Behavioral Pharmacology of Ketamine: An Overview of Preclinical Studies

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Abstract The behavioral pharmacological effects of ketamine in animals have been reviewed. Ketamine does not cause remarkable behavioral changes at doses effective for the treatment of depressive behavior in animal models. However, a transient increase in spontaneous motor activity has been reported sometimes. Ketamine is effective for the recovery of behavior caused by chronic mild stress, social defeat stress, and so on. Several mechanisms underlying this effect have been proposed, but a conclusive answer has still not been presented. (R)-Ketamine is more potent and has longer-lasting antidepressant effects than the (S)-isomer. Ketamine produces diverse behavioral changes other than antidepressant effects, such as blunting fear, cognitive impairments, and social withdrawal. Behavioral changes related to schizophrenia-like symptoms such as impairment of prepulse inhibition of the acoustic startle response and impairment of latent inhibition have been reported. However, relatively high doses seem to be necessary to yield these effects. Several lines of preclinical evidence have also shown the reinforcing and rewarding properties of ketamine, which are relevant to the abuse liability. To overcome these side effects and to optimize its clinical efficacy as a rapid-onset antidepressant for treatment-resistant patients, detailed preclinical studies targeting proper dosing regimen for clinical applications will be important.

Keywords Preclinical studies · Gross behavioral observation · Animal models of depression · Emotion · Cognition · Social interaction · Abuse liability

Abbreviations

im	Intramuscular
ip	Intraperitoneal
iv	Intravenous
sc	Subcutaneous

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1 Introduction

Ketamine, a dissociative anesthetic agent, was developed in the early 1960s as a substitute for phencyclidine (PCP). The term dissociative means that it differentially acts on subcortical and cortical regions in the brain. Indeed, it is known that ketamine alters the functional connectivity of the human brain (Joules et al. 2015). The mechanisms of action of ketamine are complex. However, it is well known that the major target site of ketamine is the *N*-methyl-D-aspartate (NMDA) receptor. Ketamine blocks the opening of the channel and thereby reduces mean channel open time and at the same time decreases the frequency of channel opening via an allosteric mechanism (Orser et al. 1997). Further, it is also known that ketamine inhibits monoamine transporters and therefore potentiates monoaminergic neurotransmission (Nishimura et al. 1998).

Ketamine has been widely used as an anesthetic, especially for short diagnostic and surgical procedures since it does not cause muscle relaxation. It is a standard anesthetic in veterinary medicine. However, the nonmedical use of ketamine has increasingly been recognized as an abuse-related problem. In Europe, concomitant use of ketamine with 3,4-methylenedioxymethampehtamine (MDMA) for recreational purposes has become a concern. In 2003, a WHO expert committee on drug dependence warned that a critical review regarding ketamine is needed (WHO technical report series, 915, 2003: 15). In Japan, ketamine was designated as a narcotic drug in the Narcotics and Psychotropics Control Act in 2007.

Recently, the antidepressant action of ketamine has attracted attention. One of the major drawbacks of traditional antidepressants is the slow onset of their therapeutic efficacy. Both preclinical and clinical studies have shown that a single administration of ketamine is effective for the treatment of depression (see review, Grady et al. 2018; Zanos and Gould 2018). Although ketamine is expected to be a promising antidepressant drug, we must deliberately evaluate other behavioral effects. Ketamine produces diverse behavioral effects on emotion and cognition. It also causes schizophrenia-like behavioral symptoms. Moreover, ketamine has reinforcing and rewarding properties, which lead to abuse.

In this chapter, I will review the behavioral pharmacological effects of ketamine in animals. This review focuses on (1) its effects on gross behaviors; (2) the effects related to its therapeutic efficacy as an antidepressant; and (3) its effects on emotion, cognition, and those related to abuse liability, which might cause adverse reactions in clinical settings.

2 General Behavioral Effects

Subanesthetic doses of ketamine do not cause remarkable behavioral changes in animals. We conducted gross behavioral observations on the effects of ketamine in rats by means of the functional observational battery (FOB) used in our laboratory.

