INVITED REVIEW

mGlu2/3 receptor antagonists for depression: overview of underlying mechanisms and clinical development

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Abstract

Triggered by the ground-breaking finding that ketamine exerts robust and rapid-acting antidepressant effects in patients with treatment-resistant depression, glutamatergic systems have attracted attention as targets for the development of novel antidepressants. Among glutamatergic systems, group II metabotropic glutamate (mGlu) receptors, consisting of mGlu2 and mGlu3 receptors, are of interest because of their modulatory roles in glutamatergic transmission. Accumulating evidence has indicated that mGlu2/3 receptor antagonists have antidepressant-like effects in rodent models that mirror those of keta- mine and that mGlu2/3 receptor antagonists also share underlying mechanisms with ketamine that are responsible for these antidepressant-like actions. Importantly, contrary to their antidepressant-like profile, preclinical studies have revealed that mGlu2/3 receptor antagonists are devoid of ketamine-like adverse effects, such as psychotomimetic-like behavior, abuse potential and neurotoxicity. Despite some discouraging results for an mGlu2/3 receptor antagonist decoglurant (classified as a negative allosteric modulator [NAM]) in patients with major depressive disorder, clinical trials of two mGlu2/3 receptor antagonists, a phase 2 trial of TS-161 (an orthosteric antagonist) and a phase 1 trial of DSP-3456 (a NAM), are presently on-going. mGlu2/3 receptors still hold promise for the development of safer and more efficacious antidepressants.

Keywords mGlu2/3 receptor antagonist · Ketamine · TS-161 · Decoglurant · Antidepressant

Introduction

Major depressive disorder (MDD) remains a prevalent world-wide health problem. Although a number of antide- pressant medications, most of which stem from monoamine- based drug discovery, are currently available, they are far from ideal in terms of efficacy and the onset of antidepres- sant action. Therefore, new antidepressants with increased efficacy and a shorter therapeutic lag time are required. Because dysfunctions of the glutamatergic system have been implicated in the pathophysiology of depression, glu- tamatergic systems have recently gained significant attention as a target for the drug discovery of novel antidepressants [1, 2]. The importance of the glutamatergic systems for developing novel antidepressants has been highlighted by the ground-breaking findings of the antidepressant effects of ketamine, a non-competitive antagonist of N-methyl- D-aspartate (NMDA) receptor. Since the rapid and robust antidepressant effects of ketamine in patients with MDD, including those with treatment-resistant depression (TRD), were first shown in 2000 [3] and 2006 [4], the antidepressant effects of ketamine and their mechanisms have been inten- sively investigated. Currently, Spravato®, a nasal spray that delivers esketamine which is a stereoisomer of ketamine, is available in the US and European markets as an adjunctive therapy for the treatment of TRD patients and for depres- sive symptoms in adults with MDD who exhibit acute sui- cidal ideation or behavior. However, esketamine retains the unwanted side effects of ketamine, including dissociative/ psychotomimetic symptoms and abuse potential, which ham- pers the adoption of esketamine in daily practice. Therefore, novel approaches that can dissociate the ketamine-like anti- depressant effects from ketamine-like adverse effects have been actively investigated. These approaches target proposed mechanisms underlying the antidepressant effects of keta- mine, most of which are molecules within the glutamatergic

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system including GluN2B-containing NMDA receptor and α-amino-3-hydroxy-5-methyl-isoxazole-4-propionate (AMPA) receptor [5]. In addition to these approaches, the possible use of another stereoisomer of ketamine, arketamine, and a metabolite of ketamine, (2R,6R)-hydroxynorketamine, have been rigorously investigated. To date, arketamine looks promising as a novel antidepressant without exerting ketamine-like adverse effects based on data in both rodents and TRD patients [6, 7]. Among the components of the glutamatergic system, we have been focusing on group II metabotropic glutamate (mGlu2/3) receptors, which have a modulatory role in glutamatergic activity mainly the presynaptic regulation of glutamate flow. In this review, we will summarize the role of mGlu2/3 receptor in depression and the possibility of mGlu2/3 receptor antagonists as an alternative of ketamine by introducing both the efficacy in animal models and the underlying mechanisms. Moreover, we will touch on clinical trials of mGlu2/3 receptor antagonists.

