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Review

Roles of glutamate signaling in preclinical and/or mechanistic models of depression

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ABSTRACT

Accumulating evidence suggests that the glutamatergic system plays important roles in the pathophysiology and treatment of major depressive disorder (MDD). Abnormalities in the glutamatergic system are definitely observed in this disorder, and certain glutamatergic agents exhibit antidepressant effects in patients with MDD. In this review, we summarize the preclinical findings suggesting the involvement of glutamate signaling in the pathophysiology and treatment of MDD. Preclinical animal models for depression are often characterized by changes in molecules related to glutamatergic signaling. Some antidepressants exert their effects by affecting glutamatergic system components in animals. Animals with genetically modified glutamatergic function exhibit depression-like behaviors or anti-depressive behavior. In addition, several types of glutamatergic agents have shown antidepressant-like effects in preclinical models for depression. Many types of glutamate receptors (NMDA, AMPA, and metabotropic glutamate receptors) or transporters appear to be involved in the etiology of depression or in the mechanisms of action of antidepressants. These functional proteins related to glutamate signal transduction are potential targets for a new generation of antidepressants with fast-onset effects, such as the NMDA antagonist ketamine.

Contents

Abbreviations: MDD, Major depressive disorder; SSRI, selective serotonin reuptake inhibitor; SSRI, serotonin and norepinephrine reuptake inhibitor; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; NMDA, *N*-methyl-D-aspartate; mGluR, metabotropic glutamate receptor; EAAT, excitatory amino acid transporter; CSF, cerebrospinal fluid; MRS, magnetic resonance spectroscopy; GABA, γ-aminobutyric acid; OB, Olfactory bulbectomy; LH, learned helplessness; vGluT, vesicular glutamate transporter; CMS, chronic mild stress; FSL, Flinders Sensitive Line; WKY, Wistar Kyoto; ECS, electroconvulsive shock; NBQX, dihydroxy-6-nitro-7-sulfoamoylbenzo(*f*)-quinozaline; mTOR, mammalian target of rapamycin; DTG, 1,3 di-o-tolylguanidine; NO, nitric oxide; SNAP, S-nitroso-*N*-acetyl-penicillamine; L-NNA, *NG*-nitro-L-arginine; ODQ, 1H-[1,2,4]oxadiazole[4,3-a]quinoxalin-1-one; EMQMCM, (3-ethyl-2-methyl-quinolin-6-yl)-(4-methoxy-cyclohexyl)-methanone methanesulfonate; AIDA, (*RS*)-1-aminoindan-1,5-dicarboxylic acid; MTEP, 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine; MPEP, 2-methyl-6-(phenylethynyl)-pyridine; ACPT-I, (1*S*,3*R*,4*S*)-1-aminocyclo-pentane-1,3,4-tricarboxylic acid; HomoAMPA, 2-amino-4-(3-hydroxy-5-methylisoxazol-4-yl) butyric acid; (*RS*)-PPG, (*RS*)-4-phosphonophenylglycine; PHCCC, *N*-phenyl-7-(hydroxyimino)cyclopropa[*b*]chromen-1a-carboxamide; LPS, Lipopolysaccharide.

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1. Introduction

Major depressive disorder (MDD), also called major depression, is a chronic recurring illness, and its lifetime prevalence is approximately 16.6% in the United States (Kessler and Wang, 2008). Unipolar depressive disorders comprise the first and fifth leading causes of disability-adjusted life-years in high-income countries and in low- and middle-income countries, respectively (Lopez and Mathers, 2006). Drugs that increase the synaptic availability of monoamines (serotonin, norepinephrine, and dopamine), including tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and dopamine reuptake inhibitors, have been used to treat depression for more than 50 years (Belmaker, 2008; Chen and Skolnick, 2007; López-Muñoz and Alamo, 2009). Nevertheless, these antidepressants require at least 2 weeks to exert their effects, and the treatment guidelines for MDD recommend the continuous use of these antidepressants for 4 to 8 weeks due to their delayed onset of response (Nakajima et al., 2010). These findings suggest that downstream neural adaptation (*e.g.*, the brain-derived neurotrophic factor (BDNF)-TrkB receptor signaling pathway) rather than elevation of synaptic monoamine levels may be responsible for the therapeutic effects of these drugs (Hashimoto, 2010; Lanni et al., 2009; Racagni and Popoli, 2008). The undesirable side effects of currently used antidepressants are frequently the reason for lack of compliance (Racagni and Popoli, 2010). In addition, between one-third and two-thirds of patients do not respond to the first antidepressant prescribed, and treatment-resistant depression represents an area of unmet medical need (Little, 2009; Shelton et al., 2010). Although efforts to develop novel antidepressants have made progress in reducing these side effects, the currently available antidepressants do not show convincing evidence for a shorter delay of onset of therapeutic effects or improved efficacy in the treatment of treatment-resistant patients.

L-glutamic acid (glutamate) is accepted as the major excitatory neurotransmitter in the central nervous system (CNS), and glutamine synthesis from glutamate and ammonia occurs exclusively in glial cells (Hashimoto, 2009a, 2011) (Fig. 1). Glutamine plays major roles in nitrogen and carbon homeostasis, and in the detoxification of ammonia, in addition to acting as a precursor for the synthesis of glutamate in specialized excitatory neurons (Hashimoto, 2009a, 2011). Glutamate released from presynaptic neurons can interact with postsynaptic glutamate receptors, including kainate, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), and *N*-methyl-D-aspartate (NMDA) receptors. In addition, glutamate can interact with metabotropic glutamate receptors (mGluRs) on presynaptic and postsynaptic neurons (Hashimoto, 2011). The released glutamate is taken up by the surrounding glial cells via excitatory amino acid transporters (EAATs), converted to glutamine, transported back to the presynaptic neurons, and reconverted to glutamate (Hashimoto, 2009a, 2011).

There is growing evidence that the glutamatergic system plays important roles in the neurobiology and treatment of MDD (Hashimoto, 2009a, 2011; Mitchell and Baker, 2010; Sanacora, 2009a, 2009b; Skolnick et al., 2009; Zarate et al., 2010). In this article, the authors review the role of glutamate signaling in preclinical and/or mechanistic models of depression.

2. Roles of glutamate in the pathophysiology of depression

2.1. Blood, cerebrospinal fluid (CSF) and brain levels of glutamate

Several papers have reported altered glutamate levels in the blood, CSF, and brain of patients with MDD. Increased glutamate levels were observed in the serum (Kim et al., 1982) and plasma (Altamura et al., 1993; Mauri et al., 1998; Mitani et al., 2006) of patients with MDD, and antidepressant treatment reduced the serum glutamate levels in patients with MDD (Maes et al., 1998). Although depressive patients have been reported to show higher glutamine levels in the CSF (Levine et al., 2000), a later study showed low glutamate levels in the CSF (Frye et al., 2007). Increased glutamate levels were observed in the frontal cortex in postmortem brain samples from depressive patients (Hashimoto et al., 2007). A noninvasive *in vivo* proton magnetic resonance spectroscopy (^{1}H-MRS) study revealed increased levels of glutamate in the occipital cortex of patients with MDD (Sanacora et al., 2004). Other ^{1}H-MRS studies found reduced Glx (glutamate and glutamine) levels in the anterior cingulate cortex (Auer et al., 2000) and dorsomedial/dorsal anterolateral prefrontal cortex (Hasler et al., 2007), and reduced metabolic ratios of Glx/creatine (Glx = glutamate, glutamine, and γ-aminobutyric acid (GABA)) and glutamine/creatine in the hippocampus (Block et al., 2009) in patients with MDD. Taken together, these findings suggest that abnormalities in glutamate/glutamine cycling in the brain are likely to be involved in the pathophysiology of MDD (Hashimoto, 2009a, 2011; Valentine and Sanacora, 2009).

2.2. Levels of glutamatergic receptors in depression

Several studies have demonstrated differences related to glutamate receptors (NMDA receptors, AMPA receptors, and mGluRs) in postmortem brain samples from individuals with MDD. Receptor binding assays and immunoblotting analyses revealed a reduction in the binding of [^{3}H]L-689,560, a potent antagonist of the glycine modulatory site on NMDA receptors, as well as a reduction in the immunoreactivity of NR1, a subunit of NMDA receptors, in the superior temporal cortex in MDD patients (Nudmamud-Thanoi and Reynolds, 2004). An *in situ* hybridization study demonstrated that the mRNA levels of the NR2A and NR2B subunits of NMDA receptors and the GluR1, GluR3, and GluR5 subunits of AMPA receptors in the perirhinal cortex, but not in the hippocampus or entorhinal cortex, were significantly lower in patients with MDD than in

