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REVIEW ARTICLE

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Rapid anti-depressant-like effects of ketamine and other candidates: Molecular and cellular mechanisms

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Abstract

Major depressive disorder takes at least 3 weeks for clinical anti-depressants, such as serotonin selective reuptake inhibitors, to take effect, and only one-third of patients remit. Ketamine, a kind of anaesthetic, can alleviate symptoms of major depressive disorder patients in a short time and is reported to be effective to treatment-resistant depression patients. The rapid and strong anti-depressant-like effects of ketamine cause wide concern. In addition to ketamine, caloric restriction and sleep deprivation also elicit similar rapid anti-depressant-like effects. However, mechanisms about the rapid anti-depressant-like effects remain unclear. Elucidating the mechanisms of rapid anti-depressant effects is the key to finding new therapeutic targets and developing therapeutic patterns. Therefore, in this review we summarize potential molecular and cellular mechanisms of rapid anti-depressant-like effects based on the pre-clinical and clinical evidence, trying to provide new insight into future therapy.

1 | INTRODUCTION

Major depressive disorder (MDD) is a mental disorder associated with mood disorders, characterized by depressed mood, decreased interest, cognitive impairment and even suicidal ideation. It is the main cause of global disability,[1] and almost 20% of people will suffer one episode of depression at some point in their lifetime.[2] Treatments of depression mainly include cognitive behavioural therapy and drug intervention. The pathogenesis of depression is associated with disorder of monoamine neurotransmitter levels. Based on the pathogenesis, drug treatments include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic anti-depressants (TCAs) and monoamine oxidase inhibitors (MAOIs). Though traditional medications may alleviate depressive symptoms in some degree, they work slowly. It takes weeks to months for patients to benefit from drug treatment when up to 30% of those patients still do not relieve symptoms and even develop resistance after receiving medication.[3]

Unlike traditional anti-depressants, ketamine could reduce suicidal ideation and improve mood in a short period of time[4] (Tables 1 and 2). Ketamine is a commonly used anaesthetic and analgesic drug. Clinical study showed that intravenous injection of 0.5 mg/kg of ketamine for 40 minutes could induce a strong and rapid anti-depressant-like response in patients with depression,[5] even in those who failed to treatment with traditional drugs. This effect could last 1-2 weeks.[6,7] (R,S)-ketamine is a racemic mixture comprising equal parts of (R)-ketamine (arketamine) and (S)-ketamine (esketamine). Esketamine has five times greater affinity for *N*-methyl-D-aspartate receptor (NMDAR) than arketamine.[8] Esketamine was approved by Food and Drug Administration (FDA) for adult patients with treatment-resistant depression (TRD) in 2019. It is the first anti-depressant in 30 years with a new mechanism. Several clinical trials demonstrated that esketamine nasal spray plus oral anti-depressant improved symptoms.[9] The response arose at 28 days[10] and appeared to persist for more than 2 months.[11] However, the clinical application of

