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Rapid-acting antidepressants targeting modulation of the glutamatergic system: clinical and preclinical evidence and mechanisms

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ABSTRACT

Major depressive disorder (MDD) is a devastating mental illness that affects approximately 20% of the world's population. It is a major disease that leads to disability and suicide, causing a severe burden among communities. Currently available medications for treating MDD target the monoaminergic systems. The most prescribed medications include selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors. However, these medications have serious drawbacks, such as a delayed onset requiring weeks or months to reach efficacy and drug resistance, as one-third of patients are unresponsive to the medications. Therefore, it is imperative to develop novel therapies with rapid action, high efficacy and few adverse effects. The discovery of the rapid antidepressant effect of ketamine has triggered tremendous enthusiasm for studying new antidepressants that target the glutamatergic system in the central nervous system. Many agents that directly or indirectly modulate the glutamatergic system have been shown to provide rapid and lasting antidepressant action. Among these agents, ketamine, an antagonist of metabotropic glutamate 2/3 receptors, and scopolamine, an unspecific muscarinic acetylcholine receptor antagonist, have been extensively studied. In this review, we discuss the clinical and preclinical evidence supporting the antidepressant efficacy of these agents and the current understanding of the underlying mechanisms.

INTRODUCTION

Major depressive disorder (MDD) is a worldwide devastating mental disorder characterised by a low mood, reduced interest and impaired cognitive functions.[1] It has a lifetime prevalence of up to 20% of the world's population, affecting both sexes and most ages, and is one of the leading causes of disability.[2] Currently available medications mainly target the monoaminergic systems, such as selective serotonin and norepinephrine reuptake inhibitors. However, they have significant drawbacks, including slow onset and drug resistance.[3] Current antidepressants were discovered in the 1960s, and there had been no breakthroughs in finding mechanistically different antidepressants until the recent discovery of ketamine's rapid antidepressant action.[4–6] Ketamine is an N-methyl D-aspartate receptor (NMDA) antagonist that exerts rapid and long-lasting antidepressant effects in patients with MDD and treatment-resistant depression (TRD). The antidepressant action of ketamine is believed to be achieved by modulating the glutamatergic system.[6] Following ketamine, many other agents that directly or indirectly modulate glutamate synapses have been found to have rapid antidepressant efficacy in clinical and preclinical studies. Other extensively studied agents include antagonists of metabotropic glutamate 2/3 receptors (mGluR2/3) and scopolamine, a non-specific muscarinic acetylcholine receptor (mAChR) antagonist.[3 7 8] To date, clinical trials have provided strong evidence supporting the efficacy and safety of ketamine in the treatment of MDD, TRD, bipolar depression, post-traumatic stress disorder (PTSD) and suicidal ideations.[9 10] Clinical trials also support the efficacy of scopolamine in treating depression and bipolar depression; however, the effectiveness of scopolamine in TRD is still under study.[11] Clinical studies on the efficacy of mGluR2/3 antagonists in depression are still in the early phase, and few outcomes have been published. The mechanisms underlying the rapid antidepressant actions of these agents have been extensively studied in animal models of depression. It is generally agreed that ketamine, mGluR2/3 antagonists and scopolamine share a convergent mechanism: enhanced glutamatergic activity which activates brain-derived neurotrophic factor (BDNF) and the mammalian target of rapamycin complex-1 (mTORC1) signalling system, leading to neurogenesis.[12 13] In this article, we review the clinical and preclinical evidence of the antidepressant efficacy of

ketamine, mGluR2/3 antagonists, and scopolamine and the underlying mechanisms.