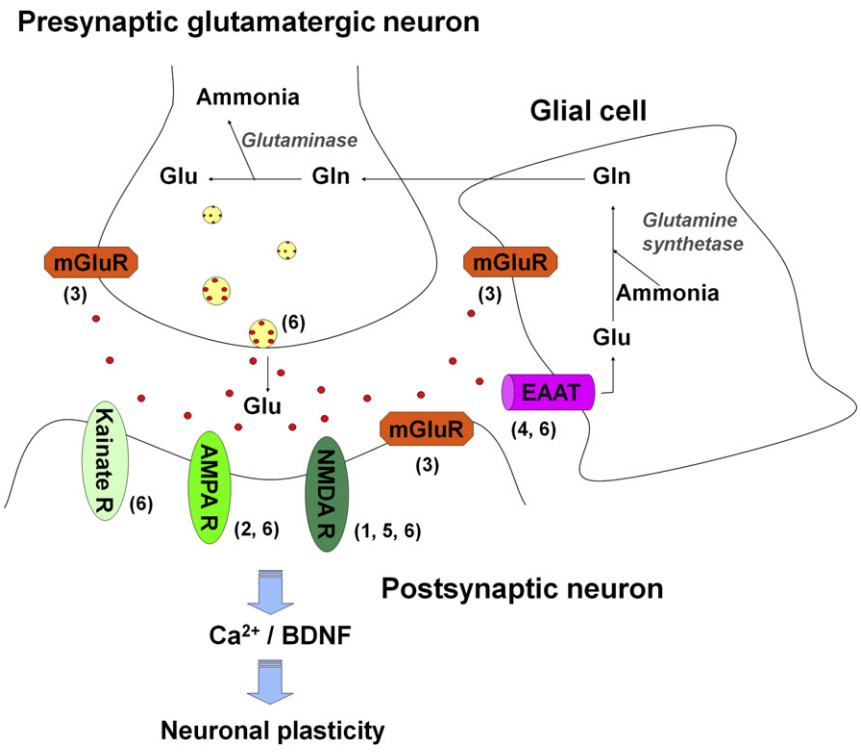

Fig. 1. Major functional components for glutamatergic neurons and potential targets of glutamatergic agents exerting antidepressant-like actions. Glutaminase hydrolyzes glutamine to glutamate and ammonia in presynaptic neurons. Glutamate is released into the synaptic cleft and stimulates glutamate receptors (kainate receptors, NMDA receptors, AMPA receptors, and mGluRs) in postsynapses, presynapses, and glial cells. Glutamate is taken up by EAATs on glial cells. Glutamine synthetase converts glutamate and ammonia to glutamine, which is transported to presynaptic neurons. Glutamatergic agents are considered to act on the numbered targets in the Figure as follows targets: (1) NMDA receptor antagonists (ketamine, NR2B subunit antagonists, memantine, magnesium, and zinc); (2) positive modulators of AMPA; (3) group I mGluR antagonists, group II mGluR antagonists and agonists, and group III mGluR agonists; (4) EAAT2 enhancer (ceftriaxone); (5) possible indirect NMDA receptor modulator (minocycline); and (6) possible inhibitor of glutamate release, antagonist of NMDA, AMPA, and kainate receptors, and potentiator of glutamate uptake (riluzole). AMPA R, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; NMDA R, *N*-methyl-D-aspartate receptor; mGluR, metabotropic glutamate receptor; EAAT, excitatory amino acid transporter; Gln, glutamine; Glu, glutamate; BDNF, brain-derived neurotrophic factor; Ca^{2+}, calcium ion.

control subjects (Beneyto et al., 2007). Furthermore, Western blotting analyses showed decreased levels of the NR2A and NR2B subunits of NMDA receptors in the anterior prefrontal cortex of patients with MDD (Feyissa et al., 2009). In contrast, receptor binding assays and autoradiography in patients with MDD revealed increased binding of [^{3}H]CGP39653 to a glutamate site on NMDA receptors in the hippocampus, but not in the entorhinal or perirhinal cortex (Beneyto et al., 2007). In addition, two recent reports demonstrated elevated levels of mGluR2/3 protein (Feyissa et al., 2010) and reduced levels of mGluR5 protein (Karolewicz et al., 2009), which are both subtypes of mGluRs, in the prefrontal cortex of patients with MDD. A recent study using the selective mGluR5 antagonist [^{11}C]ABP-688 and positron emission tomography reported reductions in mGluR5 binding in multiple areas of the frontal, temporal, and parietal cortices of patients with MDD (Deschwanden et al., 2011). Taken together, these data appear to suggest abnormalities of glutamate receptors in the pathophysiology of MDD.

3. Antidepressant effects of NMDA receptor antagonists in patients with MDD

The non-competitive NMDA receptor antagonist ketamine has been used as a standard anesthetic agent for many years in both pediatric and adult patients. A single dose of ketamine was reported to exert robust and rapid antidepressant effects in patients with MDD (Berman et al., 2000; Zarate et al., 2006a). The onset of these effects occurred within 2 h postinfusion and the responses were sustained for 1 week in treatment-resistant MDD (Zarate et al., 2006a). Direct targeting of NMDA receptor complexes may bring about rapid and relatively sustained antidepressant effects (Zarate et al., 2006a, 2010).

Non-competitive open-channel NMDA receptor antagonists, including phencyclidine and ketamine, are likely to produce psychotomimetic effects when they are used acutely (Javitt and Zukin, 1991; Krystal et al., 1994, 2005). Considering the acute psychotomimetic side effects of ketamine, subtype-selective compounds or those with different mechanisms might shed light on the question. The selective antagonists of the NR2B subunit of NMDA receptors have appeared to pose little risk through the allosteric mechanism that is different from the non-competitive open-channel blocking (Kemp and McKernan, 2002). However, the concern on the role of NR2B in producing the subjective and reinforcing effects associated with phencyclidine in rodents and primates is raised (Mony et al., 2009). A recent double-blind, randomized, placebo-controlled study demonstrated that the selective NR2B antagonist CP-101,606 (traxoprodil) had significant antidepressant effects on day 5 after infusion with good tolerability and little dissociative reaction at the lower infusion level in patients with treatment-resistant MDD (Preskorn et al., 2008). However, CP-101,606 has a high affinity at endoplasmic reticulum protein sigma-1 receptors in the brain, suggesting a possible role of sigma-1 receptors in the action of this drug (Hashimoto, 2009b). Nonetheless, selective NR2B antagonists may be fruitful targets for the development of new antidepressants with a faster onset than currently available drugs.

Memantine is a low affinity, non-competitive, open-channel NMDA receptor antagonist. This drug is well tolerated and is approved for the treatment of moderate to severe Alzheimer's disease (Thomas and Grossberg, 2009). In a clinical report, memantine (5–20 mg/day) failed to improve depression in patients with MDD (Zarate et al., 2006b). In contrast, a small open-label trial of memantine (20–40 mg/day) revealed a significant reduction in depressive symptoms within 1 week in patients with MDD (Ferguson and Shingleton, 2007). The

target dose of memantine is up to 20 mg/day for the treatment of Alzheimer's disease (Thomas and Grossberg, 2009). Memantine is considered to improve the cognitive deficits in a pathological condition-dependent manner in patients with Alzheimer's disease (Parsons et al., 2007). High doses might be necessary for memantine to exert antidepressant effects. Furthermore, memantine (20 mg/day) significantly reduced the baseline level of depression in patients with comorbid alcohol dependence, and was as effective for this purpose as escitalopram (20 mg/day) (Muhonen et al., 2008). Nevertheless, the antidepressant effects of memantine remain unproven (Hashimoto, 2009a).

4. Roles of glutamate in preclinical and/or mechanistic models of depression

4.1. Abnormalities of glutamatergic function in animal models of depression

Animal models of depression are widely used to study the pathophysiology of MDD and the mechanisms of action of established and candidate antidepressants. Most animal models of depression are based on stress exposure during brain development or in adulthood, or on genetic manipulations and selective breeding. In this section, the authors review the literature concerning the abnormalities of glutamate signaling in animal models of depression (Table 1).

Table 1
Abnormalities of the glutamatergic system in animal models of depression.

Models	Animals	Brain regions	Interests	Changes of the interests	References
OB	Rats	Cerebral cortex and amygdala	NMDA receptor	Decreased	Ho et al. (2001)
		Cortex, olfactory region, hypothalamus, thalamus, amygdala, and hippocampus	NMDA receptor	Decreased	Robichaud et al. (2001)
		Medial prefrontal cortex	NMDA receptor	Increased	Webster et al. (2000)
	Mice	Hippocampus	mGluR1	Increased	Wierońska et al. (2008)
			mGluR2/3, 4 and 7	Decreased	Wierońska et al. (2008)
LH	Rats	Cortical, striatal and hippocampal slices	Glutamate uptake	Decreased	Almeida et al. (2010)
		Cerebral cortex and hippocampus	vGluT1, EAAT2 and 4	Decreased	Zink et al. (2010)
CMS	Adult rats	Prefrontal cortex and hippocampus	GluR1	Decreased	Toth et al. (2008)
		Nucleus accumbens	GluR1	Increased	Toth et al. (2008)
	Young rats	Prefrontal cortex	GluR1	Decreased	Toth et al. (2008)
	Rats	CA1 of hippocampus	mGluR5	Increased	Wierońska et al. (2001)
		CA3 of hippocampus	mGluR5	Decreased	Wierońska et al. (2001)
FSL	Rats	Hippocampus	NR1	Decreased	Ryan et al. (2009)
				Increased by maternal separation	Ryan et al. (2009)
			GluR2/3	Increased by maternal separation	Ryan et al. (2009)
			mGluR2/3	Decreased	Matrisciano et al. (2008)
WKY	Rats	Dentate gyrus of hippocampus	mGluR7	Increased	O'Mahony et al. (2010)

NMDA = *N*-methyl-D-aspartate; mGluR = metabotropic glutamate receptor; vGluT = vesicular glutamate transporter; EAAT = excitatory amino acid transporter; OB = olfactory bulbectomy; LH = learned helplessness; CMS = chronic mild stress; FSL = Flinders sensitive line; WKY = Wistar Kyoto.

Olfactory bulbectomy (OB) is an established animal model of depression in rats. OB induces behavioral abnormalities that can be ameliorated by chronic antidepressant treatment. Studies using receptor binding assays (Ho et al., 2001) and quantitative autoradiography (Robichaud et al., 2001) have revealed reductions in the NMDA receptor binding densities in the cerebral cortex and amygdala in OB rats. On the other hand, another autoradiography study indicated an elevation of NMDA receptors in the medial prefrontal cortex (Webster et al., 2000). A possible explanation for the increased NMDA receptor binding density observed in the latter study may lie in the fact that pentobarbital was used as the anesthetic during OB. Pentobarbital has been shown to increase the [^{3}H]MK-801 binding density in the cortex of rodents (Oh et al., 1997; Short and Tabakoff, 1993). A recent study showed an increase of mGluR1 and a decrease of mGluR2/3, mGluR4 and mGluR7 in OB mice (Wierońska et al., 2008).

The learned helplessness (LH) model is a widely accepted animal model of depression based on environmental stress (Maier, 1984). In this model, animals are exposed to either controllable or uncontrollable stressful events, such as tailshock or footshock. In LH rats, a decrease of glutamate uptake in the cortex, striatum and hippocampus (Almeida et al., 2010) and reduced expression of vesicular glutamate transporter 1 (vGluT1), excitatory amino acid transporter-2 (EAAT2) and EAAT4 in the hippocampus (Zink et al., 2010) have been observed.