The battery covers a wide range of behavioral changes such as tremor, convulsion, respiration, reactivity to handling, exophthalmos, salivation, piloerection, pupil size, rearing, posture, urination, defecation, and sensory reactivity to stimuli. According to our observation, ketamine at 3 mg/kg ip increased the number of rearing from 5 to 60 min after administration. However, this sign was not clear at 10 mg/kg. No other remarkable changes were observed.

Ketamine at relatively high doses seems to increase spontaneous motor activity. For example, ketamine at 10–100 mg/kg ip temporarily increased locomotion, sniffing, swaying, and falling. These signs were similar to those of PCP and different from stimulant drugs (Koek et al. 1987). In mice, ketamine increased motor activity at 30 mg/kg ip (Hayase et al. 2006; Lin et al. 2016). However, at 100 mg/kg ip motor activity was decreased after a temporary increase (Hayase et al. 2006). In rats, ketamine at 25 mg/kg ip increased activity and stereotypy for 30 min after administration (Razoux et al. 2007).

The effects of ketamine on steady-state and ongoing behavior have been studied by means of schedule-controlled behavior for food reinforcement established by operant conditioning. Ketamine at doses up to 10 mg/kg ip had no effect on the nose-poking behavior of mice. Doses higher than 30 mg/kg decreased the response rate maintained by a fixed ratio (FR) 30-s schedule, in which every 30 responses were reinforced and a relatively high baseline response was maintained. On the contrary, in responses maintained by the fixed interval (FI) 300-s schedule, in which the first response occurred 300 s after the previous reinforcement was reinforced and a relatively low baseline response was maintained. Ketamine at 30–100 mg/kg ip increased the response rate but decreased the response rate at the highest concentration of 180 mg/kg (Wenger and Dews 1976). The effect of ketamine on schedule-controlled behavior varies depending on the preadministration baseline rate of the response. This effect is called rate dependence and is common to various kinds of psychoactive drugs. The rate-dependent effect of ketamine has also been demonstrated in S-ketamine at doses above 15 mg/kg ip in rats under the FI 300 s schedule (Meliska et al. 1980). However, they showed that R-ketamine at doses above 30 mg/kg ip did not increase the response rate but only decreased it.

3 Behavioral Effects Related to Antidepressant Therapeutic Efficacy

3.1 Overview

In 1988, Reynolds and Miller reported that tricyclic antidepressants, such as desmethylimipramine and imipramine, inhibited [^{3}H]-MK801 binding to the NMDA receptor. The IC_{50} value of desmethylimipramine was 7.4 μM and that of imipramine was 22.5 μM (Reynolds and Miller 1988). This in vitro finding was confirmed in vivo by analysis of the protective action of ketamine against lethality by a large

dose (up to 80 mg/kg ip) of NMDA in mice (Leander 1989). The fact that antidepressant drugs have antagonistic activity on NMDA receptors led to the glutamate hypothesis of depression (see review Sanacora et al. 2012).

In accordance with this hypothesis, the clinical efficacy of ketamine on depression patients has been reported in the early 2000s. For example, Berman et al. (2000) showed that a single administration of ketamine at 0.5 mg/kg iv in patients with major depression was effective for improving symptoms as measured by the Hamilton Depression Rating Scale. Although the number of patients in this study was small, the effect of ketamine was clear compared with the placebo control. Preclinical studies on the antidepressant effects of ketamine using animal models have been accelerated after that.

3.2 Findings with Various Models of Depression

In an early study, ketamine at 10 mg/kg ip recovered suppression of sucrose preference and novelty-food seeking after chronic mild stress in rats (Li et al. 2011). In this study, it was also shown that ketamine recovered the expression levels of synapsin-1 and PSD95 and excitatory postsynaptic currents in the prefrontal cortex.

Lipopolysaccharide (LPS) induces cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) and it is known that these proinflammatory cytokines are elevated in depression patients. Thus, administrating LPS is used to induce depression-like behavioral changes in animals (Zhu et al. 2010). In the LPS-induced depression model in mice, ketamine at 6 mg/kg ip recovered sucrose preference and reduced immobility time in forced swimming test. This effect was thought to be mediated by antagonism of the NMDA receptor because the effect of ketamine was blocked by pretreatment with the α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor antagonist 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(f)quinoxaline-2,3-dione (Walker et al. 2013).

