent model of MS (Bjelobaba et al., 2018). Repeated administration of (R)-ketamine (10 mg/kg/day) in EAE model mice attenuated the reduction of body weight and ameliorated the clinical EAE scores compared with the saline-treated group. In addition, (R)-ketamine treatment also attenuated the marked increases in the pathological scores, microglial activation, and blood-brain barrier integrity in the spinal cord (Wang et al., 2021). Therefore, (R)-ketamine might block or delay the progression of MS clinical symptoms (Fig. 4).

CPZrione (CPZ), a selective and sensitive copper-chelating agent, has been used to produce toxic demyelination that resembles demyelination in MS. Interestingly, spontaneous remyelination can be observed as early as 4 days after CPZ withdrawal, indicating that CPZ model could be an excellent tool to discover potential therapeutic drugs that can prevent demyelination and stimulate remyelination (Franklin and Firenich-Constant, 2017; Torkildsen et al., 2008). In the brain of CPZ-treated mice, repeated intermittent administration of (R)-ketamine (10 mg/kg/day, twice weekly for 6 weeks) could ameliorate demyelination and activated microglia compared with saline-treated mice (Wang et al., 2022). Pretreatment with ANA-12 (TrkB antagonist) significantly blocked the beneficial effects of (R)-ketamine on the demyelination and activated microglia in the brain of CPZ-treated mice (Wang et al., 2022). Given the role of BDNF-TrkB signaling on the beneficial effects of (R)-ketamine in other models (Fujita et al., 2020, 2021; Qu et al., 2021; Tan et al., 2020, 2022; Yang et al., 2015, 2018), BDNF-TrkB signaling might play a role in the mechanisms of (R)-ketamine in CPZ-treated mice. Interestingly, (R)-ketamine could facilitate remyelination in the brain after CPZ withdrawal (Wang et al., 2022). Furthermore, (R, S)-ketamine (25 mg/kg) increased MBP (myelin basic protein)-immunoreactivity in deep layers of infralimbic region of medial prefrontal cortex of rats, suggesting a role of MBP in the effects of (R, S)-ketamine (Pascual-Anton et al., 2021). Therefore, (R)-ketamine might attenuate demyelination and accelerate remyelination in patients with MS (Fig. 4).

Altered composition of gut microbiota reportedly plays a role in MS pathogenesis (Farshabfani et al., 2021; Ghezzi et al., 2021). We previously reported that (R)-ketamine could improve the altered composition of gut microbiota in mice with depression-like behaviors (Qu et al., 2017; Yang et al., 2017b), suggesting a gut–microbiota–brain axis in depression (Chang et al., 2022). Moreover, (R)-ketamine improved the altered composition of gut microbiota in CPZ-treated mice. Interestingly, significant correlations were observed between demyelination (or microglial activation) in the brain and the relative abundance of several microbiomes, indicating a crosstalk between the brain and gut microbiota (Wang et al., 2022). Oral (R,S)-ketamine (20 mg) effectively treated pain and allodynia in a patient with MS (Sakai et al., 2004). In another case report, (R,S)-ketamine (0.5 mg/kg, intravenous) produced antidepressant effects in a treatment-resistant patient with MS suffering from depression (Messer and Hailer, 2017), suggesting that (R,S)-ketamine may be useful for treating severe depression in patients with MS. Chronic fatigue is also a very common and disabling symptom among patients with MS. A pilot double-blind, active-control study of MS cases (n = 18) showed that a single infusion of (R,S)-ketamine (0.5 mg/kg, intravenous) reduced fatigue severity scale scores at week 1 and significantly reduced the modified fatigue impact scale scores at day 28 (Fitzgerald et al., 2021). This study suggests that chronic fatigue in patients with MS can be potentially treated with (R,S)-ketamine. Nonetheless, further study with a large sample size is needed to ascertain the beneficial effects of (R, S)-ketamine for chronic fatigue in patients with MS.

On the basis of the current data, we propose that (R)-ketamine could be a new prophylactic or therapeutic drug for MS. A future randomized, double-blind, placebo-controlled trial is needed to confirm (R)-ketamine’s beneficial effects on MS. (R)-ketamine might also effectively treat depression and suicidal ideation in patients with MS.

6. Stroke

Stroke, which is the most common acute cerebrovascular disease, is one of the leading causes of mortality and disability worldwide. Although being administered to few patients with ischemic stroke, the recombinant tissue plasminogen activator (tPA) has a narrow time window and exhibits hemorrhagic transformation risk (Wardlaw et al.,
A meta-analysis of prospective studies showed that depression increases the risk of developing stroke, independent of other risk factors, including hypertension and diabetes (Dong et al., 2012); thus, depression should be treated to prevent the subsequent onset of stroke. Furthermore, post-stroke depression occurs in numerous patients with stroke, leading to a greater disability as well as increased mortality (Robinson and Jorge, 2016). In a recent meta-analysis, treatment with selective serotonin reuptake inhibitors (SSRIs) was associated with a significant reduction of post-stroke depression occurrence compared with the placebo group (Richter et al., 2021). However, SSRI therapy increased the risk for bone fracture and nausea in participants with stroke history. Therefore, new therapeutic drugs should be developed.