The forced swim test and tail suspension test are relatively short-term aversive stress exposure models whereas LH and the chronic mild stress (CMS) paradigms were developed to study the neural changes that result from stresses of a more chronic nature. The CMS paradigms aim to model a chronic depressive-like state that develops gradually over time in response to stress, and are thus considered to be more naturalistic in their induction. Most of the procedures employed for CMS share certain common features, such as the use of a variety of stressors, the use of stressors with mild severity, and the use of stress exposure schedules that are semi-random and unpredictable (Willner, 1997). In CMS models, changes in AMPA receptors and mGluRs are observed. Specifically, the level of mGluR5 protein was increased in the CA1 region and decreased in the CA3 region of the hippocampus in a rat CMS model, and the authors speculated that these changes in the mGluR5 protein level may be involved in the pathophysiology of depression (Wierońska et al., 2001). Another study showed that CMS induced anhedonia and decreased the AMPA receptor GluR1 subunit levels in the prefrontal cortex and hippocampus of adult rats and prefrontal cortex of young rats but increased GluR1 in the nucleus accumbens of adult rats (Toth et al., 2008).

Putative genetic animal models such as Flinders Sensitive Line (FSL) rats and Wistar Kyoto (WKY) rats are also used for pharmacological evaluation of both existing antidepressants for MDD and those still under development (Malkesman and Weller, 2009). These two genetic models of MDD also show abnormalities in glutamate receptors.

The spontaneously depressed FSL rat model is a well-validated model of MDD carrying a genetic vulnerability associated with distinct features of pathology. FSL rats showed face, construct, and predictive validity and exhibited several behavioral features of human depression, such as psychomotor retardation, increased amount and reduced latency of rapid-eye-movement sleep, and reduced appetite and weight, as well as several neurochemical abnormalities (Overstreet et al., 2005). FSL rats showed reduced expressions of the NR1 subunit of NMDA receptors (Ryan et al., 2009) and mGluR2/3 (Matrisciano et al., 2008) and decreased BDNF levels (Elfving et al., 2010) in the hippocampus. Furthermore, maternal separation induced marked increases in the synaptic NR1 subunit and GluR2/3 subunits of AMPA receptors in FSL rats (Ryan et al., 2009).

WKY rats are derived from Wistar rats, which were originally bred as normotensive controls for a spontaneous hypertensive strain. The WKY rat strain differs from other strains in terms of its behavioral, physiological, and neuroendocrine responsiveness to environmental as well as pharmacological challenges (Malkesman and Weller, 2009). WKY rats have also been suggested to have behavioral and endocrinological similarities to depressed humans (McArthur and Borsini, 2006). WKY rats were reported to show higher mGluR7 mRNA expression in the suprapyramidal layer of the dentate gyrus of the hippocampus (O'Mahony et al., 2010).

These findings suggest that animal models of depression show enhancement of the glutamatergic system induced by decreased glutamate uptake via reduced expression of glial glutamate transporters and changes in the levels of NMDA receptors, AMPA receptors, and mGluRs, and that these neurochemical changes may cause depressive-like behaviors.

4.2. Depressive-like behaviors in genetic models of deficient glutamate function

Animal models of deficient glutamate function can be generated using genetic approaches (*e.g.*, gene transgenic, knockout, or mutation-knock-in manipulation). In this section, we review studies on depressive-like behaviors using genetic models (Table 2).

The synaptic vesicle protein vesicular glutamate transporter (vGluT1) plays key roles in the synaptic release and efficacy of glutamatergic synaptic transmission. Mice heterozygous for vGluT1 (vGluT1$^{+/-}$) exhibited increased immobility times in the forced swim test (Elizalde et al., 2010; Garcia-Garcia et al., 2009; Tordera et al., 2007) and decreased sucrose intake (Elizalde et al., 2010; Garcia-Garcia et al., 2009), similar to rats subjected to CMS. Furthermore, microarray studies in vGluT1$^{+/-}$ mice revealed regulation of genes involved in apoptosis, neurogenesis, synaptic transmission, protein metabolic processes or learning and memory (Tordera et al., 2011). These findings demonstrate that animals with glutamate transporter dysfunction show depressive-like behaviors.

Two reports using NMDA receptor NR2A subunit dysfunction models suggested important roles of the NR2A subunit in the depression-related behaviors of animals. NR2A-knockout mice showed antidepressant-like profiles in the forced swim test and tail suspension test in comparison with wild-type controls (Boyce-Rustay and Holmes, 2006). Meanwhile, NR2A-knock-in mice with a Tyr-1325-Phe mutation showed antidepressant-like behaviors in the tail suspension test and forced swim test (Taniguchi et al., 2009).

In contrast to the NMDA receptor dysfunction models, AMPA receptor dysfunction models show depression-like behaviors. AMPA receptor subunit 1 (GluR-A)-knockout mice (GluR-A$^{-/-}$) displayed increased LH, decreased serotonin and norepinephrine levels, and disturbed glutamate homeostasis with increased glutamate levels and increased NMDA receptor expression (Chourbaji et al., 2008). AMPA receptors mediate transmission in a manner that is positively regulated by phosphorylation at Ser831 and Ser845 in GluR1 subunits. Dual-phosphomutant GluR1 mice, in which Ser831- and Ser845-GluR1 were inactivated by alanine replacements, exhibited increased immobility in the tail suspension test compared with their wild-type counterparts (Svenningsson et al., 2007).

The involvement of ionotropic glutamate receptors in the control of mood disorders and the mechanisms of antidepressants has been studied much more extensively than the role of the metabolic glutamate receptors. However, recent attention has been directed toward the potential roles of the mGluRs. mGluR5-knockout mice exhibited an antidepressant-like phenotype in the forced swim test (Li et al., 2006). Furthermore, the behavioral profiles of mice with targeted deletion of the gene for mGluR7 (mGluR7$^{-/-}$) were examined to test the role of mGluR7 in depression. These mGluR7-knockout mice displayed substantially less behavioral immobility in both the forced swim test and tail suspension test (Cryan et al., 2003) as well as increased BDNF protein levels in the hippocampus (Mitsukawa et al., 2006), which were well correlated with the antidepressant-like phenotype observed behaviorally.

The above-described findings suggest that vGluT1, NR2A, GluR-A, mGluR5, and mGluR7 may play pivotal roles in the modulation of emotional behaviors in rodents.

Table 2
Depressive-like behaviors in genetic mice with deficient glutamate function.

Mutations	Behavior tests	Results	References
vGluT1($^{+/-}$)	Forced swimming	Increased the immobility time	Tordera et al. (2007) Elizalde et al. (2010) Garcia-Garcia et al. (2009)
	Anhedonia	Decreased sucrose intake	Elizalde et al. (2010) Garcia-Garcia et al. (2009)
NR2A($^{-/-}$)	Forced swimming	Decreased the immobility time	Boyce-Rustay and Holmes (2006)
	Tail suspension	Decreased the immobility time	Boyce-Rustay and Holmes (2006)
NR2A with Tyr-1325-Phe mutation	Forced swimming	Decreased the immobility time	Taniguchi et al. (2009)
	Tail suspension	Decreased the immobility time	Taniguchi et al. (2009)
GluR-A($^{-/-}$)	Learned helplessness	Elevated the number of failures and prolonged the escape latencies	Chourbaji et al. (2008)
GluR1 with Ser-831-Ala and Ser-845-Ala mutation	Tail suspension	Increased the immobility time	Svenningsson et al. (2007)
mGluR5($^{-/-}$)	Forced swimming	Decreased the immobility time	Li et al. (2006)
mGluR7($^{-/-}$)	Forced swimming	Decreased the immobility time	Cryan et al. (2003)
	Tail suspension	Decreased the immobility time	Cryan et al. (2003)

mGluR = metabotropic glutamate receptor; vGluT = vesicular glutamate transporter.

5. Effects of chronic treatments with antidepressants and electroconvulsive shock (ECS) on glutamatergic functions in animal models of depression and normal animals

5.1. Effects of chronic treatments with antidepressants in animal models of depression

Although there are comparatively few reports on the effects of chronic treatments with antidepressants on glutamatergic functions in animal models of depression, the involvement of glutamatergic functions in the efficacy of antidepressants has been reported (Table 3). In a study using OB mice, chronic treatment with amitriptyline was initiated from 14 days after OB and continued for 14 days. OB caused a significant increase in the mGluR1a level. Chronic amitriptyline treatment (10 mg/kg) reversed the changes in the mGluR1a level in OB animals (Wierońska et al., 2008). FSL rats subjected to early maternal separation exhibited upregulation of the NR1 subunit of NMDA receptors and GluR2/3 subunits of AMPA receptors in hippocampal synaptosomes. These changes in the expression levels of NR1 and GluR2/3 were significantly inhibited by chronic treatment with escitalopram (Ryan et al., 2009). In a previous study, maternal separation was shown to worsen the depressive-like behaviors of FSL rats, and escitalopram only partly reversed these changes (El Khoury et al., 2006).

Table 3
Effects of chronic treatment with antidepressants on the glutamatergic system in animal models of depression.

Models	Animals	Brain regions	Antidepressants	Interests	Effects on the changes of interests	References
OB	Mice	Hippocampus	Amitriptyline	mGluR1a	Recovered the increase	Wierońska et al. (2008)
				mGluR2/3 and 7	Recovered the decrease	Wierońska et al. (2008)
FSL	Rats	Hippocampus	Escitalopram	NR1 and GluR2/3	Inhibited the increase by maternal separation	Ryan et al. (2009)
Chronic restraint stress	Rats	CA3 of hippocampus	Tianeptine	EAAT2	Inhibited the increase	Reagan et al. (2004)
Unpredictable footshock stress	Rats	Prefrontal/frontal cortical synaptpsomes	Fluoxetine, desipramine, venlafaxine and agomelatine	Depolarization-evoked glutamate release	Inhibited the increase	Musazzi et al. (2010)

mGluR = metabotropic glutamate receptor; OB = olfactory bulbectomy; LH = learned helplessness; FSL = Flinders sensitive liner; EAAT = excitatory amino acid transporter.