Social isolation is another method to induce depression-like behavioral changes in animals (Wallace et al. 2009). Isolated housing for 7–8 weeks caused a decrease in sucrose preference and prolonged immobility time in the forced swimming test in male rats, whereas a decrease in sucrose preference was not evident in females (Sarkar and Kabbaj 2016). In this study, ketamine at a relatively low dose (2.5 and 5 mg/kg ip) improved these symptoms. It was also found that isolated housing decreased spine density and levels of synapsin-1, PSD95, and GluR1 in the medial prefrontal cortex and these changes were also restored by ketamine.

Another important aspect of depression is a loss of cognitive flexibility (Castaneda et al. 2008). Subjecting rats to cold stress (4 °C) daily for 6 h for 14 consecutive days induced an impairment of cognitive flexibility, as revealed by impairment of reversal learning in the attentional set-shifting experiment (Fig. 1). A single administration of ketamine at 10 mg/kg ip improved performance in this test (Patton et al. 2017). This effect may be mediated by the Janus tyrosine kinases and signal transduction activators of transcription proteins (JAK/STAT) signaling pathway.

Fig. 1 Reversal learning in attentional set-shifting apparatus in rats. Food-restricted rats were placed in the start box (left) and allowed to select one of the two pods (right). Each pod contained a different digging medium and a different odor applied to the rim of the pods. In the original discrimination training, rats had to associate one stimulus dimension (e.g., odor) with food. The other dimension (e.g., digging medium) was an irrelevant distractor. In the reversal learning, the cue/reward association was switched. (This figure is originally drawn based on Lapiz and Morilak (2006))

3.3 Quest for Mechanism

Because the mechanisms of action of ketamine related to its antidepressant effect will be discussed in detail in another chapter, I will only cover several select topics relevant to its behavioral effects.

The rapid onset of the antidepressant effects of ketamine has attracted attention. In an earlier study, it was demonstrated that blockade of the NMDA receptors by ketamine deactivates the eukaryotic elongation factor 2 (eEF2) kinase and reduces phosphorylation of eEF2. This induces rapid synthesis of brain-derived neurotrophic factor (BDNF), resulting in an antidepressant effect (Autry et al. 2011).

The NMDA receptor in the cortex is a heteromultimeric complex and contains two GluN1 subunits and two GluN2 subunits. Of the GluN2 subunits, GluN2A and GluN2B subunits are dominant. The target site of the antidepressant effects of ketamine were studied using cortical neurons from mice with a selective deletion of GluN2B (Miller et al. 2014). In these mice, the effect of a single administration of ketamine at 50 mg/kg ip did not reduce immobility time in the tail suspension test, suggesting that this subunit is one of the major sites of action of the antidepressant effects of ketamine. GluN2B seems to play an important role in the manifestation of depressive signs because mice having a deletion of this subunit are insensitive to chronic corticosterone treatment, which usually causes enhanced signs of depression.

Although ketamine is an NMDA receptor antagonist, several biochemical studies have shown that ketamine increases glutamate neurotransmission in the prefrontal cortex. As for this seemingly paradoxical effect of ketamine, one study suggested that ketamine acts on the NMDA receptors in hippocampal GABAergic interneurons as an antagonist and this antagonism activates the glutamate system in the prefrontal cortex (Donegan and Lodge 2017).

However, mechanisms other than glutamate neuronal transmission can also take part in the antidepressant effects of ketamine. One candidate mechanism involves the secretion of proinflammatory cytokines as mentioned in the LPS model. In one study, chronic unpredictable stress caused upregulation of cytokines such as IL-1β,

IL-6, TNF-α, and indoleamine 2,3-dioxygenase and this upregulation was attenuated by ketamine at 10 mg/kg ip (Wang et al. 2015).

Recently, a relationship between the gut microbiota and depression has been noted. One study demonstrated that treatment with ketamine at 2.5 mg/kg ip for 5 days markedly amplified *Lactobacillus, Turicibacter*, and *Sarcina*. In contrast, the same treatment decreased Mucispirillum and Ruminococcus, which are considered to be opportunistic pathogens (Getachew et al. 2018).