RAPID ANTIDEPRESSANT ACTION OF KETAMINE

Ketamine is a non-competitive antagonist of NMDA receptors.[14] The antidepressant effects of NMDA receptor antagonists have been reported for the first time in preclinical studies. It was found that competitive and non-competitive antagonists and partial agonists of NMDA receptors had antidepressant effects in a stress animal model, similar to clinically used antidepressants.[15] Subsequently, it was found that a single anaesthetic dose of ketamine (160 mg/kg) significantly reduced immobility in the forced swim test in a rat model of depression.[16] The first placebo-controlled, double-blinded clinical trial of ketamine in the treatment of depression was conducted on seven subjects with MDD. It was found that a single intravenous subanaesthetic dose of ketamine (0.5 mg/kg, 40 min infusion) significantly improved depressive symptoms within 72 hours.[4 6] Another placebo-controlled, double-blind crossover study showed that a single intravenous dose of ketamine (0.5 mg/kg) induced rapid antidepressant effects that occurred as early as 2 hours after infusion and lasted a week.[5] Since these pioneering studies, the antidepressant efficacy of ketamine has been generally replicated and demonstrated in clinical trials with TRD, bipolar disorder, suicidal ideation, PTSD and adolescent depression.

Approximately one-third of patients with depression respond inadequately to conventional medications and are diagnosed with TRD.[3] TRD was defined as failure to respond to at least two antidepressant medications of different classes.[17 18] Many clinical trials have demonstrated the efficacy of ketamine for the treatment of TRD. An early clinical study with a few subjects showed that a single dose of ketamine significantly improved depressive symptoms in 71% of patients with TRD after 1 day, and 35% achieved response after 1 week.[5] A subsequent study with a relatively large number of patients with TRD confirmed the rapid-onset antidepressant efficacy of a single dose of ketamine.[19] Although a single dose of ketamine is effective, the effect may be transient. Therefore, repeated doses of ketamine were tested. It was found that multiple doses of ketamine, such as six doses in 2 weeks, had a cumulative effect lasting more than 3 months in some patients, and ketamine at multiple doses was safe and well tolerated.[19–24]

Ketamine has also been shown to be effective in the treatment of bipolar depression. A randomised, placebo-controlled, double-blind, crossover add-on study showed that a single dose of ketamine (0.5 mg/kg) improved depressive symptoms as early as 40 min after the infusion, lasting 3 days in patients with bipolar TRD.[25] More than 50% of patients responded to a single dose or multiple doses (six doses) of ketamine. These doses of ketamine were well tolerated.[26] Adolescent depression is common and associated with significant morbidity and suicide. A double-blind, randomised, placebo-controlled clinical trial found that intravenous ketamine in adolescents with TRD significantly improved symptoms and was well tolerated.[27] In patients with PTSD, a single dose and repeated doses of ketamine have also been shown to improve depressive symptoms.[28–30]

In depressive patients with suicidal ideation, ketamine has also been shown to reduce suicidal ideations rapidly.[31] In an open-label study of a single infusion, ketamine (0.5 mg/kg) decreased suicidal ideation within 40 min, and the effect remained for 4 hours. Other depressive symptoms and anxiety also significantly improved.[32] In a randomised, double-blind, placebo-controlled study, a single dose of ketamine (0.2 mg/kg) reduced suicidal ideation 90 min after ketamine infusion in 88% of patients.[33] Two infusions of ketamine over 2 days showed long-term improvements in suicidal patients.[34] Thus, ketamine shows a rapid and persistent benefit for patients with suicidal behaviour.

Ketamine is a racemic mixture comprising equal parts of (R)-ketamine (or arketamine) and (S)-ketamine (or esketamine).[35] Clinical trials have found that the intravenous infusion of ketamine exerts a rapid antidepressant effect.[36 37] The antidepressant effects lasted for several days or weeks. In preclinical studies, (R)-ketamine has been shown to be more effective than (S)-ketamine, but its effect has not been established in clinical trials.[35 38] Randomised double-blind clinical trials have revealed the effectiveness of the intranasal form of (S)-ketamine in TRD and suicidal ideations.[39] The antidepressant effect of intranasal ketamine was significant and rapid, and the effect persisted for more than 2 months when applied biweekly.[36 39] The Food and Drug Administration approved the intranasal administration of (S)-ketamine in 2019 for TRD in adults. However, due to possible adverse effects such as dissociation, sedation, cognitive impairments and addiction, the use of ketamine is limited under certain conditions.[20 36]

