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The NMDA Receptor and Schizophrenia: From Pathophysiology to Treatment

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Abstract

Schizophrenia is a severe mental illness that affects almost 1% of the population worldwide. Even though the etiology of schizophrenia is uncertain, it is believed to be a neurodevelopmental disorder that results from a combination of environmental insults and genetic vulnerabilities. Over the past 20 years, there has been a confluence of evidence from many research disciplines pointing to alterations in excitatory signaling, particularly involving hypofunction of the *N*-methyl-D-aspartate receptor (NMDAR), as a key contributor to the schizophrenia disease process. This review describes the structure-function relationship of the NMDAR channel and how the glycine modulatory site (GMS) acts as an important regulator of its activity. In addition, this review highlights the genetic, pharmacologic, and biochemical evidence supporting the hypothesis that NMDAR hypofunction contributes to the pathophysiology of schizophrenia. Finally, this chapter highlights some of the most recent and promising pharmacological strategies that are designed to either, directly or indirectly, augment NMDAR function in an effort to treat the cognitive and negative symptoms of schizophrenia that are not helped by currently available medications.

Keywords

schizophrenia; serine racemase; D-serine; glycine; NMDA receptor; metabotropic glutamate receptor 5; α7 nicotinic acetylcholine receptors; cognition

1. INTRODUCTION

Schizophrenia is a chronic, disabling mental disorder that affects 0.5–1% of the population worldwide (Perala et al., 2007) that commonly presents in late adolescence and early adulthood. It is characterized clinically by positive symptoms (delusions, hallucinations, and thought disorder), negative symptoms (i.e. social withdrawal, poverty of speech, and anhedonia), and cognitive deficits (i.e attention, working memory, and executive function). While the negative and positive symptoms typically present during late adolescence or early

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CONFLICT OF INTEREST

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adulthood (Lewis & Lieberman, 2000), the cognitive deficits generally appear years before clinical diagnosis (Lesh, Niendam, Minzenberg, & Carter, 2011).

One leading hypothesis is that the pathophysiology of schizophrenia has a neurodevelopmental component (Lewis & Lieberman, 2000; Rapoport, Giedd, & Gogtay, 2012). Brain development during adolescence, the time when many schizophrenia symptoms appear or worsen, is a dynamic period marked by extensive functional and neuroanatomical changes. This period is characterized by: 1) fine-tuning of excitatory, inhibitory, and monoaminergic neurotransmitter systems, 2) stabilization of synapses to increase efficiency of neural function and diminish redundancy, and 3) beginning of integration between late maturing and early maturing brain structures (Keshavan, Giedd, Lau, Lewis, & Paus, 2014). Therefore, genetic predisposition and environmental disturbances that lead to changes or imbalances in the timing of these developmental processes could increase the risk for developing schizophrenia.

Schizophrenia is associated with various neuroanatomical and structural brain abnormalities. Diffusion tensor magnetic resonance imaging studies show that white matter alterations are present from the preclinical to the chronic stages of schizophrenia, involving the long association white matter tracts, corticospinal tracts, interhemispheric connections, cerebello-thalamo-cortical circuit, and limbic system (Canu, Agosta, & Filippi, 2015). A number of longitudinal structural magnetic resonance imaging studies have shown reduced whole brain volume and increased lateral ventricular volume in the early stages of schizophrenia and in chronically ill patients (Fusar-Poli et al., 2013; Kempton, Stahl, Williams, & DeLisi, 2010; Levitt, Bobrow, Lucia, & Srinivasan, 2010), with some abnormalities already present during the prodromal phase (Fusar-Poli et al., 2011). The decreased brain volume in schizophrenia is especially pronounced in cortical areas, as well as in the hippocampus (Levitt et al., 2010; Tamminga, Stan, & Wagner, 2010). The extent of progressive brain tissue decrease in patients (−0.5%/year) has been estimated as twice that of healthy controls (−0.2%/year) (Hulshoff Pol & Kahn, 2008). Some of these neuroanatomical alterations may be correlated with antipsychotic treatment, as the higher the cumulative exposure to antipsychotic treatment, the greater the progressive gray matter volume decreases in patients over time (Fusar-Poli et al., 2013). Studies using human *post-mortem* brain tissue suggest that decreased neuropil, including reduced dendritic length and spine density on pyramidal neurons, might be the primary contributor to reduced cortical gray matter volumes in schizophrenia (Glausier & Lewis, 2013; Konopaske, Lange, Coyle, & Benes, 2014).