Pharmacology of mGlu2/3 receptor and mGlu2/3 receptor antagonists

On a molecular basis, mGlu receptors have eight different subtypes. These receptors are divided into three groups (group I, II and III) based on amino acid similarity and signal transduction mechanisms [8, 9]. Among these subtypes, much attention has been paid to group II mGlu receptors, which consist of mGlu2 and mGlu3 receptors. mGlu2/3 receptors couple with Gi/Go proteins, leading to

the inhibition of adenylyl cyclase activity. mGlu2/3 receptors are mainly localized at the perisynaptic area of glutamatergic terminals in the frontal cortex and limbic systems, where they negatively modulate the release of glutamate [10]. Therefore, mGlu2/3 receptors play important roles in ameliorating glutamatergic tones when they are perturbed, as observed in several psychiatric conditions including schizophrenia [11], depression [12, 13] and addiction [14]. Indeed, mGlu2/3 receptor agonists were proven to be effective for a certain group of patients with schizophrenia [15] and generalized anxiety disorder [16]. A role of mGlu2/3 receptors in the pathophysiology of depression has also been reported. For example, the level of mGlu2/3 receptor protein was reportedly elevated in rodent models of depression [17, 18] and in the postmortem brains of patients with MDD [19]; in contrast, other reports have described reductions in mGlu2/3 receptor protein or mRNA in MDD patients [20] and in rodent models [21, 22]. These observations suggest that mGlu2/3 receptor abnormalities are involved in depression. In rodent studies, accumulating evidence suggests that mGlu2/3 receptor blockade may be beneficial for the treatment of depression, although limited data also suggest the opposite direction.

To date, several mGlu2/3 receptor antagonists have been synthesized (Fig. 1), and in vitro activities of representative compounds are summarized in Table 1. These antagonists are divided into two categories according to differences in the binding site of the receptor: orthosteric antagonists [23, 24] and negative allosteric modulators (NAMs) [25]. Orthosteric antagonists bind to glutamate binding sites, while
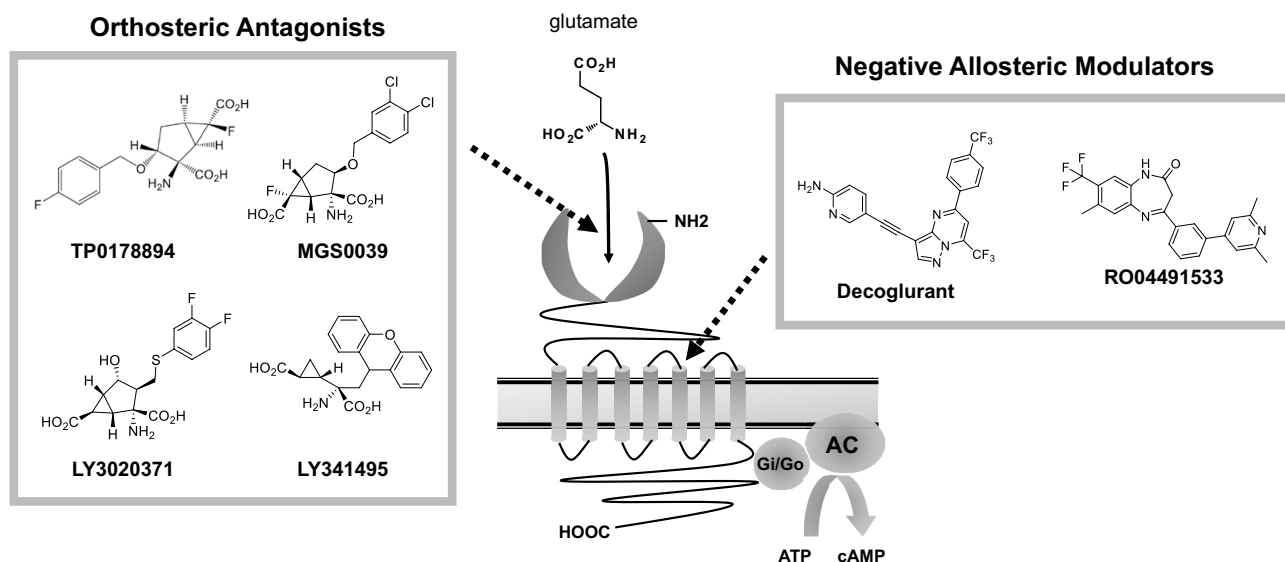

Fig. 1 Representative mGlu2/3 receptor antagonists. To date, two types of mGlu2/3 receptor antagonists have been synthesized: orthosteric antagonists (TP0178894, MGS0039, LY3020371, LY341495), and negative allosteric modulators (Decoglurant, RO04491533).