ANTAGONISTS OF GROUP II METABOTROPIC GLUTAMATE RECEPTORS (MGLURS)

Glutamate receptors mediate excitatory synaptic transmission in the central nervous system and are divided into two subtypes: ionotropic receptors and mGluRs.[40] Ionotropic receptors are ion channels that mediate synaptic transmission, whereas mGluRs regulate synaptic transmission and plasticity by interacting with G proteins. mGluRs contain eight subtypes classified into three groups according to their coupled G proteins and functions.[41] Group II mGluRs, including mGluR2/3, have been implicated in depression due to their antidepressant effects. The expression of mGluR2/3 was found to be significantly increased in the prefrontal cortex (PFC) of patients with depression. The same has been observed in animal models of depression, indicating the possible role of mGluR2/3 in depression.[42]

The rapid antidepressant effect of mGluR2/3 antagonists has mainly been found in animal studies.[43] It was first shown that the intraperitoneal injection of (1R, 2R, 3R, 5R and 6R)-2-amino-3-(3,4-dichlorobenzyloxy)-6-fluorobicyclo(3.1.0)hexane-2,6-dicarboxylic acid (MGS0039, 3 mg/kg) or (2S)-2-amino-2-((1S,2S)-2-carboxycycloprop-1-yl)-3-(xanth-9-yl) propanoic acid (LY341495, 1 mg/kg), two

potent mGluR2/3 antagonists, significantly decreased the immobility time of forced swim and tail suspension tests in rats. Since then, many preclinical studies have shown that mGluR2/3 antagonists have rapid antidepressant effects in various animal models, including learnt helplessness[44] and olfactory bulb enucleation.[45] Similar to ketamine, mGluR2/3 antagonists are also effective in models of depression in which conventional antidepressants are ineffective.[46] MGS0039 or LY341495 reversed depressive behaviours caused by chronic corticosterone administration in mice and rats, whereas traditional antidepressants did not affect this type of depression model.[46] Moreover, in chronic unpredictable stress and chronic social frustration models, a single dose of a mGluR2/3 antagonist could have a rapid antidepressant effect lasting for more than 1 week.[47 48]

In contrast to ketamine, studies have found that mGluR2/3 antagonists might not have adverse effects similar to ketamine.[49–51] mGluR2/3 antagonists can protect cognitive function. It has been shown that intraperitoneal administration of the mGluR2/3 antagonist MGS0039 enhanced social recognition memory[52–54] and had anxiolytic effects in the conditional fear stress model and Vogel conflict drinking test.[44 55] These results indicate that mGluR2/3 antagonists are promising therapeutics for depression, with fewer adverse effects than ketamine. However, clinical studies on the efficacy of mGluR2/3 antagonists in depression are still in the early phase and few outcomes have been published.[43]