Schizophrenia is a highly heritable disorder, with the relative risk being 6–17x greater among first-degree relatives and 40–50x greater in the monozygotic twin of an affected sibling compared to the general population (Cardno et al., 1999). Thus, there has been a massive effort in the field of psychiatric genetics to identify genes that confer risk to developing schizophrenia. Unfortunately, the genetics are very complex with non-Mendelian inheritance. Prior to genome-wide association studies (GWAS), candidate gene studies were utilized in an attempt to discover genetic risk factors for schizophrenia. Although these studies were able to identify numerous risk genes, there was often a failure to replicate associations across studies. We now know that these early candidate gene association studies for common genetic variation had inadequate statistical power to detect the small differences

seen in schizophrenia (Farrell et al., 2015). Although the largest schizophrenia GWAS to date (~37,000 cases and ~113,000 controls; exponentially larger sample sizes than previous studies) identified SNPs in ~600 brain-enriched genes, almost all of the previously identified candidate risk genes were not found to be associated with schizophrenia in this study (Schizophrenia Working Group of the Psychiatric Genomics, 2014). Copy number variants (stretches of DNA that are either deleted or duplicated) and rare exonic variants, can also lead to increased genetic risk for schizophrenia (Fromer et al., 2014; Kirov et al., 2012). As a whole, these recent large-scale studies have identified both common and rare genetic variants in *N*-methyl-D-aspartate receptor (NMDAR) genes, as well as components of the postsynaptic density, with increased risk for schizophrenia.

In this chapter, we describe the structure and function of the NMDAR channel, with a particular focus on how the glycine modulatory site (GMS) regulates its activity. We will then discuss how it is believed NMDAR hypofunction contributes to the pathophysiology of schizophrenia. Finally, we will highlight some of the latest pharmacological strategies aimed at both, directly and indirectly, augmenting NMDAR function.

2. NMDA RECEPTOR: STRUCTURE AND FUNCTION

In the brain, glutamate activates metabotropic and ionotropic receptors. The latter family of receptors is comprised of 18 gene products that are further divided into three subtypes based on their agonist preference: α-amino-3-hydroxy-5- methylisoxazole-4-propionate (AMPA) receptors, kainate receptors and NMDARs/GluNs. The heterotetrameric NMDAR is widely distributed throughout most of the brain and is a critical postsynaptic mediator of activity-dependent synaptic plasticity. This receptor is composed of two obligatory GluN1 subunits with either two GluN2 subunits or a combination of GluN2 and GluN3 subunits. The GluN1 subunit is encoded by a single gene (*GRIN1*), which has eight different splice variants. There are four GluN2 subunits (GluN2A-D) and two GluN3 subunits (GluN3A-B) that are encoded by separate genes, *GRIN2A-D* and *GRIN3A-B*, respectively (Paoletti, Bellone, & Zhou, 2013).

GluN1 is the obligatory NMDAR subunit that it is expressed throughout the brain and is present during the entire lifespan (Henson et al., 2008). On the other hand, GluN2A-D subunits have a complex spatial and temporal expression pattern. For example, GluN2B is expressed at low levels embryonically and increases in the hippocampus and cortex after birth. GluN2A begins to be expressed after birth and its levels continue to rise during postnatal development throughout the brain. In the adult brain, GluN2D is found only in the diencephalon and mesencephalon, while GluN2C is confined to the olfactory bulb and cerebellum. GluN3A and GluN3B, similar to GluN2 subunits, are expressed in a developmentally and spatially restricted manner. This large diversity in subunit expression and composition leads to NMDARs with distinct pharmacological and biophysical properties, including the formation of nonconventional diheteromeric (GluN1/GluN3) and triheteromeric (GluN1/GluN2/GluN3) NMDARs (Hansen, Ogden, Yuan, & Traynelis, 2014; Kehoe, Bernardinelli, & Muller, 2013).