esketamine still needs to be concerned. On the one hand, the efficacy of esketamine is controversial. It was found that in the phase 3 clinical trials, the grouping criteria were not strict. About 22% of the patients only resisted to one class of drugs, which meant that they were not strictly defined TRD. Patients participated in the randomized withdrawal trial were those who had been previously randomly assigned to esketamine and achieved stable remission, leading to a statistically higher response to the drug. In addition, in the sole positive phase 3 trial, the mean decrease on the Montgomery-Åsberg Depression Rating Scale (MADRS) was 20.8 for esketamine vs 16.8 for placebo. Besides, the result of meta-analysis showed that the standardized mean difference (SMD) of esketamine was similar to the olanzapine-fluoxetine combination, and less than the SMD of aripiprazole and quetiapine. These suggest that esketamine shows no significant advantage over placebo or other drugs approved by FDA. Moreover, one of the trials involved older patients and showed non-significant results, indicating that the efficacy of esketamine in this demographic remained unclear. Finally, the rapid onset of response was not demonstrated formally. About 8%-10% of patients who took esketamine achieved a rapid clinical response, compared with 5% of placebo. On the other hand, the results of the study 3003 were not consistent with the FDA requirement for substantial evidence of effectiveness. One site in Poland drives the overall study result due to a 100% of placebo arm relapses in this study. Removement of the outlier site changed the results from significant to non-significant.[12] So far, the use of esketamine has been limited to certified medical offices or clinics in America. Another isomer (R)-ketamine is also a potential anti-depressant which is undergoing clinical trials.[13] It is worth noting that (R)-ketamine has greater potency and longer-lasting anti-depressant effects than (S)-ketamine in rodents.[14-16] In fMRI test, it was shown that (R,S)-ketamine and (S)-ketamine significantly activated the cortex, nucleus accumbens and striatum of conscious rats, so as the NMDAR antagonist MK-801. On the contrary, (R)-ketamine produced negative response.[17] Similar pattern could be observed in clinical test.[18] These indicate that NMDAR may not be the primary target of (R)-ketamine.[19] (S)-ketamine and (R)-ketamine are also agonists of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor (AMPAR) and both activated brain-derived neurotrophic factor (BDNF)-tropomyosin receptor kinase B (TrkB) pathway. It is worth noting that their mechanisms may be different. Study showed that (S)-ketamine activated BDNF-TrkB pathway through mTOR signalling pathway while (R)-ketamine activated MEK-ERK pathway, mediating the activation of BDNF-TrkB pathway.[20] In another study, it was shown that (R)-ketamine could activate BDNF-TrkB pathway and reverse the decrease in dendritic spine density, inducing synaptogenesis in the pre-frontal cortex (PFC), CA3 and dentate gyrus (DG) of the hippocampus and eliciting sustained anti-depressant effects in depressed rodents.[15] Nevertheless, neither isomer attenuated the reduced BDNF in the PFC of susceptible chronic social defeat stress (CSDS) mice after 30 minutes, indicating that neither isomer improved the level of BDNF or induced synaptogenesis.[20] Whether the long-lasting anti-depressant effects of (R)-ketamine is related to MERK-ERK signalling is unknown. Besides, detrimental side effects of (R)-ketamine are fewer than (R,S)-ketamine and (S)-ketamine.[15,21] It was observed that (S)-ketamine caused a reduction in parvalbumin (PV)-positive cells in the medial pre-frontal cortex (mPFC) and DG, while (R)-ketamine did not. PV-positive cell is related to schizophrenia, and this may be the reason why (S)-ketamine produces psychotomimetic side effects.[15] In addition, side effects of (S)-ketamine are associated with mechanistic target of rapamycin (mTOR). The activation of mTOR signalling after drug abuse contributes to drug-related behaviours such as excessive drug intake.[22] (S)-ketamine activates mTOR signalling in the brain regions, and this may lead to drug abuse. Moreover, a study using positron emission tomography showed that in the conscious monkey, (S)-ketamine but not (R)-ketamine could reduce dopamine D2/3 receptor binding in striatum.[23] It is possible that (S)-ketamine-induced dopamine release relates to acute psychotomimetic side effects in humans. In addition to ketamine, other drugs[24-26] and treatments[27-29] can also produce rapid anti-depressant-like effects, but they are not long-lasting. At present, mechanisms for the rapid anti-depressant effects are not completely clear. Defining the mechanisms of rapid anti-depressant-like effects and finding pathways and targets for related drugs and physical therapies are important for developing new, safe and long-acting therapeutic methods. Here, we highlight the potential mechanisms of rapid anti-depressant effects.

TABLE 1 Summary of the rapid anti-depressant-like effects of ketamine in human

Patient diagnosis	Ketamine	Time (min)	Source
Major depressive disorder	0.5 mg/kg, 40-min infusion	40	Berman[5]
Bipolar I or II depression	0.5 mg/kg, intravenous infusion	40	Zarate[138]
Treatment-resistant depression	0.5 mg/kg, 40-min infusion	240	Murrough[139]
Major depressive disorder	50 mg intranasal ketamine	40	Lapidus[140]
Major depressive disorder	0.5 mg/kg, 40-min infusion	60	Hu[141]
Treatment-resistant depression	0.5 mg/kg, 40-min infusion	120	Singh[142]
Treatment-resistant depression	0.5 mg/kg, 40-min infusion	120	Phillips[4]
Treatment-resistant depression	0.5 mg/kg, 40-min infusion	40	Chen[143]
Treatment-resistant depression	1 mg/kg oral ketamine	40	Domany[144]
Major depressive disorder	0.5 mg/kg, 40-min infusion	230	Salvadore[46]

2 | NEURAL CIRCUIT

Depression is associated with multiple brain regions including pre-frontal cortex (PFC), hippocampus (HP) and amygdala.[30] These regions do not play a separate role in the onset of depression but are connected by nerve fibres, forming different neural circuits. The structure and function of these circuits are abnormal under a condition of depression.[31-33] Restoring normal connections of neural pathways may be an effective and fast way to alleviate depression symptoms. Ketamine is a non-specific NMDAR antagonist. It can change the local activities of relevant brain regions and reshape the brain circuit in a short time (Figure 1).

2.1 | Neural circuits associated with pre-frontal cortex

Pre-frontal cortex is related to cognitive function and emotional regulation.[34] Reduced activity of PFC has been observed both in depressed patients and in rodent models of depression. Dysfunction of the pre-frontal-hippocampal (PFC-HP) circuit is associated with major depression. It was demonstrated that in rat brain, functional connectivity within the PFC-HP system is increased by acute ketamine stimulation in a dose- and exposure-dependent manner.[35] In the same way, the activation of ventral hippocampus (vHipp)-mPFC pathway was proved to be necessary in anti-depressant responses of ketamine.[36]

Abnormal functional connection within dorsal PFC and anterior cingulate gyrus (ACC) is highly correlated with depression.[37] Ketamine has a positive effect on this connection. Study showed that functional connection between the right PFC and subgenual cingulate was increased in depressed patients 1 day after a single infusion of ketamine.[38]

Besides, the functional connection between the PFC and the amygdala also relates to depressive behaviour. It was reported that ketamine strengthens amygdala inputs to basal dendrites of layer V cells in mPFC and reversed depression-like behaviours.[39] Optogenetic experiment showed that light-activated mPFC-basolateral amygdala (BLA) projection produced rapid anti-depressant-like effects. Light stimulation to D1 dopamine receptor (Drd1) neurons

