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Review

Glutamate signaling in the pathophysiology and therapy of schizophrenia

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ABSTRACT

Glutamatergic neurotransmission, particularly through the N-methyl-D-aspartate (NMDA) receptor, has drawn attention for its role in the pathophysiology of schizophrenia. This paper reviews the neurodevelopmental origin and genetic susceptibility of schizophrenia relevant to NMDA neurotransmission, and discusses the relationship between NMDA hypofunction and different domains of symptom in schizophrenia as well as putative treatment modality for the disorder. A series of clinical trials and a meta-analysis which compared currently available NMDA-enhancing agents suggests that glycine, D-serine, and sarcosine are more efficacious than D-cycloserine in improving the overall psychopathology of schizophrenia without side effect or safety concern. In addition, enhancing glutamatergic neurotransmission via activating the AMPA receptor, metabotropic glutamate receptor or inhibition of D-amino acid oxidase (DAO) is also reviewed. More studies are needed to determine the NMDA vulnerability in schizophrenia and to confirm the long-term efficacy, functional outcome, and safety of these NMDA-enhancing agents in schizophrenic patients, particularly those with refractory negative and cognitive symptoms, or serious adverse effects while taking the existing antipsychotic agents.

Contents

1. Introduction

There are plenty of studies which have suggested that dysregulation of dopaminergic (Davis et al., 1991; Toda and Abi-Dargham, 2007), γ-aminobutyric acid (GABA) (Benes and Berretta, 2001; Lewis et al., 2005), glutamatergic (Goff and Coyle, 2001; Moghaddam, 2003)

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neurotransmission and their interactions (Carlsson et al., 2001) are involved in the pathophysiology of schizophrenia. Among these, the hypofunction of N-methyl-D-aspartate (NMDA) glutamatergic neurotransmission has gained much attention since two decades ago (Olney and Farber, 1995; Javitt, 2008).

Conventional antipsychotics, which block D2 dopamine receptors (Farde et al., 1986), exert effects mainly on positive symptoms. Second-generation antipsychotics (SGAs) have been suggested to be superior to conventional agents in terms of efficacy for positive symptoms, negative symptoms and cognitive deficits but the therapeutic gain is modest (Green et al., 1997; Lane and Chang, 1999; Leucht et al., 2003; Livingston, 1994). Overall, there is a considerable percentage of patients resistant or only partially responsive to available antipsychotic medications (Lieberman et al., 2005). Life threatening side-effect profiles of SGAs, particularly the metabolic syndrome, limit the clinical use of these agents (Lu et al., 2004; Newcomer, 2007; Simon et al., 2009). Moreover, most schizophrenic patients still suffer from lifelong illness and deteriorating function (Hwu et al., 2002; Malla and Payne, 2005; Tsuang et al., 2000). Hence, there is a great need to develop new therapies that will provide better long-term efficacy, functional improvement and safety profiles for schizophrenic patients.

1.1. Glutamate receptors: ionotropic and metabotropic receptors

Glutamate is the most abundant amino acid neurotransmitter in the mammalian brain. There are two types of glutamate receptors: metabotropic and ionotropic receptors. More evidence regarding the involvement of glutamatergic system in schizophrenia focuses on the ionotropic receptors which are subdivided to 3 subtypes: NMDA, quisqualate/α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate (Lodge, 2009). Relief of the depolarization blockade of NMDA receptor requires the activation of non-NMDA receptor. Studies on long-term potentiation (LTP) indicate that NMDA receptors interact with AMPA receptors (Yu et al., 2008). However, the NMDA receptor is the best studied and most relevant subtype of glutamate receptors to understand the pathophysiology of schizophrenia. The NMDA receptor has been demonstrated to play an important role in neurocognition and neurotoxicity (Lipson and Rosenberg, 1994; Kalia et al., 2008). The psychosis due to the blockade of the NMDA receptor is similar to the clinical manifestation of schizophrenia. Up to date, NMDA synapse remains to be the only therapeutic target that is confirmed to have clinical efficacy. Thus, we will focus on the glutamatergic neurotransmission via NMDA receptor in the following review.

1.2. NMDA receptor and synapse

In addition to the agonists and coagonists, the NMDA receptor can be regulated by a variety of molecules, including polyamines, proton, zinc, magnesium, phencyclidine (PCP) and ketamine. These sophisticated regulatory mechanisms suggest that NMDA receptor can adapt to endogenous and exogenous signals to maintain and facilitate a variety of vital brain functions including cognition, memory, neurodevelopment, synaptic plasticity and psychosis (Bliss and Collingridge, 1993).

The NMDA receptor is composed of multiple subunits including NR1 and one of either the NR2 (NR2 A–D) or NR3 (NR3 A–B) to form heteromeric receptor-channels with different pharmacologic and biophysical characteristics (Laurie and Seeburg, 1994) (Fig. 1). The NMDA receptor possesses a number of unique characteristics. For example, it has binding sites not only for glutamate or aspartate, but also a separate coagonist site for the endogenous ligands, D-serine, D-alanine, and glycine. Occupancy of the coagonist site can increase the frequency of opening of the channels activated by NMDA agonists, facilitating excitatory transmission in the brain (Johnson and Ascher, 1987). In fact, the binding of both glycine (or D-serine, D-alanine (Chessell et al., 1991)) and glutamate is required to open the NMDAR channel ionophore (Mayer et al., 1989; Nong et al., 2003; Thomson et al., 1989) (Fig. 1).

Since D-alanine, which presents only in the pituitary, is less likely to play physiological role in the neocortex, most studies focused on the binding of D-serine and glycine on the D-serine/glycine site of NMDAR. Endogenous D-serine/glycine site agonists also play a role in neuromodulation. Binding to the D-serine/glycine site enhances the affinity and efficacy of the glutamate neurotransmission (Fadda et al., 1988), increases the duration and frequency of the open channel state (Vyklický et al., 1990), and promotes turnover of the NMDAR (Nong et al., 2003). Distribution of D-serine parallels to that of NR1, and D-Serine binds more tightly to the NMDAR than glycine (Furukawa and Gouaux, 2003).

The NMDAR D-serine/glycine site on the NR1 subunit is not fully saturated at synapses in brain regions such as the prefrontal cortex, neocortex, hippocampus, thalamus and brainstem slices, suggesting that agonists of the D-serine/glycine site are capable of regulating NMDAR-mediated neurotransmission (Labrie and Roder, 2010). Glycine is abundant throughout the brain and serves as a major inhibitory neurotransmitter in the hindbrain. Synaptic concentrations of glycine are primarily derived from astroglial cells, and its clearance is mediated by glycine transporter 1 (GlyT-1) (Kinney et al., 2003; Lim et al., 2004). D-Serine has been found to be more potent than glycine in targeting the D-serine/glycine site of most NMDARs (Boehning and Snyder, 2003).

Treatment with DAO results in depletion of D-serine which has been shown to attenuate NMDAR activity in cerebellar and hippocampal slices, hippocampal cell cultures, and retina preparations (Mothet et al., 2000; Gustafson et al., 2007). Supporting the physiological role, DAO inhibitor can facilitate the effects of D-serine on prepulse inhibition (PPI) (Hashimoto et al., 2009). D-Serine levels were reduced in the cerebrospinal fluid of drug na ve patients with schizophrenia (Hashimoto et al., 2005; Bendikov et al., 2007). Diminished D-serine along with elevation in L-serine also suggests a dysfunction of serine racemase (SRR) activity (Hashimoto et al., 2003). Changes in SRR protein expression have been found in the postmortem brains of schizophrenic individuals (Bendikov et al., 2007; Steffek et al., 2006; Verrall et al., 2007). Similarly, glycine levels have been found to be reduced in drug-free schizophrenic individuals and inversely correlate with the severity of negative symptoms (Sumiyoshi et al., 2004; Neeman et al., 2005). However, high-dose glycine impairs the prepulse inhibition measure of sensorimotor gating in humans, which does not support the glycine treatment for cognition (O'Neill et al., 2010). Due to glycine's complex metabolism of both excitatory and inhibitory signaling, D-serine is likely a better choice than glycine when considering applying full agonist for treatment.