Chronic treatment with antidepressants also inhibits the neurochemical changes in glutamatergic neurons in rats subjected to chronic stress as well as acute stress. Increased levels of EAAT2 and dendritic remodeling were shown in the CA3 region of rats subjected to chronic restraint stress and were inhibited by tianeptine (Reagan et al., 2004). In an acute stress model, rats were subjected to unpredictable footshock stress. Acute stress induced a marked increase in depolarization-evoked release of glutamate from synaptosomes in the prefrontal/frontal cortex, and chronic drug treatments prevented these increases in glutamate release (Musazzi et al., 2010).

5.2. Effects of chronic treatments with antidepressants in normal animals

Data obtained in studies on glutamatergic functions using normal animals after chronic administration of antidepressants have also been accumulated (Table 4). Agents with antidepressant activities, namely the antidepressants fluoxetine and desipramine, the atypical antipsychotic clozapine, and the mood stabilizer lithium increased vGluT1 mRNA expression in neurons in the cerebral cortex and hippocampus, in parallel with enhanced vGluT1 protein expression in their projection fields (Moutsimilli et al., 2005). In contrast, the typical antipsychotic haloperidol, the cognitive enhancers memantine and tacrine, and the anxiolytic diazepam had no effects. These findings suggest that vGluT1 could be a useful marker for antidepressant activity.

Chronic administration of the antidepressants imipramine and phenelzine reduced the potassium-induced overflow of glutamate from rat prefrontal cortex slices in *ex vivo* analyses (Michael-Titus et al., 2000). Chronic administration of citalopram decreased veratridine-evoked glutamate release in the rat prefrontal cortex as revealed using *in vivo* microdialysis (Gołembiowska and Dziubina, 2000). In measurements of endogenous glutamate and GABA release in superfused synaptosomes that were freshly prepared from the hippocampus of antidepressant-treated rats, chronic but not acute administration of antidepressants belonging to three different classes (SSRIs, tricyclic antidepressants, and noradrenaline reuptake inhibitors) selectively reduced depolarization-evoked release of glutamate in the hippocampal synaptosomes (Bonanno et al., 2005). The basal release of glutamate and basal/evoked release of GABA from nerve terminals was not altered by the drug treatments. These findings suggest that the release of glutamate evoked by neuronal activation, but not the basal (unstimulated) release, is affected by these drug treatments. Although there is no direct evidence that stress increases glutamate release, if the consequences of stress at the molecular and cellular levels have primary roles in the induction of morphological/functional modifications in mood disorders, then antidepressants may work by limiting excessive release of glutamate in response to stressful neuronal activation (Bonanno et al., 2005).

Chronic administration of the two antidepressants reboxetine and fluoxetine, which are selective inhibitors of noradrenaline and 5-hydroxytryptamine uptake, respectively, markedly reduced the

Table 4
Effects of chronic treatment with antidepressants on the glutamatergic system in normal animals.

Animals	Brain regions	Antidepressants	Interests	Changes of the interests	References
Mice	Hippocampus and cortex	Fluoxetine and desipramine	vGluT1	Increased	Moutsimilli et al. (2005)
Rats	Prefrontal cortex using microdialysis	Citalopram	Veratridine-induced glutamate release	Decreased	Gołembiowska and Dziubina (2000)
Rats	Prefrontal cortex slices	Imipramine and phenelzine	Potassium-induced glutamate release	Decreased	Michael-Titus et al. (2000)
Rats	Hippocampal synaptosomes	Fluoxetine, desipramine and reboxetine	Depolarization-induced glutamate release	Decreased	Bonanno et al. (2005)
Rats	Hippocampus	Fluoxetine and reboxetine	NR1	Decreased	Pittaluga et al. (2007)
Rats	Retrosprenial granular b cortex	Fluoxetine	NR2A, GluR1 and 2	Increased	Ampuero et al. (2010)
Rats	Hippocampus	Desipramine and paroxetine	GluR1 and 2/3	Increased	Martínez-Turrillas et al. (2005)
Mice	Nucleus accumbens, caudate putamen and hippocampus	Maprotiline	GluR1 and 2/3	Increased	Tan et al. (2006)
Rats	CA3 of hippocampus	Imipramine	mGluR1a	Increased	Bajkowska et al. (1999)
Rats	Hippocampus Cerebral cortex, nucleus accumbens, hippocampus and corpus striatum	Imipramine	mGluR1a	Increased	Matrisciano et al. (2002)
		Imipramine	mGluR2/3	Increased	Matrisciano et al. (2002)
Rats	Cortical slices	Imipramine	mGluR2/3	Inhibited the function	Palucha et al. (2007a)
Rats	CA1 of hippocampus	Imipramine	mGluR5a	Increased	Śmiałowska et al. (2002)
Rats	Frontal cortex and hippocampus	Citalopram	mGluR7	Decreased	Wierońska et al. (2007)

mGluR = metabotropic glutamate receptor; vGluT = vesicular glutamate transporter.

expression of the NR1 protein subunit of NMDA receptors in rat hippocampal synaptic membranes (Pittaluga et al., 2007). In a recent study, chronic administration of fluoxetine for 4 weeks decreased the immobility times in the tail suspension test and forced swim test. Moreover, Western blot analyses of homogenates and immunohistochemical staining revealed marked upregulation of NR2A, GluR1 and GluR2 in the retrosplenial granular b cortex (Ampuero et al., 2010). However, in analyses of the subunit contents in the postsynaptic densities and synaptic membranes, levels of NR2A and GluR2, but not GluR1, were increased. Instead, GluR1 was augmented in a microsomal fraction containing intracellular membranes. The changes in the subunit levels were associated with upregulation of the dendritic spine density and large mushroom-type spines. These molecular and structural adaptations may be involved in neuronal network stabilization following long-term fluoxetine treatment.

Chronic antidepressant treatment increased the immunoreactivity of the AMPA receptor subunits GluR1 and GluR2/3 in the brain region associated with MDD (Martínez-Turrillas et al., 2005; Tan et al., 2006). Chronic treatment with antidepressants also affects the expression and function of mGluRs. Chronic treatment with imipramine increased the number of mGluR1a-immunoreactive neurons in a pyramidal layer of the CA3 hippocampal field (Bajkowska et al., 1999). A study using Western blot analyses showed that repeated injections, but not a single injection, of imipramine upregulated the expression and modulated the functions of mGluR2/3 in the rat brain (Matrisciano et al., 2002). In contrast, data obtained in binding studies showed that chronic treatment with imipramine did not induce any changes in the density of mGluR2/3 in the rat cerebral cortex or hippocampus. However, 3′,5′-cyclic adenosine monophosphate accumulation studies revealed that the inhibitory properties of mGluR2/3 were significantly diminished after repeated imipramine treatment (Pałucha et al., 2007). The expression of mGluR5a was significantly increased in the CA1 field of the rat hippocampus after chronic imipramine administration (Śmiałowska et al., 2002), whereas mGluR7 immunoreactivities were decreased by chronic citalopram treatment in the frontal cortex and hippocampus in rats (Wierońska et al., 2007).

5.3. Effects of chronic treatments with ECS in normal animals

Repeated ECS has long been used as the most effective and safe therapy for patients who are refractory to antidepressants, although the underlying mechanism of its antidepressant actions is still unknown. In this section, studies on the effects of chronic ECS treatment on the glutamatergic system in normal animals are reviewed (Table 5). Using *in situ* hybridization techniques, repeated ECS was found to markedly increase the mRNA expression for the GluR1 subunit of AMPA receptors, but not the NMDAR1A-G subtypes of NMDA receptors, relative to control treatments (Naylor et al., 1996). The mGluR1a and mGluR5a immunoreactivities were also significantly increased in the rat hippocampus after chronic ECS treatment (Śmiałowska et al., 2002). Chronic ECS treatment increased the number of mGluR1a-immunoreactive neurons in a pyramidal layer of the CA3 hippocampal field (Bajkowska et al., 1999). A recent study showed that chronic ECS treatment markedly increased the phosphorylation of the regulatory NMDA receptor subunit NR2B (Ser1303) and the AMPA receptor subunit GluR-A (Ser831) in the hippocampus, with no effects on the obligatory subunit NR1 (Fumagalli et al., 2010). Enhancing of phosphorylation of NR2B (Ser1303) reduces the interaction of NMDA receptor subunit NR2B and calcium/calmodulin-dependent protein kinase II, suggesting the reduction of the NMDA receptor-mediated signal transduction. Phosphorylation of GluR-A (Ser831) potentiates AMPA currents. These reports suggest that ECS treatment may, at least in part, exert its clinical activity through the modulation of glutamatergic synapses via potentiation of AMPA receptor functions (Fumagalli et al., 2010). Repetitive transcranial magnetic stimulation, which has recently been used as a physical therapy, also increased NMDA receptors in the ventromedial hypothalamus, basolateral amygdala, and parietal cortex (Lisanby and Belmaker, 2000).

6. Effects of glutamatergic compounds in preclinical and/or mechanistic models of depression

Chemical compounds that intervene in glutamatergic signaling often have effects on depressive behaviors in animals (Fig. 1). The antidepressant effects of glutamatergic agents in preclinical models are summarized in Table 6.

6.1. NMDA antagonists

NMDA receptor antagonists such as MK-801 (dizocilpine) or CGP37849 exerted antidepressant effects in preclinical animal models for depression (Machado-Vieira et al., 2009; Paul and Skolnick, 2003; Skolnick et al., 2009). However, many NMDA antagonists have unfavorable side effects, such as psychotomimetic effects and cognitive impairment. Among the NMDA antagonists, several agents are relatively tolerable in humans. In fact, ketamine is used as an anesthetic and memantine is used for the treatment of Alzheimer's disease. This section focuses on the antidepressant effects of glutamatergic compounds that can antagonize NMDA receptors in behavioral models.