TABLE 2 Summary of the rapid anti-depressant-like effects of ketamine in animal

Species	Behavioural test		Time	Source
C57BL/6 mice	Sucrose consumption test Forced swim test Novelty-suppressed feeding test Elevated plus maze	3 mg/kg ip	30 min	Autry[50]
C57BL/6 mice	Forced swim test Novelty-suppressed feeding test	3 mg/kg ip	30 min	Gideons[145]
Mice	Forced swim test	2.5 mg/kg ip	30 min	Maeng[146]
C57BL/6 mice	Tail suspension test Forced swim test Sucrose preference test	10 mg/kg ip	120 min	Zhang[147]
Sprague-Dawley rat	Forced swim test	15 mg/kg ip	120 min	Silva[148]
CD1 mice	Forced swim test	10 mg/kg ip	60 min	Clarke[102]
C57BL/6J mice	Forced swim test	10 mg/kg ip	1 d	Fitzgerald[149]
CD1 mice	Forced swim test	5 or 10 mg/kg ip	60 min	Landrigan[150]
Sprague-Dawley rat	Forced swim test	10 mg/kg ip	30 min	Zhang[151]
Sprague-Dawley rat	Forced swim test	10 or 30 mg/kg ip	40 min	Podkowa[152]
C57BL/6N mice	Forced swim test	10 mg/kg ip	30 min	Petryshen[153]
NMRI mice	Forced swim test Tail suspension test	3 mg/kg ip	60 min	Kordjazy[154]

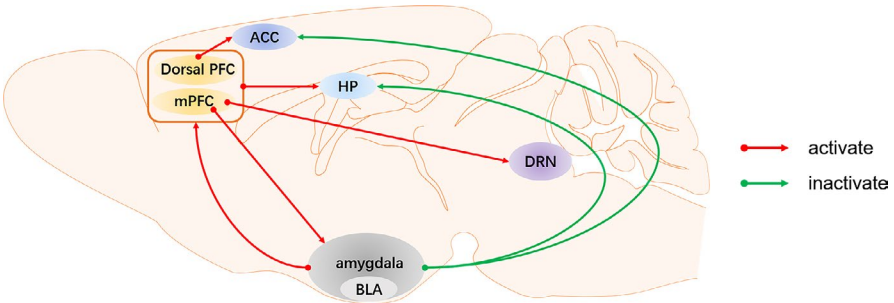

FIGURE 1 The neural circuits of depression affected by ketamine. ACC, anterior cingulate gyrus; BLA, basolateral amygdala; Dorsal PFC, dorsal pre-frontal cortex; DRN, dorsal raphe nucleus; HP, hippocampus; mPFC, medial pre-frontal cortex

in the brain region of mPFC increased the neuronal activity in the BLA area exclusively, indicating that the Drd1 neurons mediated BLA area to participate in the rapid anti-depressant-like effects.[40] However, whether ketamine stimulates mPFC and amygdala in the same time has not been proved.

In addition, the PFC-dorsal raphe nucleus (DRN) circuit has been confirmed to be implicated in depression.[41-43] The mPFC is one of the various areas projecting densely to the DRN,[44] which has abundant 5-HT cell bodies located in. Activation of 5-HT neurons can improve depression-like behaviours in elevated plus maze and forced swim test (FST).[45] Combining whole-cell recordings with optogenetic approaches, it was found that the mPFC axon monosynapse was connected with 5-HT neurons and GABAergic neurons in the DRN.[46] The mPFC pyramidal cell, projecting to 5-HT neurons in DRN, is a kind of glutamatergic neuron. The action potential of pyramidal cells is controlled by GABA interneurons. Ketamine blocks NMDAR located on GABA interneurons, leading to decrease in GABA activity, facilitating the firing activity of pyramidal cells and inducing glutamate release. As a result, high level of extracellular glutamate activates the post-synaptic AMPAR.[47,48] In a word, ketamine activates 5-HT neurons in DRN and increases the release of 5-HT by stimulating AMPAR in mPFC.

2.2 | Neural circuits associated with ventral tegmental area

Anhedonia, which is related to structure and function abnormalities of the reward circuit, is a core clinical feature of award-control disorder and also a core symptom of depression. The ventral tegmental area (VTA) is a heterogeneous brain region, mainly composed of dopaminergic (DAergic) neurons (60%-65%).[49] VTA projects to mPFC and nucleus accumbens (NAc) and forms the mesolimbic dopamine system with the latter one. The mesolimbic dopamine system is related to depression. Studies have shown that DAergic neurons in the VTA-NAc circuit directly participated in the regulation of coding and expressing of depressive behaviour with anhedonia.[50,51] Animal experiments demonstrated that stress could activate VTA DAergic neurons and stimulate DAergic transmission to the NAc.[52] Similarly, clinical evidence proved that ketamine was able to increase activity in VTA, and this effect persisted for 1 week after ketamine injection, accompanied by depression-like behaviour improved.[53] VTA-NAc circuit may be considered to contribute to the pathophysiology and symptomatology of depression, but whether the rapid anti-depressant-like effects of ketamine works through VTA-NAc circuit is lack of evidence.