Other regulators involved in the metabolism of D-serine such as D-amino acid oxidase (DAO) (Verrall et al., 2007; Bendikov et al., 2007), protein-interacting with kinase C (PICK1) (Beneyto and Meador-Woodruff, 2006) and alanine–serine–cysteine transporter 1 (Asc-1) (Burnet et al., 2008) were also found to be related to the D-serine levels. Depletion of D-serine was found to be associated with NMDAR-mediated neurological functions and NMDAR-induced neurotoxicity, as well as NMDAR-dependent LTP in many brain regions especially the hippocampus (Gustafson et al., 2007; Shleper et al., 2005; Mothet et al., 2006). D-Serine supplement can entirely reverse the effects of decreased NMDAR-mediated neurotransmission (Mothet et al., 2000, 2006; Yang et al., 2003; Panatier et al., 2006; Gustafson et al., 2007), moreover, enhance NMDAR signaling demonstrated both in vitro (Chen et al., 2003; Martina et al., 2003; Yang et al., 2003; Chapman et al., 2003) and in mice which lack DAO activity (Wake et al., 2001), Acs-1 (Xie et al., 2005) or have diminished GAD67 expression (Reynolds et al., 2004; Torrey et al., 2005). In human genetic studies, significant associations between DAO (Ohnuma et al., 2009) and G72 (DAOA)/G30 (Shinkai et al., 2007) gene polymorphisms and schizophrenia were also observed in case–control association analyses.

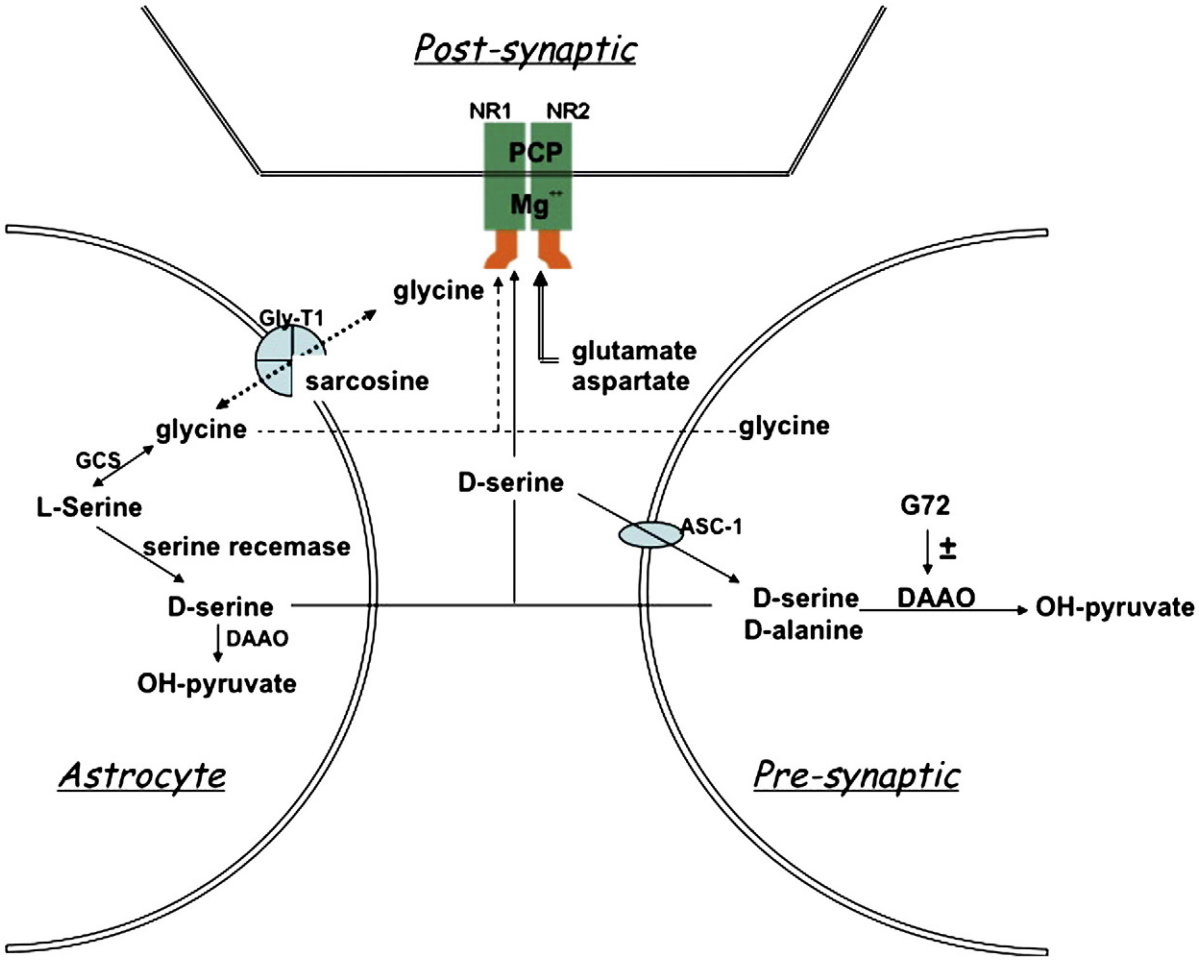

Fig. 1. The known regulators and potential drug targets of NMDA synapse which include the "glycine" coagonist site on NR 1 subunit, serine racemase, D-amino acid oxidase (DAAO), D-amino acid oxidase activator (DAOA, G72) and D-serine uptake site (ASC-1). Aspartate and glutamate are agonists; glycine and D-serine are coagonists of the NMDA receptor. Magnesium blockage is released upon depolarization. PCP is a channel blocker. D-Serine is synthesized by serine racemase from L-serine. D-Serine is localized to both neurons and glial cells and is uptaken via ASC-1. D-Serine is metabolized by DAAO into hydroxy pyruvate. The degradation is inhibited by benzoate. Role of DAOA as an activator or inhibitor is unclear. Glycine is uptaken by GlyT-1 and metabolized to L-serine by GCS. Sarcosine inhibits the glycine uptake through GlyT-1. ASC-1, arginine–serine–cysteine transporter-1; ASP, aspartate; DAAO, D-amino acid oxidase; DAOA, D-amino acid oxidase; GCS, glycine cleavage system; GLU, glutamate; GlyT-1, glycine transporter 1; NR1,2, NMDA receptor subunit 1,2; and PCP, phencyclidine.