6.1.1. Ketamine

The non-competitive NMDA receptor antagonist ketamine has recently attracted attention for its rapid-onset antidepressant effects (Machado-Vieira et al., 2009; Hashimoto, 2009a, 2011; Zarate et al., 2010; Domino, 2010). Ketamine decreased the immobility time in the forced swim test in rats (Engin et al., 2009; Garcia et al., 2008a, 2008b; Li et al., 2010; Yilmaz et al., 2002) and mice (da Silva et al., 2010; Maeng et al., 2008; Rosa et al., 2003), and in the tail suspension test in mice (da Silva et al., 2010; Kos et al., 2006). Ketamine reversed the inescapable electrical footshock-induced behavioral changes (*e.g.*, reduced ambulation and rearing in the open field, and increased immobility time in the forced swim test) in mice (Chaturvedi et al., 1999). Chronic treatment with ketamine reversed the CMS-evoked reduction in sweet food intake, an anhedonia-like behavior, in rats (Garcia et al., 2009). Acute and sustained antidepressant effects of ketamine were also demonstrated in mice as well as in humans (Maeng et al., 2008). A single injection of ketamine significantly reversed the increase in the number of escape failures and the latency to escape in the LH paradigm, in which the animals are

Table 5
Effects of chronic treatment with electroconvulsive shock on the glutamatergic system in normal rats.

ECS treatments	Brain regions	Interests	Changes of the interests	References
10 times every other day	Hippocampus	NR2B (ser1303) and GluR-A (ser831)	Increased the phosphorylation	Fumagalli et al. (2010)
10 times every other day	Hippocampus	GluR1	Increased	Naylor et al. (1996)
21 days every other day	CA3 of hippocampus	mGluR1a	Increased	Bajkowska et al. (1999)
21 days every other day	Hippocampus	mGluR1a	Increased	Śmiałowska et al. (2002)
	CA3 of hippocampus	mGluR5a	Increased	Śmiałowska et al. (2002)

mGluR = metabotropic glutamate receptor; ECS = electroconvulsive shock.

Table 6
Effects of glutamatergic compounds on behavioral models of depression.

Compounds	Animals	Models	Results	Reference
NMDA receptor antagonist				
Ketamine	Rats	Forced swimming	Decreased the immobility time	Engin et al. (2009) Garcia et al. (2008a, 2008b) Li et al. (2010) Yilmaz et al. (2002)
		Learned helplessness	Reversed the increase in the number of escape failures	Li et al. (2010)
		Chronic mild stress	Reversed the reduction in sweet food intake Reversed the reduction in sucrose preference	Garcia et al. (2009) Li et al. (2011)
	Mice	Forced swimming	Decreased the immobility time	da Silva et al. (2010) Maeng et al. (2008) Rosa et al. (2003)
		Tail suspension	Decreased the immobility time	da Silva et al. (2010) Kos et al. (2006)
		Forced swimming after footshock	Reversed the increase in the immobility time	Chaturvedi et al. (1999)
		Open field after footshock	Reversed the decreases in ambulation and rearing	Chaturvedi et al. (1999)
		Learned helplessness	Reversed the increases in the number of escape failures and the latency to escape	Maeng et al. (2008)
NR2B antagonist Ro25-6981	Rats	Forced swimming	Decreased the immobility time	Li et al. (2010)
		Chronic mild stress	Reversed the reduction in sucrose preference	Li et al. (2011)
	Mice	Forced swimming	Decreased the immobility time	Maeng et al. (2008)
Other NMDA receptor antagonists				
Memantine	Rats	Forced swimming	Decreased the immobility time	Moryl et al. (1993) Réus et al. (2010) Rogóż et al. (2002)
			Synergistically decreased the immobility time when combined with antidepressants	Rogóż et al. (2002)
			Synergistically decreased the immobility time when combined with sigma agonists	Skuza and Rogóż (2003) Skuza and Rogóż (2006)
	Mice	Forced swimming	Decreased the immobility time	Almeida et al. (2006)
Magnesium	Rats	Forced swimming	Decreased the immobility time	Poleszak et al. (2005)
	Mice	Forced swimming	Decreased the immobility time	Decollogne et al. (1997) Poleszak (2007) Poleszak et al. (2004) Poleszak et al. (2007)
		Forced swimming after immobility stress	Reversed the increase in the immobility time	Poleszak et al. (2006)
Zinc	Rats	Forced swimming	Decreased the immobility time	Kroczka et al. (2001) Nowak et al. (2003) Szewczyk et al. (2010)
		Olfactory bulbectomy (passive avoidance)	Reversed the increase in the number of trials needed for learning	Nowak et al. (2003)
		Olfactory bulbectomy (open field)	Reversed the hyperactivity	Nowak et al. (2003)
		Chronic mild stress	Reversed the decrease in sucrose drinking	Sowa-Kućma et al. (2008)
		Chronic unpredictable stress	Reversed the decrease in footshock-induced fighting behavior	Cieślik et al. (2007)
	Mice	Forced swimming	Decreased the immobility time	Kroczka et al. (2001) Rosa et al. (2003) Szewczyk et al. (2010)
		Tail suspension	Decreased the immobility time	Rosa et al. (2003)
AMPA receptor positive modulators				
Aniracetam	Aged rats	Forced swimming	Decreased the immobility time	Nakamura and Tanaka (2001)
	Young rats	Forced swimming	No effects	Nakamura and Tanaka (2001)
	Rats	Reduction of submissive behavior	Decreased the submissive behavior	Knapp et al. (2002)
Piracetam	Rats	Reduction of submissive behavior	Decreased the submissive behavior	Knapp et al. (2002)
Ampakines	Rats	Reduction of submissive behavior	Decreased the submissive behavior	Knapp et al. (2002)
CX614	Mice	Forced swimming	Decreased the immobility time	Szewczyk et al. (2010)
LY392098	Rats	Forced swimming	Decreased the immobility time	Li et al. (2001)
	Mice	Forced swimming	Decreased the immobility time	Li et al. (2001) Li et al. (2003)
		Tail suspension	Decreased the immobility time No effects	Li et al. (2001) Farley et al. (2010)
		Sucrose preference	No effects	Farley et al. (2010)
		Unpredictable chronic mild stress (Tail suspension)	Decreased the immobility time	Farley et al. (2010)
		Unpredictable chronic mild stress (sucrose preference)	No effects	Farley et al. (2010)
LY451646	Mice	Forced swimming	Decreased the immobility time	Bai et al. (2001)
		Tail suspension	Decreased the immobility time	Bai et al. (2001)

(*continued on next page*)

Table 6 (*continued*)

Compounds	Animals	Models	Results	Reference
Group I mGluRs				
mGluR1 antagonists				
EMQMCM	Rats	Forced swimming	Decreased the duration of floating and increased the durations of mobile and escape behaviors	Belozertseva et al. (2007)
			Decreased the immobility time	Molina-Hernández et al. (2008a, 2008b)
	Mice	Tail suspension	Decreased the immobility time	Belozertseva et al. (2007)
AIDA	Rats	Forced swimming	No effects	Smolders et al. (2008)
	Mice	Tail suspension	Decreased the immobility time	Smolders et al. (2008)
mGluR5 antagonists				
MTEP	Rats	Forced swimming	Decreased the duration of floating and increased the duration of mobile behaviors but did not alter the escape behaviors	Belozertseva et al. (2007)
			Decreased the immobility time	Molina-Hernández et al. (2008a, 2008b)
			No effects	Pałucha et al. (2005)
		Olfactory bulbectomy (open field)	Reversed the hyperactivity	Pałucha et al. (2005)
		DRL-72 s task	Increased the number of reinforcers	Molina-Hernández et al. (2006)
	Mice	Forced swimming	Decreased the immobility time	Li et al. (2006)
		Tail suspension	Decreased the immobility time	Belozertseva et al. (2007)
				Pałucha et al. (2005)
MPEP	Rats	Forced swimming	No effects	Tatarczyńska et al. (2001)
		Olfactory bulbectomy (passive avoidance)	Reversed the increase in the number of trials needed for learning	Pilc et al. (2002)
				Wierońska et al. (2002)
	Mice	Forced swimming	Decreased the immobility time	Li et al. (2006)
		Tail suspension	Decreased the immobility time	Belozertseva et al. (2007)
				Tatarczyńska et al. (2001)
			No effects	Smolders et al. (2008)
Group II mGluRs				
mGluR II antagonists				
LY341495	Rats	Forced swimming	Decreased the immobility time	Chaki et al. (2004)
	Mice	Forced swimming	Decreased the immobility time	Bespalov et al. (2008)
		Tail suspension	Decreased the immobility time	Chaki et al. (2004)
MGS0039	Rat	Forced swimming	Decreased the immobility time	Chaki et al. (2004)
		Learned helplessness	Reversed the increase in the number of escape failures	Yoshimizu et al. (2006)
	Mice	Tail suspension	Decreased the immobility time	Chaki et al. (2004)
				Karasawa et al. (2005)
Prodrug of MGS0039	Rats	Forced swimming	Decreased the immobility time	Yasuhara et al. (2006)
	Mice	Tail suspension	Decreased the immobility time	Yasuhara et al. (2006)
mGluR II agonists				
LY354740	Mice	Forced swimming	No effects	Kłodzińska et al. (1999)
		Tail suspension	No effects	Kłodzińska et al. (1999)
LY379268	Rata Flinders-sensitive line rats	Forced swimming	No effects	Smolders et al. (2008)
		Forced swimming	Enhanced the effects of antidepressants	Matrisciano et al. (2007)
				Matrisciano et al. (2008)
Group III mGluRs				
Group III agonist				
ACPT-I	Rats	Forced swimming	Decreased the immobility time	Kłak et al. (2007)
				Pałucha et al. (2004)
				Tatarczyńska et al. (2002)
mGluR6 agonist				
HomoAMPA	Rats	Forced swimming	No effects	Pałucha et al. (2004)
mGluR8 agonist				
(RS)-PPG	Rats	Forced swimming	Decreased the immobility time	Pałucha et al. (2004)
mGluR7 agonist				
AMN082	Rats	Forced swimming	Decreased the immobility time	Pałucha-Poniewiera et al. (2010)
	Mice	Forced swimming	Decreased the immobility time	Palucha et al. (2007)
		Tail suspension	Decreased the immobility time	Palucha et al. (2007)
				Pałucha-Poniewiera et al. (2010)
mGluR4 positive allosteric modulator				
PHCCC	Rats	Forced swimming	No effects	Kłak et al. (2007)
			Enhanced the effects of ACPT-I	Kłak et al. (2007)
EAAT2 enhancer				
Ceftriaxone	Mice	Forced swimming	Decreased the immobility time	Mineur et al. (2007)
		Tail suspension	Decreased the immobility time	Mineur et al. (2007)