2.3 | Neural circuits associated with lateral habenula

Lateral habenula (LHb), located in the epithalamus, is a component of the habenula nucleus. It is the main relay station for transmitting information between the marginal forebrain and midbrain. It can control the midbrain reward pathway and mediate the transmission of negative feedback information of dopamine neurons in marginal forebrain and midbrain marginal. It is also closely related to 5-HT system. On the one hand, the indirect excitatory glutamate projection of LHb to ventral tegmental area DAergic neurons was closely related to learned helplessness behaviour in rats. In learned helplessness model, excitatory synapses projected by LHb neurons into VTA were enhanced, leading to an increased probability of pre-synaptic release.[54] On the contrary, stimulating GABAergic neurons would mediate inhibitory synaptic transmission, subsequently inhibiting the post-synaptic discharge of LHb neurons and increasing the spontaneous discharge rate of VTA DAergic neurons.[55] On the other hand, most DRN serotonergic neurons received monosynaptic glutamatergic inputted from LHb, suggesting that LHb could bidirectionally regulate the activity of 5-HT neurons in DRN.[56] The above two experiments applied the methods of optogenetics and chemical genetics, respectively, to identify LHb-related neural projections function in depression. At present, there is little evidence on ketamine acting on LHb-related circuits. Nevertheless, a recent study found that abnormal clustered excitatory post-synaptic potentials appeared in the medial and LHb nucleus in congenitally learned helpless (cLH) rats and chronic-restraint stress (CRS) mice. Ketamine could block the clustered discharge pattern in the LHb and improve the symptoms of depression rapidly. The mechanism was associated with NMDAR and low-voltage-sensitive T-type calcium channels (T-VSCCs). In the study, ketamine but not AMPAR antagonist NBQX eliminated the burst firing in the LHb of cLH rats and rescued the depression-like behaviours quickly. The same results could be seen in specific NMDAR antagonist 2-amino-5-phosphonopentanoic acid (AP5) and T-VSCCs blocker mibefradil and ZD7288. Moreover, bilateral infusion of mibefradil into the LHb of cLH rats and systematic injection of the T-VSCCs blocker 2-ethyl-2-methylsuccinimide (ethosuximide) in CRS mice elicited rapid anti-depressant effects.[57] According to this research, blocking T-VSCCs may produce rapid anti-depressant effects. Nevertheless, ethosuximide did not exert the same potent anti-depressant effects in CSDS-susceptible mice[58] or non-medicated adult MDD patients.[59] Differences exist in different depressive animal models since the pathogenesis is diverse. More than that, the internal environment of the human body is more complicated than that of animal. Even one pathway is affected by ketamine, other alternatives can be activated instead. Studies on other T-VSCCs blockers and the possible targets need to be done.

2.4 | Neural circuits associated with amygdala

The amygdala is involved in coordinating the function of cortical networks when evaluating the biological significance of affective stimuli. Liu et al[39] discovered that ketamine activated amygdala and increased the amygdala output to the PFC through the anterior marginal area in the chronic unpredictable stress (CUS) model of rats. By using fMRI and resting-state fMRI (rsfMRI), it was found that in healthy subjects without any mental, neurological or medical

illness, ketamine reduced neural reactivity in the bilateral amygdalo-hippocampal complex during emotional stimulation, which was different from amygdala-PFC circuit.[60]

It is hypothesized that the amygdala and its interaction with the pre-genual anterior cingulate cortex (pgACC) could predict the response of patients to ketamine. Clinical studies have demonstrated that MDD patients were either in working memory task mode or stimulated by rapidly presenting fearful faces, and the pgACC was highly activated but could be inactivated by ketamine within 4 hours. Pre-treated with ketamine, patients with the lowest pgACC activation had the greatest improvement in depressive symptoms when working memory load increased. Moreover, the functional connection between the pgACC and the amygdala was negatively correlated with the change in anti-depressant symptoms.[61,62] Notably, another study showed that a single bilateral infusion of (R)-ketamine into basolateral amygdala and central nucleus of the amygdala had no anti-depressant effects.[63] Unlike (R)-ketamine, (S)-ketamine induced acute proteomic changes in the amygdala in wild mice after 2 hours, which may contribute to its the fast antidepressant effects.[64] In clinical trial, it was found that (S)-ketamine decreased then the connectivity among the amygdala, ACC and insula.[65] Maybe (S)-ketamine is the key to the function of (R,S)-ketamine on the amygdala.

3 | SYNAPTIC PLASTICITY

Another crucial mechanism of ketamine rapid anti-depressant-like effects is synaptic plasticity. Synapse is the basic structure of information transmission and processing between neurons. Synaptic plasticity, including changes in the number, structure and function of synapse, is a kind of adaptive change which enables brain to do self-repair. It is critically important for individuals to maintain normal functions when facing changing internal and external environments. Synaptic plasticity includes long-term potentiation (LTP) and long-term depression (LTD). Stress can interfere with the normal balance in synaptic plasticity, inhibiting LTP and/or promoting LTD, resulting in synaptic weakening and neuronal atrophy. Impairment of synaptic plasticity in hippocampus and pre-frontal cortex is particularly pronounced in depression.[66]