SCOPOLAMINE: A MACHR ANTAGONIST

Hypersensitivity of the cholinergic system has been proposed to mediate the pathogenesis of depression.[56] This notion was supported by early findings that cholinesterase inhibitors, such as physostigmine, led to or aggravated depressive symptoms in healthy people and depressive patients.[57] Thus, antagonism of the cholinergic system has been proposed to exert antidepressant effects. Scopolamine is a non-selective antagonist of mAChRs that has been shown to exert a rapid antidepressant effect.[58 59] The first clinical trial to study the effects of scopolamine in patients with depression was conducted in 1991.[60] Intramuscular injection of scopolamine (0.4 mg, three doses) was found to exert a small but significant antidepressant effect 24 hours after the injection. Subsequently, several well-designed double-blind placebo-controlled trials have been conducted. Intravenous infusions of scopolamine at three doses (4.0 µg/kg, 15 min per dose) with 3–4 day intervals between doses resulted in significant reductions in depressive symptoms.[7] Patients with depression and bipolar disorder were included in the trial. The antidepressant action of scopolamine was later replicated in a second double-blind placebo-controlled trial conducted by the same group of patients with purely unipolar depressive patients. It has also been found that scopolamine exerts an antidepressant effect with greater efficacy in women.[61] However, the antidepressant action of scopolamine has not been replicated in some clinical studies, and it remains unclear whether scopolamine exerts comparable antidepressant effects in patients with bipolar disorder.[11 59 62] A clinical trial is ongoing in patients with only bipolar disorder.[63] Clinical trials are also needed to investigate the antidepressant effects of scopolamine in TRD.

MECHANISMS UNDERLYING RAPID ANTIDEPRESSANTS

Ketamine, mGluR2/3 antagonists and scopolamine have been shown to share a common mechanism for their rapid antidepressant actions: the activation of BDNF–mTORC1 signalling cascades leading to neurogenesis.[13 64] It was also agreed that these new antidepressants initially enhance α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptor activity in pyramidal neurons in the PFC and hippocampus, which increases the production and release of BDNF. BDNF subsequently activates the BDNF–mTORC1 signalling pathway, leading to neurogenesis and restoration of neuronal circuitries.[13 65 66]

Increased activity of AMPA receptors

An increase in glutamate concentration in the PFC and the subsequent increase in AMPA receptor activity play crucial roles in the rapid antidepressant action of ketamine, scopolamine and mGluR2/3 antagonists.[12 13] Considerable evidence has been reported to support the idea that enhanced AMPA receptor activity mediates the initial action of these antidepressants. Systemic administration or microinjection of the AMPA receptor antagonist 2,3-dioxo-6-nitro-7-sulfamoyl-benzo(f)quinoxaline into the medial PFC blocked the antidepressant effects of all these agents.[67]

Enhanced BDNF production and release

BDNF is a growth factor that regulates neuronal growth, synaptogenesis and synaptic plasticity[68] and also plays an important role in the pathophysiology of depression and treatment.[69] Conventional antidepressants and electroconvulsive therapy enhance BDNF and tropomyosin receptor kinase B (TrkB) mRNA expression in the hippocampus and cortical regions.[70 71] Deletion of BDNF in the hippocampal dentate gyrus region reduced the antidepressant action.[72] It was found that the expression level of BDNF decreased in the brain of depressed patients.[73 74] The direct injection of BDNF into the hippocampus resulted in an antidepressant effect.[75] Infusion of BDNF antibodies into the medial PFC blocks the antidepressant effect.[76] Patients with depression carrying Met/Met, showing a deficit in BDNF production and release, did not respond to ketamine.[77 78] Similarly, the rapid antidepressant action of scopolamine was attenuated in BDNF Val/Met knock-in mice and prevented by the infusion of an anti-BDNF antibody into the medial PFC.[79] The mGluR2/3 antagonists LY341495 and MGS0039 also require the activation of BDNF signalling pathways for their rapid antidepressant actions.[47]

BDNF–mTORC1 signalling pathways

BDNF binds to its primary receptor, TrkB, to activate several signalling pathways.[68] It enhances the activity of AMPA receptors by increasing AMPA receptor translation and surface expression.[80] Subsequent activation of

the phosphatidylinositol 3-kinase and mitogen-activated protein kinase signalling pathways leads to the activation of mTORC1, which facilitates phosphorylation of the synaptic p70S6 kinase and suppression of 4E binding proteins, resulting in the synthesis of proteins related to synaptogenesis and dendrite spine growth.[13] Preclinical studies have shown that ketamine, mGluR2/3 antagonists and scopolamine all increase phospho-mTOR, phosphor-p70S6 kinase in the hippocampus and medial PFC of rodents.[81] Pretreatment with the selective mTORC1 inhibitor rapamycin prevented the antidepressant actions.[13] Thus, the mTORC1 signalling pathway is an integral molecular mechanism underlying the antidepressant action.