1.3. Metabotropic glutamate receptor

mGluRs are relevant to schizophrenia as they have a role in modulating NMDAR-mediated neurotransmission. mGluRs are guanine nucleotide binding proteins [G] protein coupled receptors. When mGluRs are activated by glutamate, they release GDP, which subsequently alters activities of enzymes, ion channels, and vesicle transport. There are 8 subtypes of mGluRs, classified into 3 groups based on signaling pathways, pharmacology properties, and similarities in DNA sequences. Group 1 mGluRs use G_q proteins, and when activated by glutamate, signaling cascade involves phospholipase C which cleaves phosphatidylinositol-4-5 bisphosphate into diacylglycerol and inositol 1, 4, 5-triphosphate results in calcium release. Group 2 and Group 3 mGluRs interactions with $G_{1/o}$ species and signaling proteins include adenyl cyclase, which creates cyclic adenosine monophosphate (cAMP). mGluRs have been found at presynaptic glutamate terminals and GABA interneurons (Herron et al., 1986). Group 1 mGluRs can be found near synaptic dendritic spines, mGluR5 is located in the cortex, and hippocampal mGluR2 and mGluR3 are located both pre and postsynaptically on glutamatergic and GABAergic neurons. mGluR3 is also found in glia. One of the most striking effects of mGluR activation in a number of areas in the brain is promoting NMDAR-mediated neurotransmission (Conn et al., 2008). Specifically, Group 1 mGluRs increase presynaptic glutamate release, while Group 2 mGluRs decrease presynaptic glutamate release.

There exists a positive feedback mechanism between mGluR5 and NMDAR in which activation of mGluR5 potentiates NMDAR generated currents, and NMDAR mediated depolarization results in activation of a serine/threonine protein phosphatase that dephosphorylates mGluR5, which reverses desensitization of mGluR5, thereby allowing mGluR5 to be depolarized again (Alagarsamy et al., 1999). mGluR5 is located in the hippocampus and cortex, especially postsynaptic in CA 1 pyramidal cells. mGluR5 is also found in GABA neurons. Animal models of GluR5 knockouts exhibit decreased EPSP in the hippocampus and deficient NMDA dependent LTP and learning, indicating that mGluR5 is needed to maintain normal NMDAR-mediated neurotransmission. In addition, mGluR5 antagonists increase the effects of NMDAR antagonists. Group 2 mGluRs decrease glutamate release from presynaptic terminals, and likely function as autoregulation to protect neurons from excitotoxicity.

Group 2 mGluRs agonists block the effects of psychotomimetic agents on glutamatergic neurotransmission (Conn et al., 2008). Interestingly, however, activating mGluR2s has a paradoxical effect on dopamine release. Van Berckel et al. (2006) studied a mGluR2 agonist, LY354740 effect in four baboons. Amphetamine administration increased DA synaptic concentration as evidenced by decreased

D2 receptor binding by [^{11}C]raclopride, detected by PET scanning. In baboons treated by LY354740 there were even less unoccupied D2 receptors, indicating that stimulation of Group 2 mGluRs, thereby decreasing glutamatergic neurotransmission, increased in amphetamine induced release of dopamine in non human primates. However, the relationship between glutamate and dopamine is complex, as midbrain DA neurons are both activated by glutamate directly and inhibited indirectly by glutamate's effects on GABAergic interneurons. In terms of potential drug development, research has focused on Group 1, which includes mGluR1 and mGluR5, and Group 2, which includes mGluR2 and mGluR3.

2. Neurodevelopmental origin and genetic vulnerability of schizophrenia

Since NMDA receptor is essential and ubiquitous, it is highly regulated. Only when genetic insult(s) reaches a threshold of low NMDA function and impair the neurodevelopment, the nervous system will become vulnerable to schizophrenia. Findings from genetic studies suggest that the accumulation of multiple variations of candidate genes, rather than any single gene, may serve as a general model for the pathogenesis of schizophrenia (Girirajan and Eichler, 2010). Several susceptible factors have been identified, including D-amino-acid oxidase (DAO) (Chumakov et al., 2002), G72 (also called D-amino acid oxidase activator (DAOA)) (Detera-Wadleigh and McMahon, 2006), dysbindin-1 (Talbot et al., 2004), neuregulin-1 (NRG1) (Stefansson et al., 2002), regulator of G-protein signaling 4 (RGS4) (Chowdari et al., 2002), Disrupted-in-Schizophrenia 1 (DISC1) (Millar et al., 2000), the C-terminal PDZ domain ligand of neuronal nitric oxide synthetase (CAPON) (Brzustowicz et al., 2004), neuronal PAS domain protein 3 (NPAS3) (Pickard et al., 2005) and microdeletion of chromosome 22q11 (Bassett and Chow, 1999). Most of these schizophrenia-associated genes influence the neuronal differentiating and migration processes (Kamiya et al., 2005).

Schizophrenia is a chronic and devastating mental disorder, of which the onset is primarily in late adolescence and adulthood. Various lines of evidence, including susceptibility genes (Jaaro-Peled et al., 2009; Shi et al., 2008; Walsh et al., 2008), environmental risk factors (Cannon et al., 2002), interaction between genetic and environmental factors (Cardno et al., 1999; Singh et al., 2004) and epigenetic changes (Singh and O'Reilly, 2009), have supported that there are deficits during neurodevelopment that underlie the pathophysiology of the disorder. These risk factors have been proposed to operate synergistically on both neurodevelopment and glutamate-associated signaling (Hayashi-Takagi and Sawa, 2010).

Reorganization of synapses occurs extensively during postnatal brain development until young adulthood, and one of the major changes is reorganization of glutamatergic synapses in which the NMDA receptor plays a key role (Matsuzaki et al., 2004). NR2A and NR2B subunits have different conductance and calcium permeability. NR2A and NR2B subunits are highly expressed in the forebrain corticolimbic regions and undergo a developmental shift: progressively switching from richness in NR2B subunits in the early postnatal brain into richness in NR2A subunits during development (Quinlan et al., 1999; Sheng et al., 1994). A primary role of this shift is to change the threshold for modifying synaptic strength. Therefore, the NR2A/NR2B ratio contributes significantly to the development of cortical functions (Yashiro and Philpot, 2008). This developmental switch will result in changes in brain plasticity and synaptic transmission (van Zundert et al., 2004). Another important neurodevelopmental process called "synaptic pruning," in which synapses are reorganized into more efficient configurations, also involves glutamatergic synapses (Bourgeois and Rakic, 1993). Plausible scenario of schizophrenia includes "faulty" molecular switch early on or over-pruning later during adolescents (Gao et al., 2000; Insel, 2010) which is consistent with a decrease in NMDA receptor density reported in post-mortem brain from schizophrenic patients (Sokolov, 1998).

Consistent with this, N-acetylaspartate, a glutamatergic synapse marker, also changes during adolescence, as evident in magnetic resonance spectroscopy studies (Kadota et al., 2001). Neuroanatomic and neuroimaging studies found that glutamate receptor binding alters in the prefrontal cortex, thalamus, and hippocampus in subjects with schizophrenia (Pilowsky et al., 2006). These findings are supported by molecular studies that glutamatergic spines may be altered as reflected in reduced expression of Cdc42 and Duo mRNAs in patients with schizophrenia (Hill et al., 2006). Many schizophrenia risk factors involve the postsynaptic components, including NRG1 receptor erbB4 (Li et al., 2007), nNOS (Cheah et al., 2006), DISC1 (Hayashi-Takagi et al., 2010), NMDA receptor subunit 2B (GRIN2B) (Hashimoto et al., 2007) and postsynaptic density (PSD) (Sheng and Hoogenraad, 2007). One of the critical synaptic components, D-serine, an endogenous co-agonist of the NMDA receptor generated from L-serine by serine racemase (SRR) (Wolosker et al., 1999) and degraded by DAO (Nagata, 1992), is also involved in the pathology of schizophrenia (Fig. 1). Taken together, glutamatergic synapse, particularly the NMDA synapse, may contribute to the pathophysiology for schizophrenia. Exploiting these novel findings, rather than the dopaminergic and serotoninergic theory, can instill hope for new treatment strategy.