3.1 | Classical mechanisms of synaptic plasticity

N-methyl-D-aspartate receptor is ionotropic glutamate receptors and widely distributed in the central nervous system. It is a heterotetramer with subunits including GluN1, GluN2A, GluN2B, GluN2C, GluN2D, GluN3A and GluN3B.[67] NMDAR is ion channels of Na^+ and Ca^{2+}. Under physiological conditions, the permeability of NMDAR is blocked by Mg^{2+} in resting state. When stimulated, glutamate released by the pre-synaptic membrane acts on AMPAR and enhances its ion flow, releasing Mg^{2+} and unblocking the NMDA receptor channel. Then, a large amount of Ca^{2+} goes into neurons, resulting in excitatory toxicity and death of nerve cells. Ketamine acts on NMDAR and blocks the influx of Ca^{2+}, resulting in neurons survival and reversion of synaptic structural defect. Activation or inhibition of NMDAR triggers a series of cascades, altering expression level and function of AMPAR, leading to decrease or increase in AMPAR-mediated synaptic transmission BDNF. Meanwhile, inhibition of NMDAR also leads to inactivation of eukaryotic elongation factor 2 (eEF2), resulting in reducing eEF2 phosphorylation and enhancing BDNF protein synthesis[68] and regulating synaptogenesis (Figure 2). Other drugs also produce anti-depressant effects. Cannabidiol, neuropeptide VGF (non-acronymic) C-terminal peptide TLQP-62 and NV-5138 increased activity of BDNF-mTOR signalling in the mPFC to induce rapid anti-depressant effects.[69-71] D-Methadone is a non-competitive NMDAR antagonist and could decrease immobility of rats in FST in 24 hours.[72] Another NMDAR blocker Ro 25-6981 also exhibited anti-depressant effects in pre-clinical

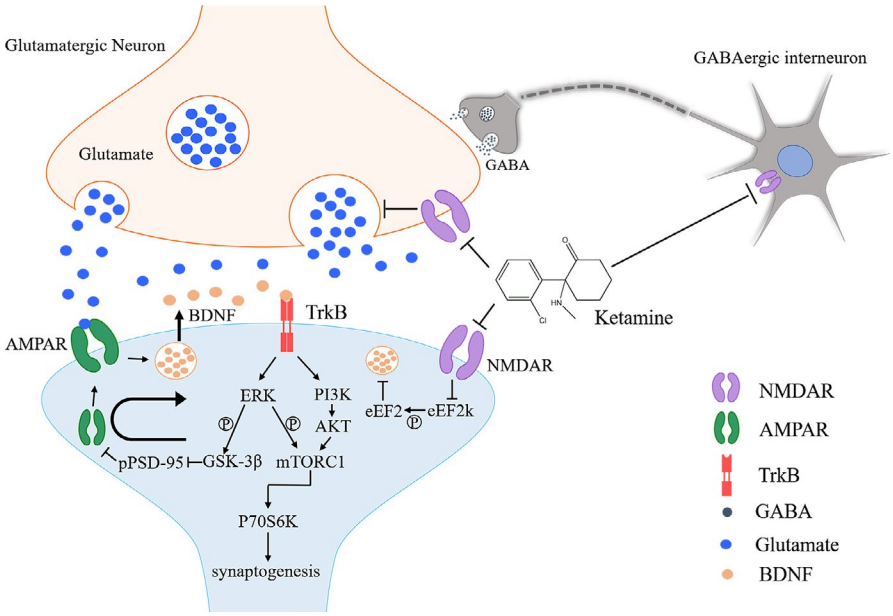

FIGURE 2 Proposed mechanisms of ketamine act on synaptic plasticity. AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor; BDNF, brain-derived neurotrophic factor; eEF2, eukaryotic elongation factor 2; GSK-3β, glycogen synthase kinase-3β; mTORC1, mechanistic target of rapamycin complex 1; NMDAR, *N*-methyl-D-aspartate receptor; P70S6K, P70S6 kinase; PSD-95, post-synaptic density-95; TrkB, tropomyosin receptor kinase B

and clinical tests.[73,74] However, a meta-analysis showed that non-ketamine NMDAR antagonists were superior to placebo only on days 5-8, while ketamine reduced depression in 40 minutes.[75] Not all non-ketamine NMDAR antagonists elicit robust anti-depressant effects such as ketamine, suggesting that NMDAR may not be the key role in the anti-depressant mechanisms of ketamine. Inhibition of NMDAR causes changes in its downstream molecules and signalling pathways, and these changes can be seen in depression-related brain regions.[76] But now, there are more and more reports of rapid anti-depressants that are less related to NMDAR. Maybe we should stop focusing on NMDAR only and begin to pay more attention to other potential targets. Other mechanisms of anti-depressant effects of ketamine will be discussed below.