Middle cerebral artery occlusion (MCAO) is the most widely used animal model of ischemic stroke. Subsequent administration (1 and 24 h after MCAO) of (R)-ketamine (10 mg/kg), not (S)-ketamine (10 mg/kg), attenuated brain injury and behavioral abnormalities in mice after MCAO (Xiong et al., 2020). Furthermore, earlier (R)-ketamine treatment (10 mg/kg, twice, 30 min before and 24 h after MCAO) significantly protected the mice against brain injury and behavioral abnormalities after MCAO (Xiong et al., 2020). Therefore, (R)-ketamine may have a protective effect against neuronal injury and behavioral abnormalities after MCAO. In particular, (R,S)-ketamine treatment rapidly exerted significant and lasting antidepressant-like effects in rats after MCAO and chronic unpredictable mild stress by modulating NMDAR/CaMKII-induced synaptic plasticity (Abdoulaye et al., 2021).

SSRI therapy is associated with decreased bone mineral density (BMD) and increased risk for fracture in humans (Rizzoli et al., 2012). Reduced BMD is a known consequence of stroke, associated with an increased incidence of fractures (Carda et al., 2009). A meta-analysis showed that reduced BMD predicts the risk of stroke (Myint et al., 2014). Collectively, it is unlikely that the use of SSRI therapy is recommended for patients with stroke or post-stroke depression. We reported that (R)-ketamine (10 mg/kg), not (S)-ketamine (10 mg/kg), significantly attenuated the increased plasma levels of receptor activator of nuclear factor κB ligand (RANKL) and decreased BMD in mice with depression-like behaviors (Xiong et al., 2019; Zhang et al., 2018). Additionally, subsequent repeated intermittent administration of (R)-ketamine (10 mg/kg/day, twice weekly for 6 weeks), not (S)-ketamine (10 mg/kg/day, twice weekly for 6 weeks), significantly ameliorated cortical and total BMD reduction in ovariectomized mice (animal model of postmenopausal osteoporosis) (Fujita and Hashimoto, 2020; Wan et al., 2022). A recent study suggested that gut microbiota may play a role in the beneficial effects of (R)-ketamine on BMD reduction in ovariectomized mice (Wan et al., 2022). Interestingly, Kadriu et al. (2018) reported that a single infusion of (R,S)-ketamine (0.5 mg/kg, intravenous) improved the abnormal inflammatory bone markers (i.e., RANKL) of treatment-resistant patients with MDD. Therefore, (R)-ketamine might be a potential therapeutic drug for bone metabolism abnormalities in patients with depression or those with osteoporosis (Wei et al., 2022). Given its neuroprotective actions, (R)-ketamine has the potential to be a new prophylactic and therapeutic drug for ischemic stroke or post-stroke depression. A randomized, double-blind, placebo-control study of (R)-ketamine should be conducted among patients with acute stroke or those with post-stroke depression.

7. Conclusion and future directions

In addition to its antidepressant-like effects, (R)-ketamine has beneficial effects in various animal models of neurological disorders. The endotoxin lipopolysaccharide (LPS) could be a causative or contributing factor of neurological disorders such as AD and other dementias and PD (Brown, 2019). (R)-ketamine could ameliorate systemic inflammation, splenomegaly, and behavioral deficits in LPS-treated mice (Ma et al., 2022; Zhang et al., 2021b) as well as in systemic inflammation models (i.e., depression, colitis, and sepsis) (Fujita et al., 2021; Zhang et al., 2021a, 2021c). Collectively, (R)-ketamine has potent antidepressant-like and anti-inflammatory actions in various models, such as psychiatric, neurological, and other inflammation-related diseases (Figs. 1–4). However, the precise molecular mechanisms involved...
in the beneficial effects of (R)-ketamine are currently unknown (Hashimoto, 2020a, 2020b; Jelen et al., 2021; Ma and Hashimoto; Scotton et al.,; Wei et al., ). Further investigation is needed to fully understand the molecular and cellular mechanisms of (R)-ketamine and identify novel targets for (R)-ketamine.

In conclusion, depression is a risk factor for AD and other dementia, PD, and stroke although the etiology of depression in patients with these neurological disorders is complex and multifactional in individual patients (Rickards, 2005). There is a bidirectional relationship between neurological disorders and psychiatric disorders such as depression (Hederson, 2016), suggesting that understanding of the overlap would improve symptoms in patients with psychiatric and neurological disorders. Perception Neuroscience, Ltd. (New York, USA) currently conducts phase 2 study of (R)-ketamine (or PCN-101) in treatment-resistant patients with MDD. This review demonstrated that (R)-ketamine could treat depressive symptoms in patients with neurological disorders such as dementia, PD, MS, and stroke. Thus, (R)-ketamine could be a new prophylactic or therapeutic drug for neurological disorders. However, future randomized, placebo-controlled, clinical studies are needed to confirm whether (R)-ketamine can prevent or delay the onset of these neurological disorders.

Declaration of competing interest

Dr. Hashimoto is the inventor of filed patent applications on “The use of R-ketamine in the treatment of psychiatric diseases”, “(S)-norketamine and salt thereof as pharmaceutical”, “R-ketamine and derivative thereof as prophylactic or therapeutic agent for neurodegeneration disease or recognition function disorder”, “Preventive or therapeutic agent and pharmaceutical composition for inflammatory diseases or bone diseases”, “R-ketamine and its derivatives as a preventive or therapeutic agent for a neurodevelopmental disorder”, and “TGF-β1 in the treatment of depression” by the Chiba University. Dr. Hashimoto also declares that he has received research support and consultant from Sumitomo Pharma, Otsuka, Seikagaku Corporation, Taisho, Murakami Farm, and Perception Neuroscience. The other authors have no conflict of interest.

Data availability

No data was used for the research described in the article.

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