3. Evidence of NMDA hypofunction in schizophrenia

Much evidence suggests that hypofunction of NMDA receptor-mediated neurotransmission is a critical deficit in schizophrenia (Bachus and Kleinman, 1996; Coyle, 1996; Javitt, 2004; Olney and Farber, 1995). The involvement of the NMDA system in schizophrenia is further evidenced by the effects of the NMDA-receptor antagonists, PCP and the dissociative anesthetic, ketamine, both of which induce psychiatric and physiological changes resembling schizophrenia more closely than the symptoms induced by amphetamine/dopamine agonist (Kudoh et al., 2000; Radant et al., 1998; Krystal et al., 1994). The hypothesis originated from the study of a recreational and dissociative drug, phencyclidine, which was formerly used as an anesthetic agent, exhibiting hallucinogenic and neurotoxic effects. Developed in 1926, it was first patented in 1952 by the Parke-Davis pharmaceutical company and marketed under the brand name Sernyl. Luby et al. (1959) first studied phencyclidine as a schizophrenomimetic drug. PCP causes not only positive and negative symptoms similar to amphetamine, but also cognitive deficits associated with schizophrenia (Mouri et al., 2007; Nabeshima et al., 2006).

Animal studies of the treatment with MK801, the NMDA channel blocker, impaired cognitive flexibility and working memory in rat pups, suggesting that a brief disruption of NMDA receptors is able to produce selective cognitive deficits that are relevant to schizophrenia (Stefani and Moghaddam, 2005). Glycine transporter inhibitors could also reverse PCP-induced effects. In behavioral studies, the potency of a series of GlyT1 antagonists for the inhibition of PCP-induced hyperactivity in vivo correlated significantly with their potency in antagonizing GlyT1 in vitro (Javitt et al., 1999). In rodents, treatment with N[3-(4k-fluorophenyl)-3-(4k-phenylphenoxy)propyl]sarcosine prevents dopaminergic dysregulation following chronic or subchronic PCP administration (Javitt et al., 2004), and improves MK-801-induced cognitive deficits (Karasawa et al., 2008). Furthermore, GlyT1 heterozygous knockout mice are more resistant to PCP-induced disruption of PPI and possess better working memory (Tsai et al., 2004b).

Significant increase in positive, negative and disorganized symptoms (Lahti et al., 2001), as well as thought disorder(Adler et al., 1999), is seen in both normals and subjects with schizophrenia when given subanesthetic dose of ketamine. NMDA blockade by ketamine reproduces some of the cognitive deficits shared by patients with

schizophrenia, such as impaired performance on the Wisconsin Card Sorting Test (WCST), decrease in verbal declarative memory, delayed word recall and verbal fluency, and impaired spatial and verbal learning performance by using the virtual Morris water task (Rowland et al., 2005), suggesting impaired hippocampal and frontal functioning in schizophrenia (Malhotra et al., 1997; Newcomer et al., 1999). Moreover, glycine transporter inhibitors reverse the behavioral and neurochemical effects of PCP (Buchanan et al., 2007; Javitt et al., 2004, 1999). These findings support the hypothesis that symptoms of schizophrenia could arise from attenuated NMDAR-mediated neurotransmission. It can be further proposed that the psychotomimetic effects may be caused by not only noncompetitive antagonists but also any dysfunctional attenuation of the NMDA receptor-mediated neurotransmission.

NMDA ionophore blockers are a universally strong psychotomimetic. Nabeshima et al. (2006) testified the hypothesis that attenuated glutamate neurotransmission is involved in the pathophysiology of schizophrenia by demonstrating emotional and cognitive deficits in mice treated with PCP. Repeated PCP treatment resulted in NMDA receptor hypofunction and insufficient extracellular glutamate levels in the prefrontal cortex, indicating that NMDA antagonism impairs both pre- and postsynaptic glutamate transmissions (Nabeshima et al., 2006). However, it is inconclusive whether D-serine/glycine site inhibitors are also potent psychotomimetic agents. Ethanol, at concentrations associated with behavioral psychotomimetic effects in humans, inhibits the NMDAR at the D-serine/glycine site and disrupts the function of the post-synaptic excitatory effects of glutamate, adding to the rationale to enhance NMDA function through the D-serine/glycine site to curtail the psychosis. Inhibition effect of ethanol on the NMDAR in the fetal brain likely contributes to the CNS manifestations of fetal alcohol syndrome which has a global NMDA shutdown and extensive neurodevelopment deficits (Tsai and Coyle, 1998). Whereas MK-801 produced characteristic neuronal vacuolization and necrosis in the posterior cingulated/retrosplenial cortex, ACEA 1021, another D-serine/glycine site inhibitor, had no effect on neuronal morphology and has minor psychotomimetic and amnestic effects in rats (Kretschmer et al., 1997). Accordingly, we consider that upregulating the NMDA function by the D-serine/glycine site for the treatment of schizophrenia will not be overtly strong to produce toxic side effects by over-activating the glutamate binding site.

Two lines of studies shown below support the pharmacological model of NMDA hypofunction as being involved in schizophrenia. First, to correct hypofunction of NMDA receptor, upregulation of the NMDA receptor has been proposed as a therapy for schizophrenia (Deutsch et al., 1989; Javitt, 2008; Javitt and Zukin, 1991). Agents directly or indirectly enhance the NMDA function had been tested to determine their efficacy for the treatment of schizophrenia. Clinically, augmentation through the NMDA-glycine site is preferred to avoid the well known excitotoxicity mediated through the glutamate binding site (Coyle and Puttfarcken, 1993; Javitt, 2008; Javitt et al., 2004; Leeson and Iversen, 1994). The generally accepted goal of NMDA-enhancement is accomplished through activating the D-serine/glycine coagonist site.

The second line of evidence comes from a series of genetic linkage and association studies that point to a defect on the glutamatergic synapses that can contribute to the hypofunction of NMDA neurotransmission in schizophrenia (Harrison and Weinberger, 2005). Genetic studies in schizophrenia have been performed extensively over the last two decades, resulting in thousands of published reports cataloged in the SchizophreniaGene (SZGene) database of the Schizophrenia Research Forum (Shi et al., 2008). Up to 20 susceptibility genes, replicated or not, have been found to be associated with schizophrenia (Norton et al., 2006; O'Tuathaigh et al., 2007; Shi et al., 2008), including proline dehydrogenase (PRODH), dysbindin (DTNBP1), NRG1(Tosato et al., 2005), the DISC1 gene (Sawamura and Sawa, 2006), catechol-o-methyltransferase (COMT), V-AKT murine thymoma viral oncogene homolog 1 (AKT1) and RGS4 (Volk et al., 2010). Significant associations between DAO (Ohnuma et al., 2009) and G72 (DAOA)/G30 (Shinkai et al., 2007) gene polymorphisms and schizophrenia were also observed in case–control association analyses. Many of these genes are related to the glutamatergic neurotransmission systems, such as ionotropic glutamate receptor genes (GRIN1, GRIN2A, GRIN2B and GRIK3), metabotropic glutamate receptor genes (GRM3) and the G72/G30 locus (Qin et al., 2005; Cherlyn et al., 2010; Zhao et al., 2006).