Orthosteric antagonists contain a glutamate moiety in their molecule and bind to glutamate binding sites, which reside in the N-terminus of the receptor. Negative allosteric modulators bind to allosteric sites of the receptor that are located in the transmembrane regions

Table 1 In vitro activities of representative mGlu2/3 receptor antagonists

	Antagonist activity (IC$_{50}$, nM)		Affinity (Ki, nM)	
	mGlu2	mGlu3	mGlu2	mGlu3
TP0178894	23.3	20.9	4.27	2.83
MGS0039	20.0	24.0	2.21	4.51
LY3020371	16.2	6.21	5.26	2.50
LY341495	23.3	14.2	3.15	3.06
RO04491533	296	270	–	–

Data of TP0178894 was cited from reference [86], data of MGS0039 and LY341495 were from reference [23], data of LY3020371 were from reference [24] and data of RO04491533 were from reference [25]. Data of MGS0039 and LY341495 were obtained using rat mGlu2 and mGlu3 receptors, while others were obtained by using human mGlu2 and mGlu3 receptors

–: Data not available

NAMs bind to allosteric sites localized in the transmembrane regions of the receptor. Of note, the maximal binding value of an mGlu2/3 receptor ligand that binds to an allosteric site was nearly half that of the radioligand binding of an orthosteric ligand of the mGlu2/3 receptor [26]. Therefore, the binding modes of both classes mGlu2/3 receptor antagonists are apparently different, which may explain the differences in the in vivo outcomes of both types of antagonists.

Antidepressant profiles of mGlu2/3 receptor antagonists

The antidepressant-like effects of mGlu2/3 receptor antagonists were first reported by our group in 2004 [23], triggering subsequent studies on the antidepressant-like characteristics of mGlu2/3 receptor antagonists [27, 28]. To date, accumulating lines of evidence have indicated similarities between the antidepressant-like effects of mGlu2/3 receptor antagonists and those of ketamine [27], which is summarized in Table 2. First, mGlu2/3 receptor antagonists (MGS0039, TP0178894, LY341495) exert rapid-acting and long-lasting antidepressant effects in rodent models such as the chronic social defeat stress model [17, 29, 30] and the chronic unpredictable stress model [31–33]; in both of these models, monoamine-based conventional antidepressants must be administered for more than a week for the exertion of the full-blown antidepressant effects. mGlu2/3 receptor antagonists, on the other hand, reversed the depressive-like behaviors in these models within 24 h after administration, and the effects lasted for more than a week after a single administration, as with ketamine. Also similar to ketamine, mGlu2/3 receptor antagonists exerted the antidepressant-like effects in rodent models that were resistant to conventional antidepressants, including a corticosterone-treated model [34]. Therefore, mGlu2/3 receptor antagonists are effective in animal models that are pharmacologically regarded as TRD models. Furthermore, mGlu2/3 receptor antagonists have been shown to have not only curative effects, but also preventive effects. Highland et al. (2019) reported that mGlu2/3 receptor blockade has prophylactic effects in studies involving pharmacological manipulation and the use of knockout mice lacking the mGlu2 or mGlu3 receptor [35]. Both knockout mice lacking the mGlu2 receptor and mice treated with LY341495 during stress were resilient to the development of depressive-like behaviors induced by several stress manipulations. Moreover, a single treatment with LY341495 7 days prior to the commencement of stress exposure prevented not only the initial development of depressive-like behaviors, but also the reinstatement of maladaptive behaviors caused by re-exposure to stress, indicating that the transient

Table 2 Summary of characteristics and possible mechanisms of antidepressant-like effects of mGlu2/3 receptor antagonists and ketamine in preclinical studies

	mGlu2/3 receptor antagonists	Ketamine
Antidepressant-like effects	Rapid acting Long-lasting Efficacy for treatment-resistant model Enhancement of antidepressant-like effects of ketamine	Rapid-acting Long-lasting Efficacy for treatment-resistant model
Synaptic mechanisms	AMPA receptor activation BDNF/TrkB signaling stimulation mTORC1 signaling stimulation Increase in spine formation	AMPA receptor activation BDNF/TrkB signaling stimulation mTORC1 signaling stimulation Increase in spine formation
Network mechanisms	Activation of mPFC serotonergic transmission Activation of mesolimbic dopaminergic transmission	Activation of mPFC serotonergic transmission Activation of mesolimbic dopaminergic transmission

AMPA α-amino-3-hydroxy-5-methyl-isoxazole-4-propionate, *BDNF* brain-derived neurotrophic factor, *TrkB* tropomyosin-related kinase B, *mTORC1* mechanistic target of rapamycin complex 1, *mPFC* medial prefrontal cortex

blockade of the mGlu2/3 receptor conferred a sustained enhancement of stress resilience. The authors additionally reported that the mGlu2 receptor, but not the mGlu3 receptor, was responsible for these protective effects because the effects in knockout mice lacking the mGlu3 receptor were indistinguishable from those in wild-type mice.