3.4 For Better Clinical Applications

Since ketamine has stereoisomers, it is important to know which isomer is potent for the treatment of depression. At the preclinical level, it is well known that (R)-ketamine is more potent than (S)-ketamine (Yang et al. 2015). It is also known that (R)-ketamine is longer lasting than (S)-ketamine (Fukumoto et al. 2017). (R)-Ketamine is effective in a social defeat stress model and this effect seems to be related to the gut microbiota–brain axis (Yang et al. 2017). This effect is independent of the serotonin system because pretreatment with para-chlorophenylalanine, which depletes brain serotonin, did not affect the antidepressant effect of ketamine (Zhang et al. 2018).

The antidepressant effect of ketamine has been proven in preclinical animal studies. However, there are still questions regarding scenarios that favor the action of ketamine the most. A recent study using mice highlighted this point. Ketamine at 10 and 30 mg/kg ip showed a reduction in the immobility time in the forced swimming test only in mice exposed to chronic mild stress. In contrast, ketamine increased the immobility time in normal unstressed mice (Fitzgerald et al. 2019). The response to ketamine is quite different in model mice compared to normal mice. This finding might be important because the effect is different from traditional antidepressants which are also effective in normal animals in the forced swimming test.

4 Behavioral Effects Related to Putative Adverse Reactions

Ketamine is known to cause schizophrenia-like symptoms in humans. The effects of ketamine on emotion, cognition, and social behaviors have been mainly studied in relation to this effect. It is also known to have abuse liability. These effects may cause adverse reactions in clinical settings. In this section, I will introduce the preclinical findings related to the putative adverse reactions. For convenience, the major findings are concisely summarized in Table 1.

Table 1 Behavioral effects of ketamine related to putative adverse reactions

Domain	Behavior	Species	Dose and route	Major finding	Ref.
Emotion	Anxiety	rt	30 mg/kg ip × 5 d	No effect in EPM	Becker et al. (2003)
	Fear	rt	16 mg/kg, sc	Suppression of conditioned fear	Pietersen et al. (2007)
	Fear	rt	up to 15 mg/kg ip × 3 d	Enhancement of fear in EPM after stress	Juven-Wetzler et al. (2014)
	Fear	rt	10 mg/kg ip	Enhancement of conditioned fear with pre-reactivation	Honsberger et al. (2015)
	Fear	ms	2.5 mg/kg ip × 22 d	facilitation of fear extinction with training	Ju et al. (2017)
Cognition	Memory	rt	30 mg/kg ip	Impairment of spatial short-term memory	Moghaddam et al. (1997)
	Memory	rt	30 mg/kg ip	Impairment of spatial memory in Morris maze	Duan et al. (2013)
	Memory	rt	30 mg/kg ip	Impairment of object and location recognition	Lin et al. (2016)
	Decision making	rt	up to 20 mg/kg ip	Increase impulsive choice in low impulse individuals	Cottone et al. (2013)
Schizophrenic	PPI of ASR	rt	30 mg/kg ip × 5 d	No effect	Becker et al. (2003)
	PPI of ASR	ms	50 mg/kg ip	Impairment at the lowest sound level	Featherstone et al. (2013)
	PPI of ASR	rt	30 mg/kg ip	Impairment	Duan et al. (2013)
	PPI of ASR	rt	30 mg/kg ip	Impairment	Lin et al. (2016)
	Latent inhibition	rt	30 mg/kg ip × 5 d	Impairment	Becker et al. (2003)
	Latent inhibition	rt	25 mg/kg ip	Impairment	Razoux et al. (2007)
	Executive function	mk	up to 1 mg/kg, im	Impairment of task switching performance	Stoet and Snyder (2006)
	Social withdrawal	rt	30 mg/kg ip × 5 d	Reduction of nonaggressive social contact	Becker and Grecksch (2004)
	Social withdrawal	rt	30 mg/kg ip × 5 d	Reduction of social contact	Uribe et al. (2013)