Each of the GluN subunits consists of four domains: the intracellular C-terminal domain, the transmembrane domain that contains the ion channel, the agonist binding domain (glycine or D-serine bind to GluN1 or GluN3, while glutamate binds to GluN2), and the N-terminal domain. The C-terminal domain, through protein-protein interactions, regulates receptor trafficking and intracellular signaling. However, the C-terminal domain is the only domain that is not affected by allosteric modulators (Paoletti et al., 2013). The three helices and hairpin that comprise the transmembrane domain form the pore of the channel, giving it ion selectivity. It was only recently that the first crystal structure of the intact heterotetrameric GluN1/GluN2B NMDAR ion channel was described (Karakas & Furukawa, 2014).

NMDARs are unique compared to other members of the ionotropic glutamate receptor family. These receptors have much slower deactivation kinetics, are highly permeable to Ca^{2+}, and act as a molecular coincidence detector. In addition to the binding of its agonist glutamate to the GluN2 subunit, activation of the NMDAR requires 1) post-synaptic depolarization, which relieves the Mg^{2+} blockade of the channel and 2) either glycine or D-serine must be bound at the GMS on the GluN1 subunit (Figure 1) [Insert Figure 1 here]. It should be noted that although the endogenous high potency co-agonists glycine and D-serine are present in the extracellular space (Johnson & Ascher, 1987), the GMS is not saturated *in vivo* (Bergeron, Meyer, Coyle, & Greene, 1998). Upon NMDAR channel opening, Ca^{2+} enters the neuron and triggers a cascade of intracellular events that mediate local, acute functional synaptic plasticity and changes in gene expression that influence long-term neural structural plasticity (Greer & Greenberg, 2008).

3. GLYCINE MODULATORY SITE

Work done on both native NMDARs (Johnson & Ascher, 1987) and those expressed by oocytes (Kleckner & Dingledine, 1988) demonstrated the need for concomitant binding of glutamate and glycine for receptor activation. Furthermore, it was shown that D-serine or D-alanine could also act as NMDAR co-agonists at the GMS (Kleckner & Dingledine, 1988). D-amino acids, including D-serine are now well-established modulators of neuronal activity in mammals (Boehning & Snyder, 2003; Wolosker, Dumin, Balan, & Foltyn, 2008).

3.1. Serine racemase and D-serine

Serine racemase (SR) and D-serine were first observed in eukaryotic insects, such as silkworms and earthworms (Corrigan & Srinivasan, 1966). SR is the enzyme responsible for the both the conversion of L-serine to D-serine, as well as the α,β-elimination of water from L- or D-serine to yield pyruvate and ammonia (Figure 2) [Insert Figure 2 here]. SR is classified as a fold II pyridoxal 5′ phosphate (PLP) enzyme (Wolosker, Blackshaw, & Snyder, 1999). However, SR is more structurally similar to bacterial serine/threonine dehydratases, rather than classical amino acid racemases (De Miranda, Santoro, Engelender, & Wolosker, 2000). Even though the PLP attachment sites are conserved and there is structural similarity between SR and type II PLP family members, there are critical differences regarding allosteric regulation and reaction specificity. The crystal structure of SR revealed that the enzyme consists of two identical subunits that function as a dimer. In addition to PLP, SR has binding sites for magnesium (Mg^{2+}) and a Mg^{2+}-ATP complex, both

of which lie outside of the catalytic site (Goto et al., 2009). It is believed that ATP is not an energy requirement for enzyme activity because ADP is also equally effective in SR activation (De Miranda, Panizzutti, Foltyn, & Wolosker, 2002).