While mGlu2/3 receptor antagonists have ketamine-like antidepressant profiles, they do not show ketamine-like adverse effects in rodents [28]. For example, the mGlu2/3 receptor antagonist LY3020371 does not cause adverse effects known to be problematic with the use of ketamine, such as psychotomimetic-like behavior, cognitive impairment, motor impairment, and abuse liability, in rodent models [36]. In addition, the daily intravenous infusion of a high dose of LY3020371 for 14 days did not produce critical toxicological findings, including brain histochemistry, in either rats or cynomolgus monkeys [36]; therefore, ketamine-like neurotoxic effects were not noted. All these data clearly indicate that mGlu2/3 receptor antagonists are unlikely to have ketamine-like adverse effect profiles. Rather, mGlu2/3 receptor antagonists have been reported to have pro-cognitive effects in some animal models [37, 38], which would support the use of mGlu2/3 receptor antagonists compared with ketamine use for the treatment of MDD patients.

mGlu2/3 receptor antagonists have been reported to possess an additional characteristic that is expected to allow them to be beneficial when they are dosed with other rapid-acting antidepressants. The combination of sub-effective doses of LY341495 and ketamine exerted significant antidepressant-like effects [32, 39, 40], indicating that mGlu2/3 receptor antagonists augment the antidepressant effects of ketamine. In contrast, the combined doses of these substances did not produce the undesirable behavioral effects that are characteristic of ketamine when dosed alone, such as locomotor hyperactivity, impairment of short-term memory and disturbed motor coordination, in rodent studies involving the induction of antidepressant effects [32]. In addition to ketamine, LY341495 has been proven to enhance the antidepressant-like effect of scopolamine [41]. Like ketamine, scopolamine has been shown to exert rapid-onset antidepressant effects in patients with MDD, including those with TRD [42]; however, use of scopolamine is also limited because of adverse effects. Thus, the adjunctive use of mGlu2/3 receptor antagonists may be useful to mitigate the adverse effects of ketamine or scopolamine by allowing their doses to be lowered. Interestingly, LY341495 has recently been demonstrated to enhance the antidepressant-like effects of each ketamine stereoisomer, esketamine and arketamine, differentially [43]. While a sub-effective dose of LY341495 enhanced the antidepressant-like effects of both stereoisomers in a tail suspension test of naïve mice, it potentiated rapid (< 24 h) and sustained (> 3 days) antidepressant effects of arketamine but not esketamine in a chronic unpredictable stress model, suggesting that arketamine may play a key role in the mechanism of the enhancement of the antidepressant-like effects of ketamine by LY341495. Because arketamine has been proposed to have more potent and sustained antidepressant-like effects but fewer adverse effects than esketamine [7, 44, 45], facilitating the effects of arketamine through the use of mGlu2/3 receptor antagonists may be an interesting strategy.

In contrast to the above findings, mGlu2/3 receptor stimulation, rather than blockade, and increased mGlu2 receptor expression have also been reported to exert antidepressant-like behaviors and to confer stress resilience. For example, L-acetylcarnitine, which epigenetically increases mGlu2 receptor expression, exerts antidepressant effects [21], and knockout mice lacking the mGlu2 receptor show increased stress susceptibility [46]. However, evidence involving specific mGlu2/3 receptor agonists or mGlu2 receptor positive allosteric modulators is limited, and the mechanisms involved have not been fully elucidated [47].

Mechanisms underlying the antidepressant-like effects of mGlu2/3 receptor antagonists

There are striking similarities in the underlying mechanisms between ketamine and mGlu2/3 receptor antagonists, which may explain the ketamine-like antidepressant profiles of mGlu2/3 receptor antagonists [28]. Indeed, they share mechanisms not only at the synaptic level, but also at the network level, and it has been proposed that mGlu2/3 receptor blockade has the same downstream mechanism of ketamine, as explained below. These similarities are depicted in Table 2 and Fig. 2.