(continued)

Table 1 (continued)

Domain	Behavior	Species	Dose and route	Major finding	Ref.
Abuse liability	SA	mk	0.1 mg/kg/inf, iv	Reinforcing	Winger et al. (1989)
	SA	mk	0.03–0.3 mg/kg/inf, iv	Reinforcing	Winger et al. (2002)
	SA	rt	0.5 mg/kg/inf, iv	Reinforcing	van der Kam et al. (2007)
	SA	rt	0.125–1 mg/kg/inf. iv	Reinforcing only in novel environment	De Luca and Badiani (2011)
	SA	rt	0.5 mg/kg/inf, iv	Reinforcing but priming is required	Venniro et al. (2015)
	SA	rt	0.1 mg/kg/inf, iv	Reinforcing in males and proesterus	Wright et al. (2017)
	SA	rt	0.5 mg/kg/inf, iv	Reinforcing in OB rats	
	SA	rt	0.5 mg/kg/inf, iv	Reinforcing	Caffino et al. (2018)
	CPP	ms	1–10 mg/kg ip	Rewarding	Suzuki et al. (1999)
	CPP	ms	3, 10 mg/kg ip	Rewarding	Suzuki et al. (2000)
	CPP	rt	2.5, 5 mg/kg ip	Not rewarding but sensitization of hyperlocomotion	Strong et al. (2017)
	Other	rt	3.2–10 mg/kg ip	Not potentiate ICSS	Hillhouse et al. (2014)

PPI prepulse inhibition, *ASR* acoustic startle response, *CPP* conditioned place preference, *SA* self-administration, *ra* rat, *ms* mouse, *mk* monkey, *ip* intraperitoneal, *sc* subcutaneous, *im* intramuscular, *iv* intravenous

4.1 Emotion

There seems to be no direct effect of ketamine on anxiety. Ketamine at 30 mg/kg ip for 5 days did not cause any notable behavioral changes in the elevated-plus maze test (Becker et al. 2003).

However, ambiguous findings have been reported with respect to the effects of ketamine on fear memory. The effects seems to be dependent on environmental manipulations In one study, ketamine at 16 mg/kg sc suppressed freezing due to fear conditioning in rats, and this effect was antagonized by clozapine but not by haloperidol (Pietersen et al. 2007). In contrast, in another study, ketamine at 0.5–15 mg/kg ip for 3 days did not ameliorate but increased freezing elicited by a predator (cat)-scent exposure in rats (Juven-Wetzler et al. 2014). In this study, it was also noted that treatment with ketamine seemed to increase anxiety tested in the elevated-plus maze and the acoustic startle response.

If fear memory is reactivated by exposing animals to a conditioned context, ketamine at 10 mg/kg ip potentiated retrieval of fear memory in rats (Honsberger et al. 2015). However, if ketamine treatment (0.625–2.5 mg/kg ip for 22 days) is combined with extinction training of fear memory in mice, it reduces freezing and anxiety. This effect was related to the normalization of DNA methylation of the BDNF gene in the hippocampus and medial prefrontal cortex (Ju et al. 2017).

4.2 Cognition

Ketamine seems to deteriorate memory at relatively high doses. Short-term memory was impaired in rats administered 30 mg/kg ip as revealed by the delayed spatial alternation task (Moghaddam et al. 1997). Spatial memory, as tested in the Morris water maze, was also impaired by ketamine at 30 mg/kg ip (Duan et al. 2013). This effect was concomitant with hippocampal depression of neural transmission and these effects were antagonized by the dopamine D1 antagonist SCH23390 or the AMPA receptor endocytosis interfering peptide Tat-GluR2$_{3Y}$. Short-term memory as tested by novel object or novel location recognition was also impaired by ketamine at 30 mg/kg ip and this effect was recovered by coadministration with *N*,*N*-dimethylglycine (Lin et al. 2016).

Other than memory, impulsivity is related to various psychiatric diseases such as addiction and depression. Delay discounting is a measure used to evaluate impulsivity. In this test, preference for obtaining an immediate small reward and a delayed large reward is compared. Preference for an immediate small reward is considered an index of impulsivity. In one study, ketamine at 2.5–20 mg/kg ip has been reported to increase impulsive choices in rats. However, this effect was evident only for low-impulsive individuals (Cottone et al. 2013).