In addition to the reversible racemization of L-serine to D-serine, SR also catalyzes the irreversible α,β-elimination of water from both enantiomers to produce ammonia and pyruvate (De Miranda et al., 2002), although the reaction is more efficient with L-serine as the substrate (Foltyn et al., 2005). The exact physiological role SR αβ-elimination activity is unknown. Although pyruvate is an important metabolite, the rate of its formation from other sources, such as glycolysis, are several orders of magnitude faster than the rate of L-serine αβ-elimination, making it unlikely that SR-derived pyruvate plays an important metabolic role (Wolosker & Mori, 2012). The production of pyruvate may be the primary role of SR in the liver, since it lacks NMDARs and where D-serine is believed to not play a functional role (Wolosker et al., 1999). However in the adult forebrain, where D-serine plays an important role in regulating excitatory neurotransmission, the SR αβ-elimination reaction might provide a mechanism by which to control intracellular D-serine levels in certain brain regions (Wolosker, 2011). There is very little D-amino acid oxidase (DAO), the main degradative enzyme for D-serine, in the adult forebrain (Figure 2). Furthermore, forebrain D-serine levels are unaltered in mice that have a catalytically inactive form of DAO, demonstrating the lack of importance for this enzyme in regulating D-serine concentration (Hamase, Konno, Morikawa, & Zaitsu, 2005).

3.1.1 Cellular Localization of Serine Racemase and D-serine—D-Serine is enriched in corticolimbic regions of the brain and is localized to the same areas as NMDARs (Schell, Molliver, & Snyder, 1995). D-serine is believed to be the primary forebrain co-agonist in the forebrain for synaptic, but not extra-synaptic NMDARs (Papouin et al., 2012). Initial *in vitro* studies suggested that SR was an astrocytic enzyme, and therefore astrocytes were the major source of brain D-serine (Mothet et al., 2005; Schell et al., 1995; Wolosker et al., 1999). However, recent immunohistochemical studies have demonstrated that SR is more prominently expressed in neurons, rather than in astrocytes (Balu, Takagi, Puhl, Benneyworth, & Coyle, 2014; Ding, Ma, Nagahama, Yamada, & Semba, 2011; Ehmsen et al., 2013; Miya et al., 2008). Furthermore, using mice with conditional deletions of SR either in excitatory forebrain neurons or GFAP-expressing astrocytes, it was shown that the majority of SR was expressed in forebrain excitatory neurons, particularly in the neocortex and hippocampus, and that approximately 15 percent was expressed in astrocytes (Benneyworth, Li, Basu, Bolshakov, & Coyle, 2012). This pattern of neuronal expression was also observed in human *post-mortem* neocortex, as SR was found in both excitatory and inhibitory neurons, but not astrocytes (Balu et al., 2014). It should be noted that L-serine derived from astrocytes is the precursor for D-serine in the brain, as mice that lack the astrocyte-enriched enzyme phosphoglycerate 3-dehydrogenase, which catalyzes the first step in L-serine biosynthesis (Figure 2), display marked reductions in brain D-serine (Yang et al., 2010).

D-serine was also originally believed to be stored in, and released from astrocytes (Fossat et al., 2012; Martineau et al., 2013; Schell et al., 1995). More recent studies found that D-serine was located primarily in neurons (Curcio et al., 2013; Kartvelishvily, Shleper, Balan,

Dumin, & Wolosker, 2006). However, those studies did not validate the specificity of D-serine immunostaining in brain tissue. Utilizing SR−/− mice as a negative control to optimize staining conditions (Balu et al., 2014; Ehmsen et al., 2013), D-serine was almost exclusively stored in neurons, particularly GABAergic neurons in the neocortex and hippocampus (Balu et al., 2014). Interestingly, SR and D-serine were only co-localized in approximately ~50% of neurons, depending on the brain region (Balu et al., 2014). This separation of SR and D-serine might be related to the enzymatic profile of SR, as the αβ-elimination reaction that metabolizes D-serine is more efficient than the racemization of L-serine to D-serine.