Similarity at synaptic level

Both mGlu2/3 receptor antagonists and ketamine share underlying synaptic mechanisms that are triggered by an increase in glutamate release in the prefrontal cortex (PFC). mGlu2/3 receptor antagonists are thought to increase glutamate release through the blockade of autoreceptors on glutamate terminals, while ketamine increases glutamate release through the disinhibition of pyramidal neurons [27, 48]. Increased glutamate in the synaptic cleft activates postsynaptic AMPA receptors, which stimulates the secretion of brain-derived neurotrophic factor (BDNF) and, subsequently, the stimulation of tropomyosin-related kinase B (TrkB) receptor signaling. These events lead to an increase in dendritic spine density and synaptic connections, presumably via a mechanistic target of rapamycin complex 1 (mTORC1) signaling pathway [29, 49, 50]. Notably, AMPA receptor stimulation and a subsequent increase in BDNF secretion are considered
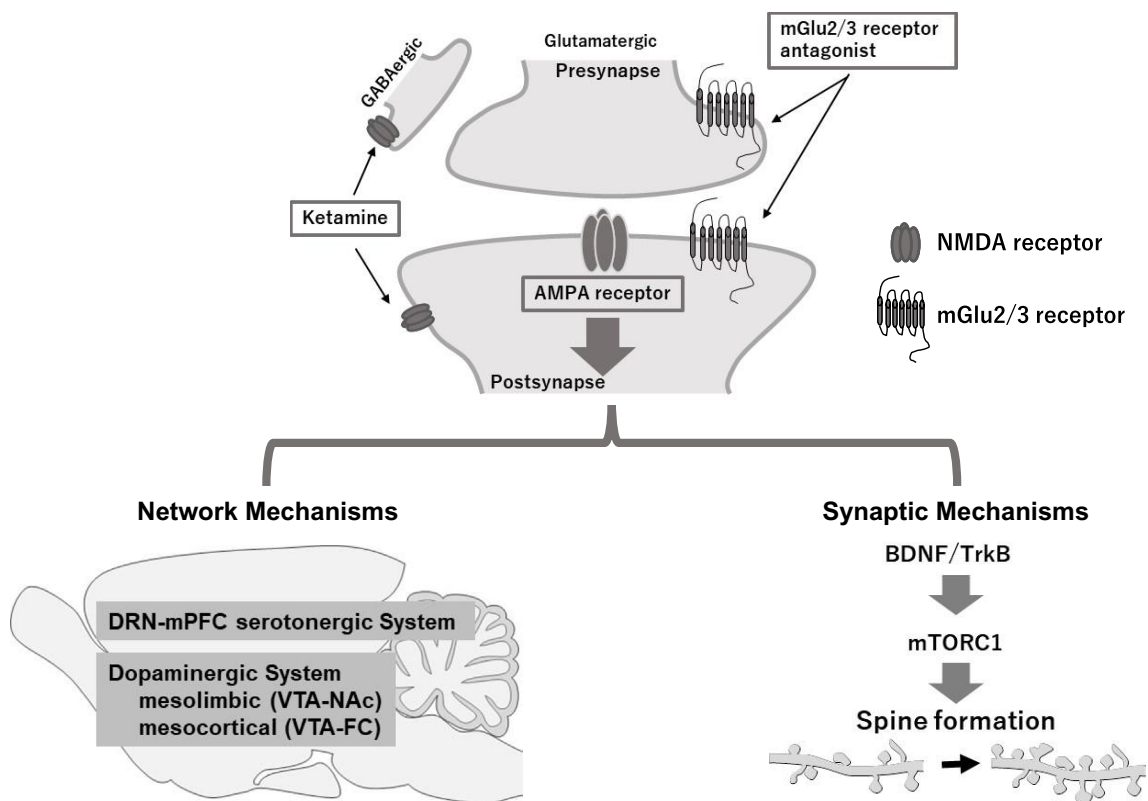
Fig. 2 Proposed mechanisms for the antidepressant effects of mGlu2/3 receptor antagonists and ketamine. mGlu2/3 receptor antagonists block perisynaptic mGlu2/3 receptors and the postsynaptic mGlu3 receptor, while ketamine blocks the NMDA receptor on GABA interneurons and on extrasynaptic NMDA receptors. Both mechanisms converge to stimulate postsynaptic AMPA receptor signaling, which triggers network and synaptic changes. At the network level, both compounds activate the DRN-mPFC serotonergic system and dopaminergic systems (both mesolimbic and mesocortical dopaminergic systems) through AMPA receptor stimulation. At the synaptic level, both compounds activate BDNF/TrkB/mTORC1 pathways via AMPA receptor stimulation, leading to an increase in spine formation. These mechanisms might contribute to the antidepressant effects of both compounds. *NMDA* N-methyl-D-aspartate, *AMPA* α-amino-3-hydroxy-5-methyl-isoxazole-4-propionate, *DRN* dorsal raphe nucleus, *mPFC* medial prefrontal cortex, *VTA* ventral tegmental area, *NAC* nucleus accumbens, *FC* frontal cortex, *BDNF* brain-derived neurotrophic factor, *TrkB* tropomyosin-related kinase B, *mTORC1* mechanistic target of rapamycin complex 1

common pathways for various agents that mimic the antidepressant effects of ketamine [51–53], and this mechanism is necessary for mGlu2/3 receptor antagonists to enhance the antidepressant-like effects of arketamine [43]. Indeed, both AMPA receptor positive allosteric modulators and BDNF have been shown to exert antidepressant-like effects [54–57]. In animal models of depression, the above-mentioned pathways and spine density are reportedly perturbed in the PFC, and both ketamine and mGlu2/3 receptor antagonists ameliorated these abnormalities [29, 58, 59]. Regarding mTORC1 signaling, mTOR knockdown in the infralimbic cortex induced depressive-like behavior in mice [60], and the mTOR pathway was disturbed in the PFC of postmortem MDD patients [61]; therefore, the reversal of dysfunctional mTORC1 signaling may be an important mechanism for the exertion of ketamine-like antidepressant effects. In contrast, an increase in mTOR activity in the PFC of postmortem MDD patients was recently reported [62], and rapamycin,

an inhibitor of mTORC1 signaling, prolonged, rather than blocked, the antidepressant effects of ketamine in MDD patients [63]. Therefore, the role of mTORC1 signaling activation in ketamine-like antidepressant actions requires further clarification.