4.3 Symptomatology Related to Schizophrenia

Several characteristic information process biases relevant to the symptoms of schizophrenia are known. One of them is a deficit of prepulse inhibition (PPI) of the acoustic startle response (ASR). Abrupt large sounds elicit the startle response. If a weaker sound is presented immediately before this large sound, the amplitude of the ASR decreases. This is the PPI of ASR and is thought to reflect sensory-motor gating function. The degree of PPI is reduced, i.e., a large ASR is observed despite presenting a prepulse in patients with schizophrenia (Kunugi et al. 2007).

Although an early study did not demonstrate an impairment of PPI of ASR by ketamine at 30 mg/kg ip for 5 days for 2 weeks in rats (Becker et al. 2003), a subsequent study reported an impairment of PPI in mice, but only at the lowest level of sound pressure (Featherstone et al. 2013). This effect seemed to be mediated by the Akt 1 gene because the effect of ketamine was not evident in Akt 1 partially deleted

mice. Other studies using ketamine at 30 mg/kg ip in rats also showed an impairment of the PPI (Duan et al. 2013; Lin et al. 2016).

Another characteristic related to the symptomatology of schizophrenia is the impairment of latent inhibition. If a neutral stimulus is presented several times prior to Pavlovian conditioning, the acquisition of the conditioned response will be retarded. This phenomenon is known as latent inhibition (LI). It is known that LI is impaired in schizophrenia patients (Swerdlow et al. 1996). Ketamine at 25 or 30 mg/kg ip for 5 days impaired LI in rats (Becker et al. 2003). Impairment of LI was also observed even after a single administration of ketamine at 25 mg/kg ip in rats (Razoux et al. 2007).

Executive functions, which are known to be deteriorated in schizophrenic patients, are also impaired by ketamine. In a study using rhesus monkeys, ketamine at doses up to 1 mg/kg, im, impaired executive function tested by a task switching experiment (Fig. 2) (Stoet and Snyder 2006).

Social withdrawal, one of the negative symptoms of schizophrenia, is induced by ketamine. Repeated administration of ketamine at a relatively high dose (30 mg/kg ip) in rats decreased social interaction; however, this effect was only evident in the nonaggressive component of social interaction (Becker and Grecksch 2004). This effect of ketamine was antagonized by clozapine but not by haloperidol. A similar dosing regimen also reduced social interaction and this effect was reversed by memantine, a modulator of the NMDA receptor (Uribe et al. 2013).

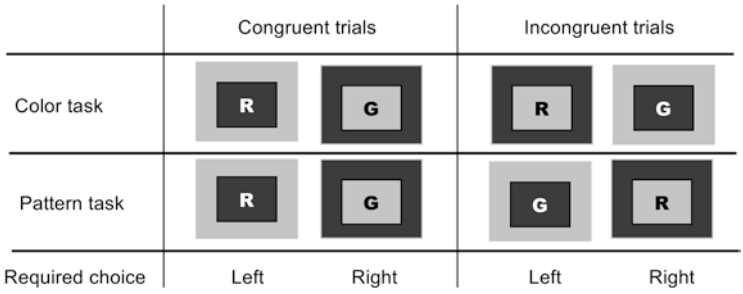

Fig. 2 Task switching experiment in monkeys. At the beginning of each trial, monkeys were instructed whether this was a color task or a pattern task by presenting a cue panel. In the color task, the monkey had to judge whether the color of the square was red or green by pressing two buttons (in this figure, red = left/green = right). In the pattern task, the monkey had to judge whether the square was brighter on the inside or on the outside (in this figure, outside = left/inside = right). In congruent trials, the correct choice side of both tasks was the same. In incongruent trials, however, the correct choice side of each task was different. (This figure is originally drawn based on Stoet and Snyder (2006))

4.4 Abuse Liability

Abuse liability, or in other words the dependence producing potential, of ketamine is discussed extensively in another chapter. In this section, I will summarize only the behavioral findings related to abuse liability.