3.1.1 | AMPAR in synaptic plasticity

AMPAR belongs to the ionic glutamate receptor and is dynamically expressed in the post-synaptic membrane. It mediates rapid excitatory synaptic transmission in the central nervous system and is related to induction and maintenance of LTP and LTD.[77-80] Increasing insertion and phosphorylation of AMPAR leads to LTP and increases the sensitivity of glutamate to synaptic transmission.[81] NMDAR antagonists facilitate glutamate release and increase synaptic glutamate concentration by blocking NMDARs on pre-synaptic neurons or GABA interneurons. On the one hand, inhibiting the pre-synaptic NMDARs leads to a release of glutamate from pre-synaptic neurons. On the other hand, suppressing the NMDARs on GABA interneurons will decrease the activity of GABA interneurons and disinhibit the pre-synaptic neurons.[82-84] Glutamate can activate AMPAR and downstream signalling pathways. On the one hand, BDNF in post-synaptic neurons will be released into the synaptic cleft immediately after AMPARs are activated, activating the TrkB on the post-synaptic membrane.[85] Then, the activation of TrkB increases the phosphorylation level of glycogen synthase kinase 3-β (GSK-3β) via ERK signalling pathway, leading to a decrease in the phosphorylation level of post-synaptic density-95 (PSD-95) and the internalization of the AMPA GluA1 subunit, allowing ketamine to enhance signalling through the AMPAR[86] and promote synapse generation.[87] On the other hand, the downstream ERK and PI3K-AKT signalling pathways activate and stimulate mechanistic target of rapamycin complex 1 (mTORC1) phosphorylation to promote synapse formation.[88] Subsequently, the phosphorylation level of P70S6 kinase (P70S6K) increases, resulting in synaptogenesis.[89] These results induced by ketamine could be eliminated by AMPAR antagonists and mimicked by AMPA-positive allosteric modulator CX614.[88]

3.1.2 | BDNF in synaptic plasticity

Brain-derived neurotrophic factor is a vital protein in the process of synaptic transmission. It regulates neural plasticity, synaptic production, neurogenesis and cell survival. BDNF is necessary for the formation and maintenance of activity-dependent synaptic connections. It has been found that the expression of BDNF in the pre-frontal cortex and hippocampus was downregulated in animal depression models, so as the level of BDNF in depressed patients.[90,91] Evidence showed that ketamine administration increases BDNF levels and improves depressive-like behaviours.[92-94] More importantly, BDNF is indispensable in anti-depressant effects. In the BDNF Met gene knock-in mice, especially Met/Met mice, synaptogenesis was significantly weakened,[95] consisted of depressed patients.[96] Clinical study showed that either 0.5 or 0.2 mg/kg of ketamine injection could reduce suicidal ideation of patients who had the Val allelic genes. However, patients with genotype Met/Met only responded at a dose of 0.5 mg/kg ketamine.[96] Sufficient BDNF content regulates synaptic plasticity and participates in reversing depression.[97-99]

Except for ketamine, acute caloric restriction (CR) is also able to elevate BDNF level. CR refers to a 30%-40% reduction in calorie intake while retaining protein, vitamins, minerals and water intake to maintain proper nutrition. Some mental illnesses, such as the typical major depression and anorexia nervosa, are characterized by reduced calorie intake. Previous studies showed that long-term strict energy limitation (5 weeks, 50% intake of the control group) may cause brain 5-HT system dysfunction, leading to the development of depression and anxiety.[100] Otherwise, strict energy limitation might lead to malnutrition[101] and other metabolic dysfunctions in the body. Our group found that 9-hour acute CR increased BDNF level in the PFC and hippocampus, resulting in neurogenesis in the subgranular region and producing anti-depressant-like effects.[27] Aiming to figure out whether the anti-depressant effects of CR are related to the 5-HT system, we combined CR with imipramine and 5-$HT_{2A/2C}$ receptor agonist (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride (DOI) for authentication. The results showed that DOI could partially reverse the anti-depressant effects of imipramine and 9-hour CR.[28] We also found that DOI could suppress the increase in BDNF level and 5-HT_{2A}R antagonist ketanserin inhibited the effects of DOI on BDNF.[102] There is a possibility that acute fasting may exert anti-depressant effects by blocking 5-HT_{2A}R. Evidence shows that the activation of 5-HTergic system leads to an activation of glutamatergic system. Activated by 5-HT receptors, glutamate pyramidal cells in mPFC release BDNF rapidly and activate BDNF signalling pathway, resulting in synaptogenesis accompanied by rapid anti-depressant effects.[103-105] These studies suggest that monoamine manner (5-HT) and non-monoamine manner (BDNF) are not separated in anti-depressant effects. This suggests us that combining monoamine with non-monoamine may be a new strategy for treating MDD. Some studies showed that CR regulated the release of orexin[106-109] and ghrelin,[110-117] producing some anti-depressant effects. But this evidence on synaptic plasticity is weak, and we mention here only for reference (Figure 3).