3.2. Glycine and Kynurenic Acid

Glycine acts as an NMDAR co-agonist in the forebrain. The affinity of GluN1 for glycine is allosterically regulated by the GluN2 subunit, with GluN2B containing NMDARs displaying higher affinity for glycine (Priestley et al., 1995). There are two types of sodium-dependent glycine transporters (GlyT), GlyT1 and GlyT2, which are considered the primary regulators of intra- and extracellular glycine levels (Betz, Gomeza, Armsen, Scholze, & Eulenburg, 2006). Although glycine concentration in mammalian CSF is high relative to its dissociation constant (K_D) for the GMS, local glycine levels are functionally regulated at the synapse. While GlyT1 and GlyT2 are both expressed in the cerebellum and spinal cord, where inhibitory glycinergic neurotransmission is concentrated, GlyT1 is also found in the forebrain (Zafra, Gomeza, Olivares, Aragon, & Gimenez, 1995). GlyT1 is widely expressed in glial cells, but is also found in neurons at glutamatergic synapses (Cubelos, Gimenez, & Zafra, 2005) and is thought to regulate NMDAR activity by affecting glycine availability (Bergeron et al., 1998). The activity of GlyT1 is itself regulated by the endogenous inhibitor, sarcosine (N-methylglycine), an intermediate and byproduct in glycine synthesis and degradation.

Kynurenic acid is a competitive antagonist at the GMS of the NMDAR (Kessler, Terramani, Lynch, & Baudry, 1989). It is derived from the metabolism of tryphtophan by several unique kynurenine aminotransferases (KATs) that catalyze the irreversible transamination of kynurenine to kynurenic acid, which is present in the human brain at high nanomolar concentrations. In addition, kynurenic acid is a non-competitive antagonist at the α7 nicotinic acetylcholine receptor (α7nAChR) (Hilmas et al., 2001) and has antioxidant properties (Lugo-Huitron et al., 2011).

4. NMDA RECEPTOR HYPOFUNCTION AND SCHIZOPHRENIA

There is substantial pharmacologic, genetic, and biochemical evidence to support NMDAR hypofunction as a key etiological component of schizophrenia. Dissociative anesthetics such as ketamine and phencyclidine (PCP), which are NMDAR channel blockers, were known since their introduction to produce the full range of schizophrenia symptoms and cognitive deficits in healthy subjects (Javitt & Zukin, 1991; Krystal et al., 1994). In healthy volunteers, low doses of ketamine that do not cause delirium or dementia produce the physiological abnormalities associated with schizophrenia, including abnormal evoked related potentials (ERPs) (Umbricht et al., 2000), eye-tracking abnormalities (Radant, Bowdle, Cowley,

Kharasch, & Roy-Byrne, 1998), and enhanced subcortical dopamine release (Kegeles et al., 2000). Meanwhile, stabilized schizophrenia patients exhibit an increased sensitivity to ketamine (Lahti, Weiler, Tamara Michaelidis, Parwani, & Tamminga, 2001).

Although there have been mixed results in showing NMDAR expression abnormalities in human *post-mortem* brain tissue, depending on the brain region examined and methodology used, there is accumulating biochemical evidence suggesting reduced NMDAR function in schizophrenia. Recent meta-analysis found significant decreases in the expression of GluN1 mRNA (medium to large effect size) and GluN1 protein (medium effect size) in the prefrontal cortex (PFC) of subjects with schizophrenia (Catts, Lai, Weickert, Weickert, & Catts, 2015). This same meta-analysis found no consistent statistically significant changes in cortical mRNA and protein expression of GluN2 (A, B, D) or GluN3A subunits in schizophrenia, with the exception of reduced GluN2C mRNA in the PFC (Catts et al., 2015; Weickert et al., 2013). In the postsynaptic density fraction obtained from human *post-mortem* dorsolateral PFC tissue, there is a marked reduction in the activity of signaling cascades downstream of the NMDAR in schizophrenia, despite an apparent increase in NMDAR density and GluN1 expression (Banerjee et al., 2015). In the hippocampus, there have been several reports of reduced GluN1 levels selectively in the dentate gyrus of patients with schizophrenia (X. M. Gao et al., 2000; Law & Deakin, 2001; Stan et al., 2015).