Table 6 (*continued*)

Compounds	Animals	Models	Results	Reference
Others				
Minocycline	Rats	Forced swimming	Decreased the immobility time	Molina-Hernández et al. (2008a, 2008b)
			No effects	Deak et al. (2005)
	Mice	Forced swimming after lipopolysaccharide treatment	Reversed the increase in the immobility time	O'Connor et al. (2009)
		Tail suspension after lipopolysaccharide treatment	Reversed the increase in the immobility time	O'Connor et al. (2009)
Riluzole	Rats	Olfactory bulbectomy	Decreased the hyperemotionality	Takahashi et al. (2011)
		Chronic unpredictable stress (sucrose preference)	Reversed the decrease in the sucrose consumption	Banasr et al. (2010)
		Chronic unpredictable stress (active avoidance)	Reversed the increase in the number of escape failures and the latency to escape	Banasr et al. (2010)

NMDA = *N*-methyl-D-aspartate; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; mGluR = metabotropic glutamate receptor; EMQMCM = (3-ethyl-2-methyl-quinolin-6-yl)-(4-methoxy-cyclohexyl)-methanone methanesulfonate; AIDA = (RS)-1-aminoindan-1,5-dicarboxylic acid; MTEP = 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl] pyridine; MPEP = 2-methyl-6-(phenylethynyl)-pyridine; ACPT-I = (1S,3R,4S)-1-aminocyclo- pentane-1,3,4-tricarboxylic acid; HomoAMPA = 2-amino-4-(3-hydroxy-5-methylisoxazol-4-yl) butyric acid; (RS)-PPG = (RS)-4-phosphonophenylglycine; PHCCC = *N*-phenyl-7-(hydroxyimino)-cyclopropa[*b*]chromen-1a-carboxamide; DRL-72 s task = differential reinforcement of the low-rate 72-s task; Ro25-6981 = (αR,βS)-α-(4-hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidinepropanol; CX614 = 2H,3H,6aH-pyrrolidino(2″,1″-3′,2′)1,3-oxazino(6′,5′-5,4)benzo(e)1,4-dioxan-10-one; LY392098 = *N*-2-(4-(3-thienyl) phenyl)propyl 2-propanesulfonamide; LY451646 = (R)-*N*-(2-(4′-cyanobiphenyl-4-yl)propyl) propane-2-sulfonamide; LY341495 = (1S, 2S)-2-[(2S)-2-amino-3-(2,6-dioxo-3H-purin-9-yl)-1-hydroxy-1-oxopropan-2-yl] cyclopropane-1-carboxylic acid; MGS0039 = (1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzyloxy)-6-fluorobicyclo[3.1.0] hexane-2,6-dicarboxylic acid; LY354740 = (1S,2S,5R,6S)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid; LY379268 = (1R,4R,5S,6R)-4-amino-2-oxabicyclo[3.1.0]hexane-4,6-dicarboxylic acid; AMN082 = *N*,*N*′-dibenzhydrylethane-1,2-diamine.

generally only responsive to monoaminergic antidepressant drugs after repeated administration over several days (Maeng et al., 2008). In addition, a single injection of ketamine, but not imipramine, reduced the immobility time in the forced swim test even after 2 weeks of treatment (Maeng et al., 2008). Ketamine resulted in significantly lower levels of Ser845-phosphorylated GluR1 (Maeng et al., 2008), which is one of the AMPA receptor subunits (Dingledine et al., 1999). Pretreatment with dihydroxy-6-nitro-7-sulfoamoylbenzo(*f*)-quinozaline (NBQX), an AMPA receptor antagonist, attenuated the ketamine-induced changes in the phosphorylation of GluR1 and antidepressant effects in the forced swim test (Maeng et al., 2008), suggesting the role of AMPA receptors in the antidepressant effects of ketamine. A recent study demonstrated that not only AMPA signaling but also the mammalian target of rapamycin (mTOR) pathway was involved in the antidepressant actions of ketamine (Li et al., 2010, 2011). Ketamine, but not ECS, fluoxetine or imipramine, rapidly increased the level of phosphorylated mTOR in the rat prefrontal cortex, and NBQX blocked the phosphorylation of mTOR after ketamine treatment. Furthermore, ketamine increased the levels of synapsin I, a presynaptic protein, and PSD95 and GluR1, which are postsynaptic proteins, in synaptoneurosomes of the prefrontal cortex as well as the spine number in the prefrontal cortex. Rapamycin, a selective mTOR inhibitor, blocked the increases in these synaptic proteins and spine density by ketamine treatment. Furthermore, rapamycin abolished the antidepressant effects of ketamine in the forced swim test and LH test in rats. Moreover, ketamine rapidly ameliorated chronic unpredictable stress-induced anhedonic and anxiogenic behaviors in rats (Li et al., 2011).

These findings suggest that rapid activation of the AMPA and mTOR signaling pathways, possibly induced by NMDA receptor blockade, may be critical for the fast-acting antidepressant effects of ketamine (Cryan and O'Leary, 2010; Hashimoto, 2011). Further investigations into the mechanisms underlying how ketamine exerts its antidepressant effects could accelerate the search for the next generation of antidepressants with a rapid onset of action. However, a hyperactive PI3K/Akt/mTOR signaling pathway is detected in many human cancers, and alterations of this pathway are associated with the development and progression of cancer. Therefore, drugs that can activate the mTOR signaling pathway may have detrimental effects in humans because of the role of this pathway in cancer and other human diseases (Hashimoto, 2011).

6.1.2. NMDA receptor NR2B subunit antagonist

NMDA receptors typically contain four subunit proteins—namely, two NR1 subunits plus two NR2 subunits—and in some cases also include an NR3 subunit. Both the NR1 and NR2 subunits contribute to the formation of the NMDA receptor ion channels (Dingledine et al., 1999; Kalia et al., 2008). NMDA receptors containing the NR2B subunit are primarily localized in the forebrain, including the hippocampus (Loftis and Janowsky, 2003), which has been implicated in the pathophysiology of MDD (Campbell and Macqueen, 2004). Ro25-6981, an NR2B selective antagonist, induced significant dose-dependent reductions in the immobility time in the forced swim test in mice (Maeng et al., 2008), and the effects were blocked by pretreatment with NBQX, an AMPA receptor antagonist. Furthermore, Ro25-6981 treatment increased the phosphorylation of mTOR and synaptic proteins as effectively as ketamine. Moreover, rapamycin blocked the Ro25-6981-induced decrease in the immobility time in the forced swim test in rats (Li et al., 2010). Ro25-6981 rapidly ameliorated chronic unpredictable stress-induced anhedonic behaviors in rats (Li et al., 2011). Therefore, this NR2B selective antagonist may exert its rapid-onset antidepressant effect by regulating the AMPA and mTOR signaling pathways in a manner similar to ketamine (Hashimoto, 2011).

6.1.3. Memantine

Memantine is a low affinity non-competitive NMDA receptor antagonist. Although memantine and ketamine appear to have similar NMDA channel-blocking properties, the therapeutic potentials of these drugs are divergent. The potential differences between memantine and ketamine include effects on the gating of blocked channels and binding of memantine to two sites on NMDA receptors (Johnson and Kotermanski, 2006). Acute and chronic treatment with memantine reduced the immobility time in the forced swim test in rats (Moryl et al., 1993; Réus et al., 2010; Rogóż et al., 2002). Synergistic effects were observed in the forced swim test in rats after combined treatments with memantine and other types of antidepressants. Coadministration of memantine and imipramine, fluoxetine, or venlafaxine showed synergistic antidepressant effects, respectively (Rogóż et al., 2002). Endoplasmic reticulum protein sigma-1 receptors are considered to be associated with the mechanisms of action of antidepressants and to play roles in the pathophysiology of depression (Hashimoto and Ishiwata, 2006; Hashimoto, 2009c). Memantine plus SA4503 (cutamesine), siramesine, or 1,3 di-o-tolylguanidine (DTG), which are a selective sigma-1 receptor agonist, a sigma-2 receptor agonist, and a sigma-1/2

receptor agonist, respectively, exerted synergistic antidepressant effects (Skuza and Rogóż, 2003; Skuza and Rogóż, 2006).

In the CNS, nitric oxide (NO) synthesis seems to be predominantly regulated by the influx of Ca^{2+} through receptor-dependent channels, especially after postsynaptic stimulation of NMDA receptors by glutamate (Esplugues, 2002). Severe stress that activates the NMDA receptor/NO pathway can impair hippocampal functions, thereby predisposing the animals to helplessness and depressive symptoms (Joca et al., 2007). The antidepressant effects of memantine were prevented by pretreatment with L-arginine, an NO synthase substrate, *S*-nitroso-*N*-acetyl-penicillamine (SNAP), an NO donor, or sildenafil, a PDE5 inhibitor, in the forced swim test in mice (Almeida et al., 2006). In addition, the antidepressant effects of memantine were potentiated by *N*G-nitro-L-arginine (L-NNA), an NO synthase inhibitor, and 1H-[1,2,4] oxadiazole[4,3-a]quinoxalin-1-one (ODQ), an NO-sensitive inhibitor of soluble guanylate cyclase. These data suggest that the antidepressant effects of memantine are dependent, at least in part, on the inhibition of NO/cyclic guanosine 3′,5′-monophosphate synthesis (Almeida et al., 2006).

6.1.4. Magnesium and zinc

Magnesium and zinc are endogenous NMDA receptor antagonists (Paoletti and Neyton, 2007). Magnesium blocks the pores of NMDA receptors as an uncompetitive antagonist like ketamine and memantine. Zinc binds to the N-terminal domain of NMDA receptors and allosterically inhibits their functions. Recent findings have indicated that magnesium and zinc may be involved in the pathophysiology and treatment of MDD (Eby and Eby, 2010; Nowak et al., 2005; Szewczyk et al., 2008).