One of the common features of an abused drug is its reinforcing property. The reinforcing property indicates the capability of a drug to act as a positive reinforcer of drug-taking behavior. In animals and also in humans, this property can be tested by drug self-administration experiments.

The reinforcing effects of ketamine have been reported in intravenous self-administration. Ketamine at 1.0 mg/kg/inf was self-administered in rhesus monkeys with a history of self-administration of cocaine or codeine (Winger et al. 1989). A subsequent self-administration study using a behavioral economics paradigm showed that ketamine had equal potency as a reinforcer to PCP (Winger et al. 2002). The reinforcing effect seems to be mediated by the glutamatergic system because the reinforcing effect of ketamine at 0.5 mg/kg/inf was decreased by the mGluR5 antagonist 2-methyl-6-(phenylethynyl) pyridine (MPEP) (van der Kam et al. 2007).

However, the reinforcing effect of ketamine was dependent on the environmental context, drug history, and sex. For example, self-administration of ketamine was evident only in rats transiently transferred from their home cages to the self-administration experiment cages. In habitual rats living in the self-administration experiment cage, the reinforcing effect of ketamine was not observed (De Luca and Badiani 2011). Moreover, the reinforcing effect of ketamine in drug naïve animals is difficult to show. Pretreatment with ketamine seems to be necessary to initiate self-administration (Venniro et al. 2015). In rats, intravenous ketamine at 0.1 mg/kg/inf was self-administered in males and proestrus females. Diestrus females did not show self-administration (Wright et al. 2017).

The rewarding effect of drugs is closely related to the reinforcing effect. The rewarding effect is tested by the conditioned place preference (CPP) experiment. In CPP, it is tested whether environmental stimuli associated with the drug effects induce an approaching behavior. In a classical study, ketamine at 10 to 30 mg/kg ip induced a dose-dependent CPP in mice and this effect was antagonized by the 5-HT_3 receptor antagonist ondansetron (Suzuki et al. 1999). The rewarding effect was confirmed in a subsequent study (3 and 10 mg/kg ip) (Suzuki et al. 2000). However, lower doses of ketamine (e.g., 2.5 or 5 mg/kg ip) in rats failed to induce CPP although ketamine causes behavioral sensitization to locomotor stimulating effects (Strong et al. 2017).

Several studies have been conducted to reveal the neurochemical mechanisms underlying the dependence-producing effect of ketamine. For example, the reinforcing property of ketamine was related to autophosphorylation of αCaMKII in the ventral striatum, medial prefrontal cortex, and hippocampus (Caffino et al. 2018). However, the precise mechanism of dependence to ketamine has not been elucidated to date. One of the most important candidates is its action on the brain reward system, the mesolimbic dopaminergic neurons originating from the ventral

tegmentum area and projecting to the nucleus accumbens. Although ketamine increases glutamate release in the nucleus accumbens (Razoux et al. 2007), ketamine at 3.2–10 mg/kg ip did not potentiate the intracranial self-stimulation (ICSS) response, suggesting that ketamine has no direct effect on dopaminergic neurons in the brain reward system (Hillhouse et al. 2014).

5 Conclusion

A growing body of preclinical evidence has shown that (R)-ketamine is effective for the treatment of depression. Ketamine is expected to exert an antidepressant effect after a single administration in treatment-resistant patients. However, in preclinical experiments, a single administration of even traditional tricyclic antidepressants and SSRIs is effective. Thus, its rapid onset should be verified in human clinical studies. Although preclinical researchers have attempted to develop animal models of treatment-resistant depression by means of exposing animals to stress, further studies are needed to verify the efficacy in refractory depression. The precise mechanisms of the antidepressant effects are still under research and diverse mechanisms have been proposed. If treatment with ketamine is combined with behavioral intervention techniques, it is possible to ameliorate emotional fear responses, which are typically seen in PTSD. Although psychotomimetic effects and abuse liability may be cautioned as a source of putative adverse reactions in clinical settings, relatively high doses seem to be related to these effects. An appropriate dosing regimen for the treatment of depression should be considered based on the animal model studies.

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