NMDA neurotransmission is influenced by these risk genes, among which only the enzyme that catabolizes D-serine and D-alanine, DAO, a flavoenzyme of peroxisomes existing in the brain, kidney and liver of mammals, and its primate-specific activator G72, are directly involved in the NMDA neurotransmission (Fig. 1). D-Serine is more potent than glycine as the neurotransmitter for the coagonist site of the NMDA receptor (Heresco-Levy et al., 2005; Scolari and Acosta, 2007; Tsai et al., 1998) and DAO is responsible for degrading D-serine, D-alanine, full agonists of the coagonist site (Fukui and Miyake, 1992; Vanoni et al., 1997). G72 regulates DAO activity, enhances metabolism of D-serine and D-alanine, and can attenuate NMDA neurotransmission. Over the past 7 years, more than 30 studies have demonstrated the association of DAO and G72 with schizophrenia (Boks et al., 2007). The genetic findings are consistent with the neurochemical findings that serum and cerebrospinal fluid levels of D-serine are reduced in patients with schizophrenia (Bendikov et al., 2007; Hashimoto et al., 2005).

4. Evidence of NMDA hypofunction in animal genetic models

Several genes associated with glutamatergic NMDA synapses show relevance to schizophrenia (Hui et al., 2009). Some of these genes were studied in animal genetic models to demonstrate their implication in the pathophysiology of schizophrenia.

Mice which express only 5%–10% of the NR1 subunit of the NMDA receptor exhibit schizophrenia-like behaviors, such as abnormalities in motor activity, sensory processing, stereotypy, sexual, and social behavior (Duncan et al., 2004; Mohn et al., 1999; O'Tuathaigh et al., 2010). Although modest impairment in olfactory function may contribute to these social deficits (Duncan et al., 2004; Moy et al., 2008), evidence from these NR1 hypomorphic mice supports the impact of impaired NMDA receptor function in murine with association to negative symptoms in schizophrenia (Halene et al., 2009). Mice with mutations in members of NR2 and NR3 subunits also show varying levels of altered behaviors, including hypoactivity, motor incoordination and changes in PPI (van den Buuse, 2010), a model of sensory gating.

Targeting the glycine binding site of the NMDA receptor 1 (NR1) subunit is another way to modulate NMDA function. Two mouse lines carrying point mutations in the glycine binding site of the NR1 subunit resulted in reduction in glycine binding affinity (Kew et al., 2000). Mutant mice express different levels of NMDA receptor subunits relative to wild type mice, and a mild reduction in glycine binding affinity. The mutation results in an impairment of LTP and spatial learning and alterations in anxiety-related behavior, providing evidence for the role of NMDA receptor dysregulation in behavioral abnormalities of schizophrenia (Kew et al., 2000).

Compound heterozygote mice which exhibit a marked NMDA receptor hypofunction by approximately 90% reduction of glycine affinity reveal deficits in hippocampal LTP, insensitivity to dizocilpine pretreatment and increased startle response but normal PPI (Ballard et al., 2002). These mice also show hyperactivity and stereotyped behavior resistant to suppression by antipsychotics and zolpidem, representing a murine model of severe NMDA receptor hypofunction which is insensitive to pharmacological inhibition (Ballard et al., 2002; van den Buuse, 2010). The involvement of severe dysfunction of NMDA in treatment-resistant schizophrenia as implicated in this model is intriguing. Given the findings, it is not surprising that treatment by antipsychotic is in vain when the deficit is severe NMDA dysfunction.

In contrast to attenuating the NMDA activity by reducing glycine binding, increasing synaptic glycine can enhance NMDA function. Pharmacological studies have suggested that the glycine transporter, GlyT1, regulates concentrations of glycine at synaptic NMDA receptor. While homozygous GlyT1(−/−) mice died within 12 h of birth, heterozygous GlyT1(+/−) mice with a 50% reduction of transcripts exhibit better spatial retention, less sensitivity to an amphetamine disruption of PPI and more sensitivity to the effects of MK-801, a non-competitive antagonist of the NMDA receptor(Tsai et al., 2004b). The finding suggests that agents which inhibit GlyT1 may have the potential in cognitive enhancement and symptom improvement by reversing the NMDA hypofunction in schizophrenia.

Regulating synaptic aspartate and glutamate, however, induces opposite effects from glycine. The glial glutamate and aspartate transporter (GLAST) regulates extracellular glutamate levels via uptake into glia. GLAST knockout mice show locomotor hyperactivity to a novel environment, which has been linked to GABAergic disinhibition of glutamate release and neuronal hyperexcitability in prefrontal cortex and is normalized by haloperidol and the mGlu2/3 receptor agonist (Karlsson et al., 2008). Poor nesting behavior and abnormal sociability, as well as significantly reduced acoustic startle response and impaired learning are also noted in GLAST knockout mice, suggesting that GLAST knockout mice exhibit behavioral abnormalities relevant to the negative and attentional/cognitive symptoms of schizophrenia. The GLAST knockout mechanism of NMDA dysfunction can be due to excitotoxicity, consequently, attenuation of NMDA function, and it provides support for the hypothesis that glutamate dysregulation contributes to the pathophysiology of schizophrenia (Karlsson et al., 2009).

DAO has been linked to risk for schizophrenia in human and animal studies (Corvin et al., 2007). Coadministration of a DAO inhibitor, 5-chloro-benzo[d]isoxazol-3-ol (CBIO), with D-serine, but not D-serine alone, significantly attenuated NMDA antagonist-induced the PPI deficits in mice (Hashimoto et al., 2009). The finding suggests that coadministration of a DAO inhibitor and D-serine has potential for the treatment of schizophrenia.

A synthetic enzyme, SR, converts L-serine to D-serine (Miya et al., 2008) (Fig. 1). Dysfunction in SR causes a reduction in D-serine level, resulting in NMDA hypofunction, indicating that SR is a risk gene candidate for schizophrenia. Genetically modified mice with impaired SR production and consequent inability to produce endogenous D-serine alter glutamatergic neurotransmission, resulting in behavioral changes of hyperactivity and impaired spatial memory to an extent mimicking human schizophrenic syndrome (Basu et al., 2009).

5. NMDA enhancing treatments

Although the NMDA antagonism can account well for the phenomenology of schizophrenia, a critical challenge is whether the NMDA hypothesis can be applied to develop new therapeutic approaches for schizophrenia (Buchanan et al., 2007; Coyle et al., 2002; Javitt, 2004). There have been several NMDA-enhancing agents that can be classified by 3 different mechanisms of action: 1) full agonists of the coagonist site: glycine, D-serine and D-alanine; 2) partial agonist of the coagonist site: D-cycloserine; and 3) GlyT1 inhibitor, that blocks the reuptake of glycine: sarcosine (Fig. 1). Studies have demonstrated clinical benefits of agonists of the coagonist site added to treatment of antipsychotics (other than clozapine) for chronically ill schizophrenia patients, not only on negative symptoms, but also on positive, cognitive, and depressive symptoms when compared with placebo add on treatment (Goff et al., 1999; Javitt et al., 2001; Tsai et al., 1998, 2004a, 2006), with small to medium effect sizes similar to those seen with atypical antipsychotics (Altamura et al., 2007).

Nevertheless, NMDA enhancing treatments have not been optimistic so far for the treatment-resistant schizophrenic patients who receive clozapine treatment. Goff et al. (1996) reported that D-cycloserine caused negative symptoms worsening in clozapine-treated patients. D-Serine and sarcosine showed neither improvement nor deterioration in any type of symptoms (Tsai et al., 1999). These findings might be explained by clozapine's effects on NMDA receptors, older age and longer illness durations of clozapine-treated patients (Tsai et al., 1999).