Similarity at network level

Both serotonergic and dopaminergic transmissions are considered to play important roles in exerting antidepressant effects. Dopaminergic and serotonergic pathways are reportedly involved in the antidepressant-like effects of both ketamine and mGlu2/3 receptor antagonists. The systemic administration of ketamine and mGlu2/3 receptor antagonists (LY341495 and LY3020371) increased the number of spontaneously active dopamine neurons in the ventral tegmental area (VTA) and dopamine release in the nucleus accumbens (NAc) and/or frontal cortex [64]. In addition,

we reported that the direct injection of mGlu2/3 receptor antagonists (MGS0039 and LY341495) into the NAc increased dopamine release in this region, indicating that mGlu2/3 receptor antagonists may activate the VTA-NAc dopaminergic system [65, 66]. The interaction of mGlu2/3 receptor antagonists with the dopaminergic system is supported by in vivo behavioral results showing that both ketamine and LY341495 potentiated a dopamine D2/3 receptor agonist (quinpirole)-induced increase in locomotor activity [64]. Moreover, the injection of LY341495 into the NAc prevented depressive-like behavior occurring during withdrawal from repeated methamphetamine treatment [67], indicating that mGlu2/3 receptor antagonists may exert antidepressant effects at least partly through the VTA-NAc dopaminergic system. Notably, this enhancement of the effects of mGlu2/3 receptor antagonists on the dopaminergic system has been shown to be mediated through AMPA receptor stimulation [64, 66].

Several lines of evidence imply the involvement of the serotonergic system in the antidepressant-like effects of both ketamine and mGlu2/3 receptor antagonists. Both ketamine and an mGlu2/3 receptor antagonist (MGS0039) increased serotonin release in the medial prefrontal cortex (mPFC) [68–70]. The depletion of serotonin cancelled the antidepressant-like effects of ketamine and mGlu2/3 receptor antagonists [70, 71]. Therefore, an increase in serotonergic transmission may be responsible, in part, for the antidepressant-like effects of both ketamine and mGlu2/3 receptor antagonists. We further investigated possible mechanisms through which both ketamine and mGlu2/3 receptor antagonists enhance the activity of the serotonergic system to exert their antidepressant-like effects. We found that the injection of ketamine or LY341495 into the mPFC increased c-Fos positive serotonin neurons in the dorsal raphe nucleus (DRN) [71], indicating a role of the mPFC-DRN pathway in these actions. This presumption was supported by the finding that AMPA receptor stimulation or an increase in glutamate in the mPFC with a glutamate transporter inhibitor (both of these manipulations activate mPFC neurons) increased the number of c-Fos positive serotonin cells in the DRN [72, 73]. Pham et al. reported that the intra-mPFC injection of ketamine increased serotonin release in the mPFC as well as the antidepressant-like effects, both of which were attenuated by AMPA receptor blockade in the DRN [70, 74]. Therefore, the activation of DRN serotonin neurons regulated by the mPFC-DRN pathway is involved in the antidepressant-like effects of both mGlu2/3 receptor antagonists and ketamine. Notably, the optogenetic stimulation of mPFC cells projecting to the DRN has been reported to exert robust antidepressant-like effects [75], and the antidepressant-like effect of ketamine or an mGlu2/3 receptor antagonist was blocked by the silencing of DRN neurons [70, 76], supporting the role of mPFC-DRN projections.

Moreover, we further demonstrated that the antidepressant-like effects of an mGlu2/3 receptor antagonist and ketamine were mediated by 5-HT1A receptor stimulation in the mPFC [76, 77]. Interestingly, subsequent activation of the phosphoinositide-3 kinase/Akt/mTORC1 pathway is responsible for the antidepressant-like effects of both compounds [76, 77], and mPFC 5-HT1A receptor activation can mimic the rapid and sustained antidepressant-like effects seen in animal models, including the chronic unpredictable stress model, through mTORC1 signaling [78]. Collectively, these findings imply that stimulation of the mPFC 5-HT1A receptor and the subsequent signaling mechanisms triggered by the release of serotonin through mPFC-DRN-mPFC projections are likely to be involved in the unique antidepressant-like effects of mGlu2/3 receptor antagonists and ketamine.