Additionally, scopolamine has similar pharmacological mechanisms to ketamine for its anti-depressant effects. Scopolamine activates AMPARs, promotes BDNF release rapidly and stimulates BDNF-mTOR

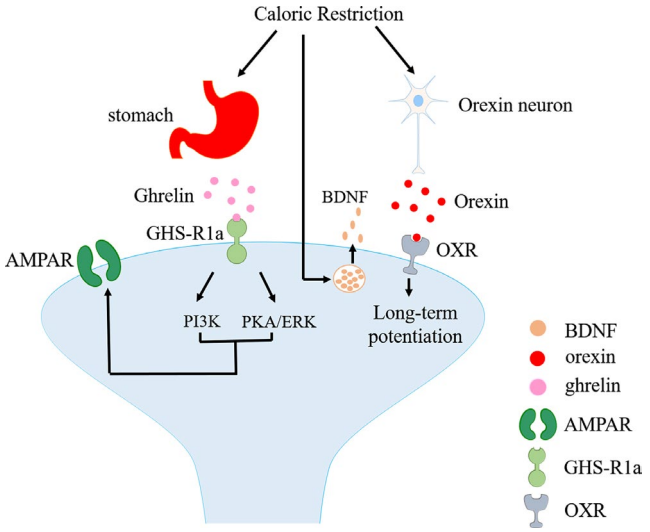

FIGURE 3 Proposed mechanisms of CR act on synaptic plasticity. AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor; BDNF, brain-derived neurotrophic factor; ERK, extracellular signal-regulated kinase; GHS-R1a, growth hormone secretagogue receptor 1a; PI3K, phosphatidylinositol 3-kinase; PKA, protein kinase A

signalling pathway.[118] The difference is that scopolamine acts on cholinergic system. Scopolamine inhibits GABAergic neuron function by combining with M1-AChR on GABA interneurons in mPFC.[119]

3.2 | Neuroglia in synaptic plasticity

Ketamine also affects glial cells in the central nervous system to regulate synaptic plasticity. Glial cells are mainly divided into three categories: astroglia, microglia and oligodendroglia. Among them, the former two are associated with depression. Astroglia is the most abundant glial cell. Its main functions are to regulate regional blood flow and energy metabolism, immune defence and amino acid neurotransmitter clearance. It is also associated with the stabilization and dissection of synaptic connections[120] and participates in antidepressant effects.[121] Pre-treated with ketamine 1 day after, immobility time in FST was significantly reduced. The volume of CA1 stratum radiatum and molecular layer of the dentate gyrus in the hippocampus and the volume of astrocytes of rats increased significantly, so as the number and length.[122] Ketamine modified the morphology of astrocytes and astrocytes, regulating the synaptic microenvironment, neurogenesis and angiogenesis.[123] Microglia is a kind of immunocompetent cell. Excessive microglial activation would cause inflammatory process, leading to astrocyte glutamatergic dysfunction and activation of microglial function in turn.[124] Evidence showed that ketamine inactivates microglial due to inhibition of ERK1/2 phosphorylation.[125] Besides, ketamine regulated STAT3 and the type I interferon pathway in microglia through eEF2, increasing the BDNF expression and promoting the synthesis of PSD95 and synapsin I (SYN1).[126] Additionally, microglial cells induce immune dysfunction by producing quinolinic acid (QUIN). QUIN is an endogenous modulator with agonistic properties on NMDA. It was observed that in acutely depressed patients, QUIN increased in subregions of the anterior cingulate gyrus.[127] Increase in QUIN comes along with decrease in kynurenic acid (KYNA), a NMDA receptor antagonist synthesized by astrocytes.[128] Ketamine could modulate the microglial reactivity and decrease QUIN production. It was reported that KYNA-to-QUIN ratio was a predictor of ketamine response in treatment-resistant depressed patients, while the reduction in QUIN after treated by ketamine was a predictor to the reduction in MADRS score.[129] Ketamine regulates functions of astrocytes and microcytes to maintain synaptic complement.

3.3 | Neuroinflammation in synaptic plasticity

Depression is considered to be relevant with the activation of chronic, low-grade inflammatory responses and cell-mediated immunity.[130,131] Chronic inflammatory reactions cause neurons apoptosis in brain regions associated with emotion regulation such as hippocampus,[132,133] leading to impairment of synaptic plasticity. Ketamine could normalize abnormal neurobehaviours induced by neuroinflammation through regulating the interleukin (IL)-1β, tumour necrosis factor (TNF)-α and IL-6.[134] In rodent model, ketamine would reverse the increase in IL-1β and TNF-α caused by lipopolysaccharide (LPS), shortening the immobility time significantly in FST and promoting hippocampal neurogenesis.[135] In addition, ketamine also plays an anti-depressant part in the central nervous system by regulating the immune system's immune response. It promoted the conversion of macrophages in CNS into M2-type cells with anti-inflammatory properties, reversing the inflammatory response through NMDAR and mTOR.[136] Zhang et al found that the desperate behaviours of susceptible mice in the social defeat stress model were improved in FST and tail suspension test (TST) after receiving intravenous injection of the inflammatory factor IL-6 receptor antibody MR16-1. MR16-1 treatment increased the expression of PSD95 and AMPAR1, so as the dendritic spines in hippocampus, and PFC and NAc in susceptible mice. Besides, MR-16 normalized the components of gut microbiota in susceptible mice by downregulating the level of IL-6 in the periphery.[137] Changes in peripheral IL-6 and gut microbiota may be vital for the pathogenesis of depression. It was found that baseline serum levels of IL-6 were both higher in ketamine responder and non-responder groups than control group. More than that, serum level of IL-6 is significantly higher in the responder group than non-responder group.[138] Another clinical study also demonstrated that higher baseline interleukin-6 (IL-6) in serum predicted better response to ketamine.[139] Serum IL-6 may be a predictive biomarker for the anti-depressant effects of ketamine in TRD patients.