Disinhibition hypothesis

While ketamine, mGluR2/3 antagonists and scopolamine act on different receptors, they all activate the glutamatergic system and BDNF–mTORC1 signalling pathways, which are believed to underlie their antidepressant action.[13] The initial mechanisms that increase glutamatergic activity and BDNF production are poorly understood. One hypothesis is the disinhibition of pyramidal neurons, which is proposed to be caused by the inhibition of GABAergic interneurons.[82 83] Silencing GABAergic interneurons in the PFC has been reported to induce a rapid antidepressant effect.[84] The antidepressant effect of ketamine requires the NMDA receptor subunit GluN2B in GABAergic interneurons but not in the pyramidal neurons in the PFC since the knockdown of these receptors in the interneurons blocks the ketamine's effect.[85] Ketamine and scopolamine have been reported to inhibit pyramidal neurons by reducing the inhibitory input into the pyramidal cells.[86] Furthermore, the antidepressant action of scopolamine was shown to depend on the inhibition of GABAergic interneurons and muscarinic receptors in the GABAergic neurons since the activation of GABAergic interneurons or knockdown of M1 receptors in the interneurons in the PFC blocked the antidepressant effect.[82 84]

Another theory is that ketamine blocks the spontaneous NMDA receptor activity of pyramidal neurons in the resting state, which inactivates eukaryotic elongation factor two kinase, leading to the disinhibition of the BDNF synthesis.[87 88] The antidepressant effect of ketamine has also been reported to be independent of the blockage of NMDA receptors. (2R, 6R)-Hydroxynorketamine is a metabolite of ketamine, which is found to exert a rapid antidepressant action but does not block the NMDA receptors, and requires the activation of AMPA receptors, BDNF and mTORC1 signalling pathways.[89]

Interaction with serotonin (5-HT) and the dopamine system

Recent studies have indicated that the serotonergic system may play a critical role in the rapid antidepressant action of ketamine and mGluR2/3 antagonists.[90 91] It was found that ketamine increased extracellular serotonin concentration in the medial PFC, which is mediated by the AMPA receptor activity in serotonergic neurons in the dorsal raphe nucleus (DRN).[92] Similar to ketamine, mGluR2/3 antagonists also require the activation of 5-HT neurons in the DRN.[67] Furthermore, 5-HT1a receptors were found to mediate the effects of both ketamine and mGluR2/3 antagonists.[93 94] The activity of dopamine neurons in the ventral tegmental area may also play a role in the rapid antidepressant action.[49] Therefore, multiple systems and signalling pathways might be involved in the mechanisms underlying the antidepressant action.

SUMMARY

The discovery of the rapid antidepressant action of ketamine is a significant step toward the development of novel antidepressants. Since then, great attention has been paid to the glutamatergic system, as it is believed to probably mediate depression and antidepressant processes and be a new target in developing new antidepressants that will have fewer drawbacks than the current antidepressants. Ketamine, a mGluR2/3 antagonist, and scopolamine have been extensively studied as novel rapid antidepressants. These studies have shed significant light on the cellular and molecular mechanisms underlying depression and antidepressant actions. It is now generally believed that BDNF–mTORC1-neurogenesis is possibly a common signalling pathway shared by different antidepressants. The intranasal form of (S)-ketamine has been approved for clinical use in the treatment of TRD. Our understanding of the underlying mechanisms of rapid antidepressant action has advanced substantially, and as a result, more new targets will be revealed to develop rapid, efficacious antidepressants. Further clinical trials are ongoing to investigate the possible extended use of ketamine. Clinical trials are being conducted for scopolamine, mGluR2/3 antagonists and other agents.

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