Magnesium showed antidepressant-like activity in the forced swim test in mice (Decollogne et al., 1997; Poleszak, 2007; Poleszak et al., 2004, 2007) and in rats (Poleszak et al., 2005), and in mice subjected to immobility stress (Poleszak et al., 2006). Administration of NMDA antagonized the antidepressant-like activity of magnesium, while NMDA alone did not show any significant effects (Poleszak et al., 2007). Therefore, it is likely that NMDA receptor-related glutamergic neurotransmission plays some role in the antidepressant-like activity of magnesium.

Zinc decreased the immobility time in the forced swim test in mice (Kroczka et al., 2001; Rosa et al., 2003; Szewczyk et al., 2010) and rats (Kroczka et al., 2001; Nowak et al., 2003; Szewczyk et al., 2010) and in the tail suspension test in mice (Rosa et al., 2003). Chronic treatment with zinc reversed the decrease in sucrose drinking in rats exposed to CMS (Sowa-Kućma et al., 2008) and reversed the reduction in footshock-induced fighting behavior in rats subjected to chronic unpredictable stress (Cieślik et al., 2007). Acute and chronic zinc treatment reversed the increase in the number of trials required for learning passive avoidance and hyperactivity in OB rats (Nowak et al., 2003). Pretreatment of mice with a subthreshold dose of zinc prevented the anti-immobility effects of MK-801 and ketamine in the forced swim test (Rosa et al., 2003). The zinc-induced antidepressant-like activities in the forced swim test in both mice and rats were antagonized by NMDA administration and the zinc-induced antidepressant-like effects in the forced swim test in mice were abolished by NBQX (Szewczyk et al., 2010), suggesting the role of AMPA receptors. Both NMDA and AMPA receptors might play a role in the antidepressant properties of zinc.

6.2. Positive modulators of AMPA receptors

As described above, AMPA receptors are involved in the antidepressant actions of NMDA receptor antagonists (Maeng et al., 2008). NMDA receptor signaling seems to interact with AMPA receptor signaling directly or indirectly during the antidepressant activities of some types of NMDA antagonists. In fact, both AMPA receptors and NMDA receptors are colocalized at individual synapses in the cortex and hippocampus in rats (He et al., 1998; Kharazia et al., 1996). An increase in the ratio of AMPA to NMDA throughput in critical neuronal circuits may cause antidepressant effects (Du et al., 2006). However, the reduction in the immobility time induced by CGP 37849, an NMDA receptor antagonist, was not antagonized by pretreatment with NBQX in the forced swim test in mice (Dybala et al., 2008). Further investigations are needed to clarify the mechanisms underlying the participation of AMPA receptors in the antidepressant effects induced by inhibition of NMDA receptors.

There are several classes of AMPA receptor potentiators, including nootropic agents and ampakines (Black, 2005; O'Neill et al., 2004). Piracetam, aniracetam, and ampakines reduced the submissive behavior of rats in the reduction of submissive behavior model, as did fluoxetine (Knapp et al., 2002). Although aniracetam failed to decrease the immobility time in the forced swim test in young rats, it significantly shortened the immobility time in the same test in aged rats (Nakamura and Tanaka, 2001). LY451646, an AMPA receptor potentiator, decreased the immobility time in the forced swim test and tail suspension test in mice (Bai et al., 2001). The other ampakine CX614 reduced the immobility time of mice in the forced swim test (Szewczyk et al., 2010). Another AMPA receptor potentiator LY392098 reduced immobility time in the forced swim test in rats and in the tail suspension test in mice (Li et al., 2001). LY392098 also reduced the immobility time in the forced swim test in mice (Li et al., 2001, 2003). LY392098 reduced the immobility time in the tail suspension test in mice that were subjected to unpredictable CMS, while there was no effect of LY392098 in the tail suspension test in non-stressed mice (Farley et al., 2010). LY392098 had no effect in the sucrose preference test in non-stressed mice or unpredictable CMS-subjected mice (Farley et al., 2010). AMPA receptor potentiators increased the BDNF levels in a similar manner to a series of antidepressants (Alt et al., 2006; O'Neill and Witkin, 2007). BDNF is considered to play an important role in the pathophysiology of MDD and to be a downstream target of a variety of antidepressant treatments (Hashimoto, 2010). These findings suggest that AMPA receptor activation may be therapeutically effective in the treatment of MDD.

6.3. mGluR-related compounds

mGluRs are G-protein-coupled receptors that are widely distributed in presynaptic and postsynaptic neurons and in the glia in the brain, and the eight receptors in this class are clustered into group I (mGluR1 and mGluR5), group II (mGluR2 and mGluR3), and group III (mGluR4, mGluR6, mGluR7, and mGluR8) (Hashimoto, 2009a, 2009b, 2009c, 2011; Krystal et al., 2010). Accumulating evidence in recent preclinical studies has implied the possible beneficial effects of bioavailable and selective agonists, antagonists, or allosteric modulators for some types of mGluRs on depression.

6.3.1. Group I mGluRs: mGluR1 antagonists and mGluR5 antagonists

An mGluR1 antagonist, (3-ethyl-2-methyl-quinolin-6-yl)-(4-methoxy-cyclohexyl)-methanone methanesulfonate (EMQMCM), decreased the floating duration and increased the duration of mobile behaviors (paddling and swimming) and the duration of escape behaviors (climbing and diving) in the modified forced swim test in rats (Belozertseva et al., 2007). It also decreased the immobility time in the forced swim test in rats (Molina-Hernández et al., 2008a,b) and decreased the immobility time with a biphasic dose–effect relationship in the tail suspension test in mice (Belozertseva et al., 2007). Another mGluR1 antagonist, (*RS*)-1-aminoindan-1,5-dicarboxylic acid (AIDA), showed no change in the forced swim test in rats, but decreased the immobility time in the tail suspension test in mice (Smolders et al., 2008).

An mGluR5 antagonist, 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl] pyridine (MTEP), decreased the duration of floating and increased

the duration of mobile behaviors but did not significantly alter the escape behaviors in the modified forced swim test in rats (Belozertseva et al., 2007). MTEP also decreased the immobility time in the forced swim test in rats (Molina-Hernández et al., 2008a,b). However, another group showed that MTEP did not change the behaviors of rats in the forced swim test (Pałucha et al., 2005). MTEP decreased the immobility time in the tail suspension test in mice (Belozertseva et al., 2007; Pałucha et al., 2005) and in the forced swim test in mice (Li et al., 2006). Repeated administration of MTEP attenuated the hyperactivity of OB rats in the open field test (Pałucha et al., 2005). MTEP increased the number of reinforcers obtained in the differential reinforcement of the low-rate 72-s task as effectively as desipramine (Molina-Hernández et al., 2006).

Another mGluR5 antagonist, 2-methyl-6-(phenylethynyl)-pyridine (MPEP), decreased the immobility time in the forced swim test in mice (Li et al., 2006). MPEP also decreased the immobility time of mice in the tail suspension test (Belozertseva et al., 2007; Tatarczyńska et al., 2001). In another report, however, MPEP did not show any significant antidepressant effects in the tail suspension test in mice (Smolders et al., 2008). MPEP also did not show any antidepressant effects in the forced swim test in rats (Tatarczyńska et al., 2001). Repeated administration of MPEP reversed the increase in the number of trials required for learning passive avoidance in OB rats (Pilc et al., 2002; Wierońska et al., 2002). Chronic treatment with MPEP increased the hippocampal BDNF mRNA levels but reduced the cortical BDNF mRNA levels, while desipramine increased the BDNF mRNA levels in both of these brain regions (Legutko et al., 2006). Overall, there appear to be some discrepancies, since some data showed little or insignificant antidepressant-like efficacies of group I mGluR antagonists in mice or rats. Compared with the effects of existing antidepressants, the potential antidepressant activities of group I mGluR antagonists require further investigation.

6.3.2. Group II mGluRs: mGluR2/3 antagonists and agonists

Group II mGluR antagonists exhibit antidepressant-like activities in rodent models. LY341495, a group II mGluR antagonist, reduced the immobility time in the forced swim test in mice (Bespalov et al., 2008) and rats (Chaki et al., 2004). LY341495 also reduced the immobility time in the tail suspension test in mice (Chaki et al., 2004). Repeated administration of MGS0039, another group II mGluR antagonist, to rats elicited a significant reduction in the increased number of escape failures in the LH paradigm (Yoshimizu et al., 2006). MGS0039 also reduced the immobility time in the tail suspension test in mice (Chaki et al., 2004; Karasawa et al., 2005) and decreased the immobility time in the forced swim test in rats (Chaki et al., 2004). The antidepressant effects of MGS0039 were prevented by pretreatment with NBQX (Karasawa et al., 2005), suggesting the role of AMPA receptors. Oral administration of the prodrug of MGS0039 also reduced the immobility time in the forced swimming test in rats and the tail suspension test in mice (Yasuhara et al., 2006).

Meanwhile, mGluR2/3 agonists may only produce antidepressant effects when combined with existing antidepressants. LY354740, an mGluR2/3 agonist, showed no effects in the forced swim test or the tail suspension test in mice (Kłodzińska et al., 1999). Furthermore, LY379268, another mGluR2/3 agonist, did not show any antidepressant effects in the forced swim test in rats (Smolders et al., 2008). However, treatment with LY379268 induced BDNF mRNA expression in the cerebral cortex and hippocampal formation in mice (Di Liberto et al., 2010). These effects of LY379268 on BDNF expression were blocked by LY341495, which did not influence BDNF expression when administered alone. LY379268 combined with fluoxetine increased cell proliferation and neurogenesis in cultured cerebellar granule neuroprecursors (Matrisciano et al., 2007). In experiments using the forced swim test in FSL rats, a model in which immobility time is known to be reduced by chronic treatment with antidepressants, short-term combination treatment with LY379268 and chlorimipramine induced a substantial decrease in the total immobility time, while short-term treatment with either drug alone had little effect (Matrisciano et al., 2007, 2008). Although the mGluR2/3 antagonists and agonists appear to work in different directions, these ligands show antidepressant-like effects and potentiate the effects of antidepressants that act on monoaminergic neurons, respectively. The mechanisms of action for group II mGluR ligands in treatment of depression when administered alone and in combination with existing antidepressants are of interest.