Role of mGlu2 receptor in the antidepressant actions of ketamine

A role of the mGlu2 receptor in the actions of ketamine has recently been reported. First, the antidepressant-like effects of ketamine were attenuated by an mGlu2/3 receptor agonist [40, 79]. In addition, the antidepressant-like effects of ketamine were no longer observed in mice lacking the mGlu2 receptor [40]. Although the precise molecular mechanism for the role of mGlu2/3 receptor blockade in the action of ketamine needs to be further elucidated, these results indicate the importance of the mGlu2 receptor in the antidepressant-like effects of ketamine and support the concept that mGlu2/3 receptor antagonists may have ketamine-like antidepressant profiles.

The antidepressant-like actions of mGlu2/3 antagonists are often attributed to the inhibition of the mGlu2 receptor, but not the mGlu3 receptor, based on findings that the antidepressant-like effects of mGlu2/3 receptor antagonists are no longer observed in knockout mice lacking the mGlu2 receptor, while they are seen in knockout mice lacking the mGlu3 receptor [40, 79, 80]. Nevertheless, several reports have indicated that mGlu3 receptor blockade may also contribute to the antidepressant-like effects. Conn's group reported that a selective mGlu3 receptor NAM exerted antidepressant-like effects that were more potent than those of a selective mGlu2 receptor NAM [81]. Moreover, both mGlu2 NAM and mGlu3 NAM reversed depressive-like behavior in a chronic variable stress model [82]. Interestingly, both mGlu2 and mGlu3 NAMs exert antidepressant-like effects via an increase in glutamate transmission in the PFC, but through mechanistically distinct manners: a presynaptic action (for mGlu2 NAM), and postsynaptic action (for mGlu3 NAM). However, no evidence is available regarding whether the blockade of either receptor alone can mimic ketamine-like antidepressant effects and if so, the underlying mechanisms. Therefore, mGlu2/3 receptor antagonists,

rather than selective antagonists for the mGlu2 or mGlu3 receptor, might be preferable as an alternative for ketamine.

Clinical trials of mGlu2/3 receptor antagonists

To date, clinical studies of several mGlu2/3 receptor antagonists have been conducted or are being conducted [83], as summarized in Table 3.

Decoglurant (RG1578/RO4995819)

Decoglurant, which was synthesized and developed by F. Hoffmann-La Roche, Ltd., is a NAM of the mGlu2/3 receptor. Decoglurant has been shown to reduce the anhedonic index in a chronic mild stress model of rats and to rescue scopolamine-induced attention deficits in non-human primates [84]; thus, it is expected to be effective for both depression and cognitive dysfunction. A randomized, placebo-controlled, double-blind, multicenter phase 2 trial of decoglurant as an adjunctive treatment to selective serotonin reuptake inhibitors or serotonin- and norepinephrine reuptake inhibitors for 6 weeks in MDD patients with inadequate responses to antidepressant treatment was conducted to evaluate decoglurant's antidepressant and pro-cognitive effects [84]. In this study, none of the decoglurant doses (5 mg, 15 mg, or 30 mg) demonstrated significant differences from the placebo in terms of the primary endpoint (change from baseline in Montgomery Åsberg Depression Rating Scale total score at the end of 6 weeks of treatment). Furthermore, no pro-cognitive effects, as assessed using the Cambridge Neuropsychological Test Automated Battery, were seen. In addition to a high placebo response and a low prevalence of patients with clinically relevant cognitive impairment at baseline, which were raised by the authors as possible reasons for the lack of efficacy [84], some other reasons can be considered as possible explanations for the failure to show any efficacy in this trial. First, whether optimal dose levels were used is uncertain. Although the authors claimed that the doses were unlikely to be suboptimal given the high brain penetrance observed in preclinical studies, whether the free fraction of decoglurant in the extracellular fluid was sufficient to block the mGlu2/3 receptor was not known. Regrettably, the concentrations of decoglurant in the cerebrospinal fluid (CSF) were not measured, therefore, no data on the target engagement of decoglurant in humans is available. Moreover, the neurophysiological and behavioral properties of decoglurant are quite different from those of ketamine and other mGlu2/3 receptor orthosteric antagonists and NAMs, and decoglurant failed to exert sustained antidepressant effects in preclinical studies [85]. Although detailed pharmacokinetic profiles of decoglurant have not been reported, the long half-life of decoglurant could be responsible for this difference, as the sustained stimulation of AMPA receptors can cause desensitization.