6. Effects on different symptom domains of schizophrenia: negative symptoms, cognitive deficits and quality of life

Negative symptoms are often refractory to antipsychotic treatment with the exception of clozapine. Although some studies suggest that newer SGAs targeting both dopamine D2 and serotonin 5HT2 receptors (Kapur et al., 1999) are superior to conventional agents for treating negative symptoms but their effects are not unequivocal (Green et al., 1997; Lane and Chang, 1999; Leucht et al., 2003; Livingston, 1994). The NMDA-enhancing agents add-on therapy has been demonstrated to be beneficial on the negative symptoms in chronic schizophrenic patients who have been receiving stable doses of antipsychotics, either conventional or SGAs (Goff et al., 1999; Javitt et al., 2001; Lane et al., 2008; Tsai et al., 1998, 2004a, 2004b, 2006). Since negative symptoms are one of the main causes of disability and poor outcome in schizophrenic patients (Altamura et al., 2007), the effects of NMDA-enhancing agents on negative symptoms thus may improve the long-term functional outcome of schizophrenia.

Deficits in cognitive functions, such as sustained attention, working memory and executive function, have been considered as core symptoms and associated with poor outcome and functioning of schizophrenia more strongly than other symptom domains, including psychotic symptoms of hallucinations or delusions (Altamura et al., 2007; Chen et al., 2004; Chen and Faraone, 2000; Chen et al., 1998; Green, 1996; Liu et al., 2006; Tsuang et al., 2006). However, the cognitive effects of current medications, including conventional or SGAs, are inconclusive at best (Breier, 1999). Furthermore, the differential effects of SGAs, as compared to the conventional antipsychotics, on cognition are small (Goldberg et al., 2007). It's noteworthy that NMDA-enhancing agents can benefit the cognitive factor of the symptom assessment. However, in the CONSIST trial, there is no cognitive effect found (Buchanan et al., 2007). However, rigorous cognitive study of D-serine and other NMDA agents had not been done. Only a small-sized study (Lane et al., 2008) addressed efficacy of glycine analog as a monotherapy for schizophrenia. Most people receive the NMDA agent as add on treatment. Head to head comparison studies to compare efficacy of NMDA treatment and SGAs is needed.

We consider that tonic blockade of the glycine site is much harder to reach than shutting down the channel, which can only be released by depolarization blockade; therefore, the glycine analogs are less potent than NMDA channel blockers to cause positive symptoms and cognitive disruption. At the same time, current clinical trials use NMDA-glycine site analogs, which reach ceiling effects at high doses. Glycine itself is a nonspecific neurotransmitter. High dose D-serine has potential renal toxicity (Kantrowitz et al., 2010). These limitations to escalating the dosages would be a main hurdle to maximize the efficacy.

Other than neurotransmission, synaptic plasticity, memory, and cognition are also regulated by the NMDA receptor (McDonald and Johnston, 1990). Thus, attenuation of NMDA receptor-mediated neurotransmission can result in loss of neuronal plasticity and cognitive deficits. Olney and Farber (1995) proposed that hypo-NMDA function induced by NMDA receptor antagonists is neurotoxic and may account for deterioration and brain atrophy. Accordingly, NMDA-enhancing agents are supposed to work as not only antipsychotics but also cognitive enhancers that can correct neurodevelopmental deficits in schizophrenia. In chronically ill patients with

schizophrenia, some cognitive improvements, although limited to PANSS cognitive subscale or WCST, have been observed with treatment of high-dose glycine (Javitt et al., 2001), D-serine (Heresco-Levy et al., 2005; Tsai et al., 1998), and sarcosine (Lane et al., 2005; Tsai et al., 2004a). However, rigorous cognitive study of D-serine and other NMDA agent had not been done. It is still premature to claim that NMDA-enhancing agents possess cognition-improving effect until there is strong evidence from long-term trials and neurocognitive studies.

On the other hand, impaired quality of life in schizophrenic patients has been increasingly emphasized and considered to have correlation with strong cognitive deficits. Significantly poorer quality of life was reported in schizophrenic patients than healthy subjects as measured by World Health Organization Quality of Life-Brief Form (WHOQOL-BREF), in physical, psychological, as well as social domains which were correlated to cognitive deficits in executive function and working memory (Alptekin et al., 2005). A 12-month, open-label trial of rivastigmine in residual schizophrenia revealed that the improvements in quality of life were parallel with that in learning and memory via the cholinergic pathway (Lenzi et al., 2003). NMDA-enhancing agents potentially can also improve the quality of life through improving cognition and memory. Indeed, sarcosine was also found to improve quality of life in patients with acutely ill schizophrenia (Lane et al., 2008). However, more long-term data are needed to confirm the effect of NMDA-enhancing agents on quality of life.

7. Clinical efficacy of NMDA enhancing agents

A recent meta-analysis of all the double-blind, placebo-controlled studies in patients with schizophrenia examined the efficacy, the dose–response, the effects of concomitant antipsychotics, and side effects of all the NMDA-enhancing agents (Tsai and Lin, 2010). The result of 800 subjects from 26 studies showed that the NMDA-enhancing agents are significantly effective in most schizophrenic symptom domains with the effect size in the order of depressive (0.40), negative (0.38), cognitive (0.28), positive symptom (0.26), and general psychopathology (0.26). The meta-analysis found that glycine, D-serine and sarcosine are better than D-cycloserine in improving the overall psychopathology without side effect or safety concern in patients receiving antipsychotic, both conventional and SGAs, other than clozapine.

Current NMDA-enhancing agents are different in their efficacy in positive, negative and cognitive symptoms as summarized in Table 1, given that these agents are not a homogenous group. For example, glycine and D-cycloserine were found to have benefits in improving the negative symptoms, but not the positive and cognitive symptoms (Goff et al., 1999; Heresco-Levy et al., 2004, 1999). Compared to D-cycloserine, glycine and D-serine treatments have more comprehensive symptom improvement profiles, including better effects on negative symptoms (Goff et al., 1999; Javitt et al., 2001; Lane et al., 2008; Tsai et al., 1998, 2004a, 2006). Adjunctive D-serine offered significant improvements in chronically stable patients in positive, negative, cognitive symptoms and even WCST performance, which reflects prefrontal function (Heresco-Levy et al., 2005; Tsai et al., 1998). Furthermore, higher serum D-serine levels were associated with more symptom amelioration (Tsai et al., 1998). Glycine can even reduce negative symptoms in treatment-resistant schizophrenia (Heresco-Levy et al., 1999). This is probably because glycine and D-serine are full agonists, which can activate NMDA coagonist sites to the maximal extent, whereas D-cycloserine is a partial agonist, that cannot optimally activate the NMDA receptor (Tsai et al., 1998, 1999). Another D-amino acid and full agonist of the NMDA-coagonist site, D-alanine, also showed similar efficacy with D-serine when added to antipsychotics for treatment of schizophrenia (Tsai et al., 2006). Adjunctive D-alanine is also beneficial in positive, negative, and cognitive symptoms in chronically stable schizophrenic patients.

To enhance the NMDA neurotransmission, another approach is via attenuating glycine's reuptake, which can increase the availability of synaptic glycine. Sarcosine (N-methylglycine) is an endogenous GlyT1 inhibitor. Adding-on sarcosine in chronically ill and stable schizophrenic patients receiving risperidone or typical antipsychotics showed that sarcosine was much more beneficial than placebo in improving positive, negative, cognitive and general psychiatric symptoms, and it was well tolerated without significant side-effect (Tsai et al., 2004a). Furthermore, in addition to add-on therapy, sarcosine monotherapy was also found to be beneficial for acutely ill patients (Lane et al., 2008), and the treatment effect was dose-dependent with 2 g better than 1 g per day.

Of note, sarcosine has revealed significantly greater benefits than D-serine and placebo in improving negative symptoms, general psychopathology, cognitive deficits and quality of life as adjuvant therapy with risperidone, not only for chronically-ill stable (Lane et al., 2010), but also for acutely exacerbated schizophrenic patients (Lane et al., 2005). It implies that transporter inhibitor might exert greater effects than agonists themselves in enhancing neurotransmission. One possibility is that the anatomical distribution of GlyT1 is more relevant than the NMDA receptor per se to the neocortical circuitries involved in schizophrenia.