There are also numerous abnormalities of NMDAR GMS modulators in the brain and the periphery of patients with schizophrenia. SR and D-serine are reduced in schizophrenia (Bendikov et al., 2007; Goltsov et al., 2006; Hashimoto et al., 2005; Labrie, Wang, Barger, Baker, & Roder, 2009; Morita et al., 2007). Kynurenic acid, an endogenous GMS antagonist, is elevated in the cerebral spinal fluid and *post-mortem* brain tissue of patients with schizophrenia (Erhardt et al., 2001; Schwarcz et al., 2001). The levels of N-acetylaspartylglutamate (NAAG), an endogenous NMDAR antagonist and mGluR3 agonist, are regulated by the enzyme glutamate carboxypeptidase II (GCP-II). The decreased activity of GCP-II and increased NAAG levels in the brains of patients with schizophrenia supports the hypothesis that NAAG-mediated signaling is disrupted in schizophrenia (Bergeron & Coyle, 2012).

Furthermore, there is evidence suggesting that altered glutamate levels could be contributing to NMDAR hypofunction in schizophrenia. A meta-analysis examining *in vivo* glutamate concentrations in schizophrenia measured by proton magnetic resonance spectroscopy found lower glutamate concentrations that progressively decreased with age in frontal brain regions, but did not find significant glutamate differences between schizophrenia and control groups in the hippocampus (Marsman et al., 2013). Although there have been inconsistent findings regarding hippocampal glutamate levels in schizophrenia, one recent proton magnetic resonance spectroscopy study found that glutamate levels were reduced in the hippocampus of patients with schizophrenia, regardless of whether they were medicated (Stan et al., 2015).

Individuals with NMDAR autoimmune encephalitis, which is associated with antibodies against the extracellular epitopes of the GluN1 subunit (IgG GluN1), initially present with psychiatric symptoms similar to schizophrenia (Dalmau et al., 2007). It is believed these

antibodies cause NMDAR internalization (Dalmau, Lancaster, Martinez-Hernandez, Rosenfeld, & Balice-Gordon, 2011). Most research now suggests that IgG GluN1 antibodies detected in cases of anti-NMDAR encephalitis are not found in patients with schizophrenia (de Witte et al., 2015; Kayser & Dalmau, 2014). Although (Steiner et al., 2013) detected serum NMDAR antibodies (IgA and/or IgM GluN) in acutely ill schizophrenic patients, reanalysis of control sera from this cohort by the same group showed that the frequency of IgA and IgM antibodies was similar to that of the patients (Steiner et al., 2014). On the other hand, a recent meta-analysis showed significantly higher odds of NMDAR antibody seropositivity in individuals with schizophrenia or schizoaffective, major depressive, or bipolar, disorders compared with healthy controls, based on high-specificity, but not low specificity, thresholds (Pearlman & Najjar, 2014). In order to fully understand the clinical and pathophysiological implications of NMDAR antibodies in psychiatric disorders, it will be important to have adequately powered longitudinal studies that employ standardized assay methods and seropositivity thresholds, and quantify NMDAR antibodies in both sera and cerebrospinal fluid (Pearlman & Najjar, 2014).

As mentioned earlier, recent large-scale studies have identified both common and rare genetic variants important for glutamatergic signaling and the postsynaptic density, with increased risk for schizophrenia. Copy number variant (CNV) analyses have implicated *de novo* mutations in genes that encode the NMDAR and proteins associated with the postsynaptic density with increased risk of schizophrenia (Fromer et al., 2014; Kirov et al., 2012; Purcell et al., 2014). Although these rare variants are highly penetrant and etiologically relevant to schizophrenia, common genetic variation seems to account for much more of the variance in liability for developing this disorder (Purcell et al., 2014). The largest schizophrenia GWAS to date (~37,000 cases and ~113,000 controls) identified 108 genetic loci, including ~600 brain-enriched genes (Schizophrenia Working Group of the Psychiatric Genomics, 2014), that are involved in dopaminergic (*DRD2)* and glutamatergic transmission including: *SRR* (serine racemase), the metabotropic 3 glutamate receptor (*GRM3*), glutamate receptor 1 (*GRIA1*), and the *GRIN2A* (GluN 2A). Interestingly, most of these identified schizophrenia genetic risk loci identified in that study were located within non-coding regions of the genome, and thus are of unknown function. However, recent work has shown that a portion of the schizophrenia GWAS risk SNPs is enriched for alleles that regulate gene expression (eSNPs) and are located within *cis*-regulatory elements (i.e., enhancer and promoter regions), suggesting a functional link between risk-associated non-coding SNPs and 3D genomic architecture (Roussos et al., 2014). Biological pathway analyses of GWAS data (~60,000 subjects from the Psychiatric Genetics Consortium) revealed that genetic variants associated with schizophrenia are enriched in pathways related to the postsynaptic density, the postsynaptic membrane, dendritic spines, and histone methylation (Network & Pathway Analysis Subgroup of Psychiatric Genomics, 2015). It should be noted that most of the loci identified by GWAS contain more than one gene. Thus, much work is needed to determine which variant(s), in which gene(s) of a particular locus, are contributing to the increased risk for schizophrenia.