6.3.3. Group III mGluRs: mGluR4, mGluR6, mGluR7, and mGluR8 agonists

A group III mGlu receptor agonist, (1*S*,3*R*,4*S*)-1-aminocyclopentane-1,3,4-tricarboxylic acid (ACPT-I), decreased the immobility time of rats in the forced swim test (Kłak et al., 2007; Pałucha et al., 2004; Tatarczyńska et al., 2002). However, a selective mGluR6 agonist, 2-amino-4-(3-hydroxy-5-methylisoxazol-4-yl) butyric acid (Homo-AMPA), did not change the behaviors of rats in the forced swim test (Pałucha et al., 2004). The reason for the ineffectiveness of this selective mGluR6 agonist in models of depression may be that there is a very low density of mGluR6 in the rat hippocampus (Shigemoto et al., 1997). Among the group III mGluRs, expressions of mGluR4, mGluR7, and mGluR8 in the rat hippocampus have been reported (Shigemoto et al., 1997). A selective mGluR8 agonist, (*RS*)-4-phosphonophenylglycine ((*RS*)-PPG), decreased the immobility time of rats in the forced swim test (Pałucha et al., 2004). AMN082, an mGluR7 agonist, induced a reduction in the immobility time in the forced swim test in rats (Pałucha-Poniewiera et al., 2010) and mice (Palucha et al., 2007) and in the tail suspension test in mice (Pałucha-Poniewiera et al., 2010; Palucha et al., 2007). A positive allosteric modulator of mGluR4, *N*-phenyl-7-(hydroxyimino)cyclopropa[*b*] chromen-1a-carboxamide (PHCCC), was not effective when administered alone but decreased the immobility time of rats in the forced swim test when coadministered with a dose of ACPT-I that was also ineffective singly (Kłak et al., 2007). Taken together, these results suggest that the stimulation of group III mGlu receptors by selective agonists or allosteric modulators may be of value in the treatment of depression.

6.4. Glutamate transporter EAAT2: the enhancer ceftriaxone

EAATs located on the plasma membrane of neurons and glial cells rapidly terminate the actions of glutamate and maintain its extracellular concentration below excitotoxic levels (Danbolt, 2001; Shigeri et al., 2004). Ceftriaxone, a β-lactam antibiotic, increased both the brain expression of EAAT2 and its biochemical and functional activities (Rothstein et al., 2005). Ceftriaxone treatment reduced the immobility time in the forced swim test and the tail suspension test in mice (Mineur et al., 2007). Removal of excess glutamate by enhanced glutamate uptake may improve depression (Sattler and Rothstein, 2007).

6.5. Minocycline

Minocycline, a tetracycline antibiotic, had no effect on the development of the immobility response during the forced swim test in rats (Deak et al., 2005). However, another study found that minocycline decreased the immobility time in the forced swim test in rats (Molina-Hernández et al., 2008a,b). A metabolic pathway of L-tryptophan, an essential amino acid, may lead to NMDA receptor activity in the brain (Hashimoto, 2009a, 2009b, 2009c; Miura et al., 2008). L-tryptophan is metabolized by indoleamine 2,3-dioxygenase, which is a rate-limiting enzyme in the kynurenine pathway, leading to the formation of L-kynurenine. Subsequent metabolism of L-kynurenine leads to the formation of kynurenic acid, an endogenous NMDA receptor antagonist, and quinolic acid, an endogenous NMDA receptor agonist. Lipopolysaccharide (LPS) increased the kynurenine/tryptophan ratio in

both the plasma and brain, and minocycline attenuated all these LPS-induced increases (O'Connor et al., 2009). Administration of L-kynurenine or LPS increased the immobility time of mice in the forced swim test and the tail suspension test (O'Connor et al., 2009), and minocycline decreased the LPS-induced increase in the immobility time of mice in both tests (O'Connor et al., 2009). These findings suggest that LPS may activate the kynurenine pathway and that minocycline may exert antidepressant-like effects through blockade of the kynurenine pathway. However, the relationship between the antidepressant-like effects and the actions of minocycline in glutamatergic signaling remain unclear. Further studies are required to address these issues.

Recently, Hashimoto and Ishima (2010) reported that minocycline potentiated nerve growth factor (NGF)-induced neurite outgrowth in PC12 cells, and that a marked increase of the eukaryotic translation initiation factor eIF4AI protein by minocycline might be involved in the mechanisms of action of this drug. Considering all these results, it is likely that the neurotrophic/neuroprotective activity of minocycline is involved in the antidepressant effects of this drug, although a further study is necessary.

6.6. Riluzole

Riluzole inhibits presynaptic glutamate release, antagonizes NMDA, AMPA, and kainate receptors, and potentiates glial glutamate uptake at rather high concentrations (Pittenger et al., 2008). Rats exposed to chronic unpredictable stress show a decrease in the ratio of sucrose *versus* water consumed in the sucrose preference test and a higher number of escape failures in the active avoidance test. These behavioral activities, respectively representative of anhedonia and helplessness, were reversed by chronic treatment with riluzole (Banasr et al., 2010). Riluzole also blocked the chronic, unpredictable stress-induced decreases in ^{13}C-acetate metabolism in glia in the prefrontal cortex. Single and subchronic riluzole treatment reduced hyperemotionality, which was manifested as increases in the attack, startle, struggle, and fight responses, in OB rats (Takahashi et al., 2011). Moreover, *in vivo* microdialysis revealed that single riluzole treatment significantly decreased the extracellular glutamate levels in the medial prefrontal cortex of OB rats. Riluzole thus seems to exert its antidepressant effects via glutamate-modulating actions in the rat prefrontal cortex. However, further studies are required to clarify the underlying mechanisms.

7. Summary

Monoamine reuptake inhibitors have been used as antidepressants for several decades now. Recent preclinical and clinical studies on depression have placed a spotlight on the roles of glutamatergic signaling in the pathophysiology of MDD and glutamatergic agents that are expected to comprise one of the next generations of antidepressants. A general hypothesis appears to be emerged from multiple lines of clinical and supportive preclinical evidences. It seems that MDD is associated with elevation of glutamate levels and reduction of glutamate levels is one of the possible mechanisms of antidepressants. Increase of glutamate levels in serum and brain of patients with MDD were observed (See Section 2.1). The expression levels of EAATs were reduced and decrease of glutamate uptake was observed in brain of LH rats (See Section 4.1). Furthermore, antidepressant treatment reduced the serum glutamate levels in patients with MDD (See Section 2.1). The chronic antidepressant treatments prevented the increase in glutamate release in rats subjected to acute stress and reduced the glutamate release in normal rats (See Sections 5.1 and 5.2). The EAAT2 enhancer ceftriaxone improved the depressive behavior in mice (See Section 6.4).

Controlling of glutamate levels in brain may be useful for the suppression of depressive symptoms. Existing antidepressant treatments may exert their effects, albeit in part, via glutamatergic signaling. Both glutamatergic and monoaminergic systems play complex and complementary roles in the limbic system. The interactions between the glutamatergic transmission and monoamine modulation systems seem to be successful in explaining some of the symptoms of depression (Pralong et al., 2002). Meanwhile, the currently available antidepressants do not completely meet medical needs in view of their slow onset and side effects as well as the existence of non-responders. The NMDA receptor antagonists with a very rapid onset, such as ketamine, would be superior in efficacy to the existing antidepressants. In fact, not only ketamine but also the NR2B antagonist CP-101,606 and high doses of memantine, exerted the antidepressant effects in the patients with MDD (See Section 3) and some preclinical data support these clinical findings. The NMDA receptor subunit NR2A dysfunction induced antidepressant-like behaviors in the genetic model (See Section 4.2). Chronic treatment of the antidepressant inhibited the increase of NMDA receptor subunit NR1A levels in the depression model (See Section 5.1). Chronic ECS treatment is thought to reduce the NMDA receptor function (See Section 5.3). Several NMDA receptor antagonists showed the antidepressant effects in animal models (See Section 6.1).

Although there appears to be no doubt that NMDA antagonists have the antidepressant action, the mechanism remains unclear. First, there is a discrepancy against the changes of the NMDA receptor levels in depression. At least, overactivation of NMDA receptors has not become definite in brain of patients with MDD. Instead, levels of NMDA receptor subunit NR1, NR2A, and NR2B were decreased in cortex in the patients with MDD (See Section 2.2). However, binding densities of specific ligands for a glutamate site on NMDA receptors were increased in hippocampus but not in cortex in the patients with MDD (See Section 2.2). These findings hint the possibility that NMDA receptors with a particular subunit in a limited region in brain may be over-activated and related to the expression of the depressive symptoms. Animal models for depression showed the controversial results about the changes of the levels of NMDA receptors and their subunits (See Section 4.1). Further in-depth preclinical investigation is necessary and may help to clarify the mechanisms. The signaling pathway through which ketamine exerts its rapid-onset, antidepressant-like effects has become increasingly apparent by using animal models. In any case, NMDA receptor antagonists generally have psychotomimetic side effects. Strengthening the selectivity for specific subunits may improve the tolerability. Alternatively, AMPA receptors or mGluRs may also be good targets.

Alterations in some types of glutamatergic receptors are shown in stress-induced animal models for depression or genetic strains with depressive features. However, it is necessary to clarify whether these changes are linked to depressive symptoms. Naturally, further investigations into the changes in glutamatergic signaling systems in patients with MDD are necessary to examine the feasibility of extending the results of these animal models to humans. Genetically modified animals may allow interpretation of the relationships between the targeted glutamatergic components and the expression of depressive symptoms. Behavioral and biological analyses of these animal models could be useful not only for unveiling the mechanisms of the disease but also for validating gene products as targets for developing new types of drugs. So far, the forced swimming test and the tail suspension test have been often used for evaluation of not only monoaminergic antidepressants but also glutamatergic compounds. It appears to be meaningful and effective to examine properties of antidepressant effects of NMDA antagonists in other models such as LH and CMS, in which acute treatments of ketamine but not monoaminergic drugs showed the antidepressant effects. These findings might partly reflect the effects in patients with treatment-resistant MDD. Evaluation of candidate drugs for their antidepressant-like actions using well-validated preclinical models could help in the search for the next generation of antidepressants.

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