F. Hoffmann-La Roche Ltd. is developing a compound which is a candidate of GlyT1 inhibitor, RG1678. Phase III studies have been launched recently for two different indications: negative symptoms and sub-optimally controlled patients. However, in the phase II study, the signal to noise ratio is not robust with weeks 2, 4, 6<0.1 and week 8<0.05, and the effect size is <0.4. The CGI-I of 30 mg group has a

Table 1
Characteristics of clinical trials of NMDA enhancing agents and their effects on domains of psychopathology.

Study	Drug and dose	Concomitant antipsychotics	Subject no.	Positive symptoms	Negative symptoms	Cognitive symptoms	Depressive symptoms	Total psychopathology
Heresco-Levy et al. (1999)	Glycine 0.8 g/kg body weight	TYP + CLO	19	−	+	+	+	+
Javitt et al. (2001)	Glycine 0.8 g/kg body weight	TYP + CLO + ATYP	12	+	+	−	−	NA
Heresco-Levy et al. (2004)	Glycine 0.8 g/kg body weight	ATYP	14	+	+	+	+	+
Buchanan et al. (2007)	Glycine 60 g/day or D-CS 50 mg/day	TYP + ATYP	157	NA	−	−	NA	NA
Goff et al. (1999)	D-CS 50 mg/day	TYP	46	−	+	−	−	NA
Tsai et al. (2006)	D-alanine 100 mg/kg/day	TYP + ATYP	32	+	+	+	−	+
Tsai et al. (1998)	D-serine 30 mg/kg/day	TYP + ATYP	29	+	+	+	−	NA
Tsai et al. (1999)	D-serine 30 mg/kg/day	CLO	20	−	−	−	−	−
Heresco-Levy et al. (2005)	D-serine 30 mg/kg/day	ATYP	39	+	+	+	+	+
Lane et al. (2005) (acute patients)	D-serine 2 g/day or Sarcosine 2 g/day)	ATYP (risperidone)	65	+	+	+	+	NA
Lane et al. (2010) (chronically stable patients)	D-serine 2 g/day or Sarcosine 2 g/day)	ATYP	51	+	+	+	+	+
Tsai et al. (2004a, 2004b)	Sarcosine 2 g/day	TYP + ATYP	38	+	+	+	NA	+
Lane et al. (2006)	Sarcosine 2 g/day	CLO	20	−	−	−	−	−
Lane et al. (2008)	Sarcosine 2 g or 1 g/day	No	20	−	−	NA	NA	−

TYP, typical antipsychotics; ATYP, atypical antipsychotics; and CLO, clozapine.

p value>0.05. The best change of function is from 10 mg group which also has a p value>0.05. One potential pitfall is that RG1678 is a noncompetitive antagonist with only 10 and 30 mg as effective and 60 mg as not. It would be difficult to titrate the dose to be close to 50% target occupancy in individual patients as Roche suggests.

With the rationale of maintaining a tonic stimulation of NMDA synapse, most trials are daily dosing. Differently, a study (Goff et al., 2008) tried once-weekly dosing with D-cycloserine for 8 weeks. A single dose of D-cycloserine also facilitated memory consolidation tested after 7 days on a thematic recall test. The finding should be considered preliminary and await confirmation. Taken together, further confirmation and parallel comparison are required to determine effective dosing ranges and to compare the effectiveness of the full agonist of the NMDA-D-serine/glycine site with the GlyT1 inhibitor and other options like DAO inhibitor for treating schizophrenia.

Adverse effects of the NMDA-enhancing agents have not been reported more than those of placebo, except for GI upset and nausea in some glycine trials (Goff et al., 1995; Heresco-Levy et al., 2005; Lane et al., 2005, 2006, 2010). Moreover, NMDA-enhancing agents were found to significantly improve extrapyramidal symptoms on both the Simpson–Angus Scale and Abnormal Involuntary Movement Scale measurements. Heresco-Levy et al. (2005) found that co-administration of D-serine can reduce the dosage of antipsychotics required to reach the same level of symptom reduction in schizophrenia while minimizing adverse effects. Seemingly, NMDA-enhancing agents have showed a good safety profile in either add-on treatment or monotherapy and efficacy when adding to antipsychotics. Nevertheless, long-term studies are needed to thoroughly evaluate the safety of the NMDA-enhancing agents.

8. Perspective

While the results of the trials with NMDA-enhancing agents are encouraging, enhancement of glutamatergic neurotransmission via pathways other than NMDA receptors for the treatment of schizophrenia is drawing more attentions. Here we discuss two examples which suggest the potential therapeutic effects from non-NMDA targets.

8.1. AMPA receptor and ampakines

Rapid excitatory synaptic transmission which releases glutamate and aspartate in the CNS acts primarily through two subtypes of ionotropic receptors: AMPA and NMDA receptors (Newpher and Ehlers, 2008). Thus, another way to enhance glutamatergic neurotransmission is via activating the AMPA receptors, which are responsible for the fast excitatory postsynaptic potentials (EPSPs) and play a role in learning and memory (Perez-Otano and Ehlers, 2004). AMPA activation can release the depolarization blockade of the NMDA receptor. Recently, investigations have shown interests in the therapeutic potential of ampakines, that allosterically produces positive modulation of AMPA receptors by increasing the amplitude and duration of glutamate-stimulated EPSPs (Goff et al., 2001). Ampakines enhance synaptic plasticity, and preclinical and preliminary clinical data suggest that they can improve cognition (Lynch, 2006; O'Neill and Dix, 2007; Swanson, 2009). There has been several ampakines under investigation, including CX546, CX516, CX717, LY415395 and C614. Nevertheless, the results of the clinical studies for these molecules are unsatisfactory, and some of the results remain undisclosed (Swanson, 2009). It remains unclear whether the limited activation by ampakines can generate enough activation of NMDA receptor required for the treatment of schizophrenia.

In addition to ampakines, noncompetitive inhibitors of AMPA receptors, such as talampanel and perampanel, also have been tested for their efficacy. These agents can potentially reduce over-excitation and slow neurodegeneration, and be as effective as adjunct therapy for refractory partial complex seizures (Howes and Bell, 2007). Talampanel has been found to have encouraging survival results when added to standard radiation and temozolomide in newly diagnosed glioblastoma (Grossman et al., 2009), and preliminary clinical trials have been planned to determine the efficacy of talampanel in subjects with amyotrophic lateral sclerosis (Pascuzzi et al., 2010). Another noncompetitive inhibitor of the AMPA receptor, perampanel, was also found to alleviate diabetic and postherpetic neuropathic pain (Swanson, 2009); however, it failed to show efficacy as an adjunctive therapy for Parkinson's disease (Eggert et al., 2010). Overall, the rationale of this treatment is protection of neurotoxicity from overactivation of non-NMDA receptor. This approach may well miss the target if the core pathology of schizophrenia is hypoNMDA function.