TS-161 (TP0473292)

TS-161 was synthesized and is being developed by Taisho Pharmaceutical Co., Ltd. as an ester prodrug of TP0178894 to improve oral bioavailability. TP0178894 is an mGlu2/3 receptor orthosteric antagonist with potent antagonist activity and high selectivity for mGlu2/3 receptors [86]. TP0178894 and its prodrug have been shown to exert rapid-acting and long-lasting antidepressant-like effects in a rodent model [30] and to exert the antidepressant-like effects in a rodent TRD model [86]. We conducted a randomized, double-blinded, placebo-controlled, single-ascending dose and 10-day multiple ascending dose study in healthy subjects. The clinical study results demonstrated that TS-161 is orally bioavailable and extensively converted into an active metabolite (TP0178894); the Cmax and AUC of the prodrug were approximately 0.1% of those of TP0178894 [86]. In addition, we measured the CSF concentrations of TP0178894 after a single administration of TS-161 and

Table 3 Summary of clinical trials of mGlu2/3 receptor antagonists

Compound	Drug-receptor interaction type	Development phase (trial status)	Population (target)	Latest clinical trial clinicaltrials.gov identifier	Company /originator
Decoglurant (RG1578, RO4995819)	NAM	2 (completed)	MDD	NCT01457677	F. Hoffmann-La Roche, Ltd
TS-161 (TP0473292)	Orthosteric antagonist	2 (on-going)	TRD	NCT04821271	Taisho Pharmaceutical Co., Ltd
MGS0210 (BCI-838)	Orthosteric antagonist	1 (completed)	(TRD)	NCT01548703	Taisho Pharmaceutical Co., Ltd
DSP-3456	NAM	1 (on-going)	(TRD)	–	Sumitomo Pharma Co., Ltd

MDD major depressive disorder, *NAM* negative allosteric modulator, *TRD* treatment-resistant depression

found that TP0178894 penetrated into the CSF, enabling an exposure level that was predicted to be sufficient to block mGlu2/3 receptors and exert the anticipated antidepressant effects [86]. Overall, TS-161 was safe and well tolerated, and only mild adverse events were seen at a dose of 100 mg, which is the dose level expected to exert pharmacological actions. A phase 2 study evaluating the efficacy of TS-161 in patients with TRD is currently on-going with an upper dose level of 100 mg per day (ClinicalTrials.gov Identifier: NCT04821271).

MGS0210 (BCI-838)

MGS0210, synthesized by Taisho Pharmaceutical Co., Ltd., is an ester prodrug of MGS0039. There are several lines of evidence that MGS0039, a selective and potent mGlu2/3 receptor orthosteric antagonist [23], exerts ketamine-like antidepressant effects in rodents and shares the underlying mechanisms of its antidepressant-like actions with ketamine [27]. MGS0210 has been proven to improve the oral bioavailability of MGS0039 in both rats and cynomolgus monkeys [87, 88] and to show antidepressant-like effects in rodent models after oral administration [88]. A phase 1 study was conducted by BrainCells Inc. in healthy subjects. Although the plasma exposure of MGS0039, an active metabolite, increased after single and 7-day multiple doses of MGS0210, the plasma exposure levels of MGS0210 were approximately tenfold higher than that of MGS0039 [89], indicating that MGS0210 is not an ideal prodrug. Nonetheless, it should be noted that dose- and time-dependent effects on some power spectra of quantitative electroencephalograms were observed during a multiple ascending dose study, suggesting that MGS0039 may penetrate the brain to engage the mGlu2/3 receptor. MGS0210 was well tolerated, and adverse events were generally mild and transient in duration [89].

DSP-3456

DSP-3456 is a NAM of the mGlu2/3 receptor that is currently being developed by Sumitomo Pharma Co., Ltd. According to the company's website [90], DSP-3456 is in the phase 1 stage of development as a potential treatment for TRD in the US. The chemical structure and detailed pharmacological profiles of DSP-3456 have not been disclosed.

Conclusions

Since the first demonstration of the antidepressant-like effects of prototype mGlu2/3 receptor antagonists (MGS0039 and LY341495) in classical animal models [23], accumulating evidence has clearly shown that the blockade

of mGlu2/3 receptors is an attractive approach for developing novel antidepressants with ketamine-like antidepressant profiles but with safety profiles that are better than those of ketamine. Among these research activities, several mGlu2/3 receptor antagonists, both orthosteric antagonists and NAMs, have been generated, and some have been tested or are being tested in clinical trials.

In this respect, the results that decoglurant, an mGlu2/3 receptor NAM, failed to show any efficacy in patients with MDD are discouraging. However, many reasons for this failure, including the clinical trial design (dose levels used, patient selection, etc.), and the validity of decoglurant as a tool for a proof-of-concept study for mGlu2/3 receptor antagonists should be considered carefully before drawing any conclusions regarding the efficacy of mGlu2/3 receptor antagonists for the treatment of depression. Currently, at least two mGlu2/3 receptor antagonists are in clinical trials. In particular, the human proof-of-concept study of TS-161 is of importance, because this compound was proven to have ketamine-like antidepressant profiles in rodent studies and the dose levels used in the trial are expected to be sufficient to block mGlu2/3 receptors. Therefore, mGlu2/3 receptor antagonists still hold promise for the development of safer and more efficacious antidepressants.

Declarations

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