3.4 | A1R in synaptic plasticity

A1 receptors (A1R) are of high affinity with adenosine and are distributed both pre- and post-synaptically. A1R is essential for

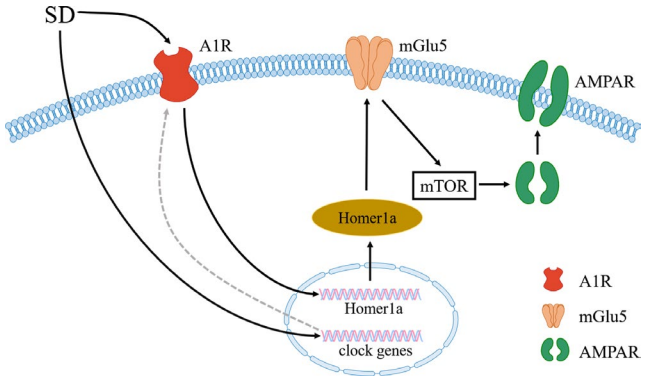

FIGURE 4 Proposed mechanisms of SD act on synaptic plasticity. A1R, A1 receptors; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor; mGlu5, metabotropic glutamate receptor 5; mTOR, mechanistic target of rapamycin; SD, sleep deprivation

sleep deprivation (SD) to exert rapid anti-depression-like effects. Therapeutic SD is a direct and rapid treatment for MDD, reducing the depressive symptoms of 50%-60% of MDD patients significantly within a few hours,[140] consistent with animal experiment.[141] It was reported that SD produced rapid anti-depressant effects by activating adenosine A1R in astrocytes and could be mimicked by the application of A1 agonist CCPA.[142] A1R exerts anti-depressant-like effects by regulating synaptic plasticity through Homer1a. Homer1a is a kind of synaptic protein upregulated by ketamine and SD, and the upregulation of Homer1a produces rapid anti-depressant-like effects. When Homer1a was knocked out in mPFC, the upregulation of A1R and the anti-depressant effects of SD were inhibited.[143,144] TAT-Homer1a, which is a fusion of the HIV TAT peptide with full-length Homer1a protein, has brain and membrane permeability. The application of TAT-H1A in vivo and in vitro increased the level of Homer1a and enhanced metabotropic glutamate receptor 5 (mGlu5) signal transduction. As a result, phosphorylation of the mTOR increased and the expression and activity of AMPAR were elevated.[145] The molecular change was consistent with those caused by ketamine and also SD. In animal studies, AMPAR level in the cerebral cortex and hippocampus was about 40% higher after arousal than after sleep. The change in AMPAR phosphorylation and other enzymes important for plasticity was consistent with synaptic strengthening during wakefulness and contraction during sleep.[146] These evidence indicates that synaptic homeostasis is regulated by wakefulness and sleep. Synaptic homeostasis refers to the ability of neurons to regulate their own excitability and synaptic strength, connected closely with synaptic plasticity. The core of the synaptic homeostasis hypothesis is that the number and intensity of cortical synapses vary widely throughout the sleep-wake cycle. It is believed that wakefulness leads to a net increase in synaptic strength of the cortical circuits, while a basic function of sleep is to reduce the proportion of cortical synapses.[147] Given to that, circadian rhythms also regulate synaptic plasticity. Circadian rhythms are reset by the transcription of clock genes, including the cycle genes PER1, PER2 and PER3. After 2-hour SD treatment on mice, the expression levels of PER1 and PER2 significantly increased.[148] Similarly, ketamine regulated circadian rhythms by affecting clock genes accompanied by a rapid anti-depressant effect. In animal experiment, it was seen that clock genes including PER2, neuronal PAS domain protein 4 and D-Box binding protein, were downregulated in mice treated with ketamine and SD.[149] Reviewing data from human, animal and neuronal cell, both low-dose SD and ketamine could regulate circadian rhythms.[150] It is hypothesized that A1R ameliorates the depression-like behaviours through regulating cycle genes and then affecting synaptic homeostasis.[151] However, we still lack evidence for that so far (Figure 4).

4 | CONCLUSION

In this review, we summarized the mechanisms of rapid anti-depressant-like effects induced by ketamine, CR and SD. Rapid anti-depressant-like effect is a result of mutual regulation of neural circuits and synaptic plasticity. On the one hand, rebuilding the neurotransmitter balance by regulating the levels of dopamine and serotonin can reshape neural circuits. On the other hand, glial cells, hormones and related receptors regulate the microenvironment and synaptic homeostasis. As a result, the functions and connections of various areas in the brain that regulate emotion return to normal. Clinically, the symptoms of depression are alleviated. Rapid anti-depressant drugs and behavioural interventions bring a glimmer of hope to it. Although depression is a refractory disease and there exist many unknowns in the pathogenesis of depression, with the application of optogenetics and the discovery of crosstalk in different pathways, more and more safe and effective rapid anti-depressant treatments are about to occur.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

FP wrote the first draft. JF, TG and QL participated in the discussion of the manuscript. BL provided critical revisions. All authors approved the final version of the manuscript for submission.

DATA AVAILABILITY STATEMENT

Data available on request.

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