8.2. Metabotropic glutamate receptor (mGluR) treatment

Based on the seemingly paradoxical theory of decreased NMDAR function, yet increased glutamatergic neurotransmission, is the research involving another group of glutamate receptors, mGluR. Research has involved finding agonists, positive allosteric modulators of mGluR5, mGluR2, and mGluR3, in order to increase activity at these receptors (Gray and Roth, 2007). This is because animal studies, and preliminary human studies have shown that activating these receptors has shown promise towards alleviating symptoms of schizophrenia (Moghaddam and Adams, 1998). For example, activating mGluR2 blocks effects of psychotomimetic agents (Krystal et al., 2005). Modulating the allosteric site has advantages — however, the orthosteric sites are conserved across all the differently mGluRs, making it difficult to develop an agent specific to a receptor subtype (Conn and Jones, 2009). The relevant mGluRs targets are:

1) *mGluR5*. This group of agents is in preclinical phase of development. Liu et al. (2008) have studied ADX47273, a positive allosteric modulator of mGluR5 in animals and in vitro. ADX47273 was noted to increase response to threshold concentration of glutamate by nine times. There was also an increase in cAMP-responsive elementbinding protein phosphorylation in the hippocampus and prefrontal cortex, which is important in glutamate-mediated signal transmission. By increasing mGluR5 activity, ADX47273 also blocked PCP or amphetamine induced hyperlocomotion in animals and decreased extracellular levels of dopamine in nucleus accumbens.
2) *mGluR2 and mGluR3*. In 2007, Patil et al. (2007) reported a Phase II clinical trial of LY2140023, which is the oral form of a selective agonist for mGluR2/3, shown to have antipsychotic effects in animal studies. It counteracted effects of PCP in rats, as knockout animals of this receptor were unaffected by this agonist. The study involved 196 patients diagnosed with schizophrenia who were randomized to placebo, olanzapine (positive control), and LY2140023. Baseline PANSS scores were in the 80's, and patients were recruited from ten different sites in Russia. They were tapered off their previous medication regimen and then treated with LY2140023 40 mg BID, olanzapine 15 mg daily, or placebo for one month. LY2140023 was safe and well-tolerated. Patients treated with LY2140023 and olanzapine showed significant improvements in both positive and negative symptoms when compared to placebo. LY2140023 did not differ from placebo with respect to elevated prolactin, EPS, or weight gain. There were more subjects in LY2140023 which did make it easier to detect significance, but is helpful in this case to find smaller effects. The study was notable for an absence of placebo effect. Significant adverse events were as follows: LY2140023 associated with affect lability, placebo with agitation, and olanzapine, increased triglycerides, weight gain, and periodontitis. There were no significant differences in efficacy between LY2140023 and olanzapine. There was a reduction in PANSS total, positive, negative, and CGI for both olanzapine and LY2140023 compared to placebo.

However, at the end of March 2009, Eli Lilly reported that LY2140023 was inconclusive in the second Phase II clinical trial involving 393 subjects for 4 weeks. LY2140023 "did not outperform" olanzapine or placebo (Russel, 2009). In contrast to the first trial, the second trial has significant placebo effect and olanzapine did not show superior efficacy as compared to placebo.

8.3. NMDA enhancement by inhibition of D-amino acid oxidase

Since DAO is responsible for degrading D-serine, D-alanine, and other D-amino acids (Fukui and Miyake, 1992; Vanoni et al., 1997), another alternative to enhance NMDA function is to inhibit DAO activity (Fig. 1). The inhibition of DAO by benzoate raises synaptic concentrations of D-serine and other D-amino acids (Bartlett, 1948; Van den Berghe-Snorek and Stankovich, 1985). Benzoic acid exists naturally in miscellaneous kinds of plants and animals, and therefore is a natural constituent of many kinds of food, including milk products (IPCS, 1993). Benzoates are also legal food additives widely used in manufacturing fruit jelly, butter, soy-bean sauce, processed meat etc. in US and many other countries and are well recognized by the World Health Organization (IPCS, 1993). Sodium benzoate has been used in the treatment of patients with urea cycle disorders (Enns et al., 2007) (i.e., hyperammonaemia due to inborn errors of urea synthesis) to facilitate nitrogen excretion by diverting nitrogen from urea synthesis to an alternative pathway (Scaglia et al., 2004). The therapeutic dose for urea cycle disorders is in the range of 250–500 mg/kg body weight per day (Batshaw and Brusilow, 1981; Batshaw and Monahan, 1987; Feillet and Leonard, 1998; Green et al., 1983; Kubota and Ishizaki, 1991; O'Connor et al., 1987; Tremblay and Qureshi, 1993) without obvious side effects, except anorexia and vomiting even when given via intravenous bolus infusions.

Three lines of evidence have provided support for the potential of the DAO inhibitor to enhance NMDA function and bring therapeutic benefits in schizophrenia: 1) DAO and DAOA show genetic associations with schizophrenia in several studies; 2) the expression and activity of DAO are found to increase in patients with schizophrenia (Madeira et al., 2008); and 3) inactivation of DAO produces behavioral and biochemical effects in rodents (Verrall et al., 2010). A randomized double-blind clinical trial (Lane HY, personal communication) showed that adding-on benzoate was significantly better than placebo in reducing scores of Clinical Global Impression and Positive and Negative Syndrome Scale in patients treated with antipsychotics. Treatment-emergent side effects which were mild, short-lived, and not warranting medical treatment were similar between sodium benzoate and placebo groups implying that benzoate yields good safety and tolerability.

9. Summary

This review has discussed the role of glutamatergic signaling, particularly the molecules of the NMDA synapse, and plays in the pathophysiology of schizophrenia from views of neurodevelopment, pathological finding, genetic vulnerability, animal models, pharmacology and clinical trials. Quite a few candidate genes have been identified to be involved in the neurodevelopment and glutamate-associated signaling relevant to schizophrenia; of them, DAO and G72 (DAOA) are directly involved in NMDA neurotransmission and the rest are indirectly related to the NMDA synapse. Likely, either individual subject has different NMDA pathology or the accumulation of multiple variations of these candidate genes, rather than any single gene, may serve as a general model for the pathogenesis of schizophrenia. Nevertheless, enhancing NMDA function can correct/rescue the hypoNMDA function from a variety of vulnerabilities in NMDA synapse regardless of its origin.

Accumulating evidence regarding the involvement of glutamatergic system in schizophrenia focuses on the ionotropic receptors which are subdivided to 3 subtypes; among which NMDA has the strongest association with schizophrenia and serves as the only therapeutic target that proves to have clinical efficacy thus far. The theory of NMDA hypofunction is supported by evidence that the NMDA-receptor antagonists, PCP and ketamine, induce psychiatric and behavioral changes which resemble schizophrenia. Findings from animal genetic models, which show that NMDA receptor hypofunction results in abnormalities of motor and social behaviors, learning, cognition and response to psychotropics, are compatible with that from clinical studies. The evidence together has demonstrated that NMDA hypofunction is a critical deficit in schizophrenia, providing support for the potential of developing agents which can enhance NMDA function for the treatment of schizophrenia.

Clinically, the addition of NMDA-enhancing agents to atypical antipsychotics resulted in significant improvements in total psychopathology, negative symptoms, cognitive symptoms, and depressive symptoms. These findings further underscore the significance of NMDA enhancement as a new therapeutic approach in an era in which atypical antipsychotics are becoming the primary drugs for most patients who have schizophrenia. There is a good possibility that this may involve a synergistic therapeutic effect of the atypical antipsychotics and NMDA-enhancing agents, providing an intriguing strategy for a large portion of patients with schizophrenia whose disorder is resistant or only partially responsive to atypical antipsychotics. In fact, the NMDA agents tested so far are a new category of safe antipsychotic agents devoid of the adverse effects of extrapyramidal symptoms, tardive dyskinesia, and metabolic syndrome. These advantages will help a substantial portion of patients who experience serious adverse effects while taking the existing antipsychotic agents. Taken together, NMDA-enhancing agents offer a completely novel therapeutic approach which holds promise as the next generation antipsychotics.

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