Finally, there is an abundance of data from pharmacologic and genetic animal models that support the hypothesis of NMDAR hypofunction contributing to the pathophysiology of schizophrenia (Balu & Coyle, 2011; Inta, Monyer, Sprengel, Meyer-Lindenberg, & Gass,

2010; Meltzer et al., 2013). In pharmacologically induced models, administration of NMDAR antagonists (phencyclidine (PCP), dizocilpine (MK-801), or ketamine) or kynurenic acid to animals leads to neurochemical, morphological, and cognitive deficits similar to what is observed in schizophrenia (Meltzer et al., 2013; Pershing et al., 2015). Genetic animal models have also provided a wealth of data suggesting that reduced NMDAR activity can lead to changes in the brain and behavior that is similar to what is observed in schizophrenia. For example, mice lacking the enzyme SR (SR−/−), have reduced D-serine and display NMDAR hypofunction (Basu et al., 2009). Similar to what is observed in schizophrenia, SR−/− mice have excitatory neurons in the cortex and hippocampus with reduced dendritic spines, reduced cortico-hippocampal volume, enlarged lateral ventricles, and increased GABA concentrations in the prefrontal cortex (Balu et al., 2012; Balu & Coyle, 2012; Balu et al., 2013; Basu et al., 2009; DeVito et al., 2011; Puhl et al., 2015). SR −/− mice also show reduced brain derived neurotrophic factor (BDNF) expression, Akt signaling, and microRNA-132 levels, which is accompanied by learning and cognitive deficits dependent on the hippocampus and prefrontal cortex (Balu et al., 2013; DeVito et al., 2011). Other genetic models have found that deleting the GluN1 subunit of the NMDAR, either constitutively, in corticolimbic inhibitory neurons, in parvalbumin inhibitory neurons, or in forebrain pyramidal neurons leads to cognitive, social, and electrophysiological (i.e., gamma band oscillations) changes reminiscent of schizophrenia (Belforte et al., 2009; Jadi, Margarita Behrens, & Sejnowski, 2015; Tatard-Leitman et al., 2015). Mice lacking the protein dybsindin, (an original candidate risk gene), which is reduced in schizophrenia, display NMDAR hypofunction, disrupted inhibitory transmission, hyperexcitability in the PFC, as well as deficits in working memory and learning (Carlson et al., 2011; Glen et al., 2014; Karlsgodt et al., 2011; Yuan et al., 2015).

4.1. Circuit based framework for reduced NMDAR function in schizophrenia

There are several neurocircuitry hypotheses for how reduced NMDAR activity contributes to the symptoms of schizophrenia. One hypothesis is that the cognitive impairments are due to hypofunctional NMDARs on cortical γ-amino- butyric acid (GABA) interneurons, particularly fast-spiking parvalbumin interneurons, leading to changes in cortical network oscillations (Jadi et al., 2015; Lisman et al., 2008). This hypothesis is supported by the fact that patients with schizophrenia have reduced parvalbumin expression in the dorsolateral PFC and abnormal gamma band oscillations (Gonzalez-Burgos, Cho, & Lewis, 2015; Jadi et al., 2015), which have been implicated in the synchronization of neural ensembles during working memory and attention. NMDAR hypofunction on cortical interneurons could also lead to an increased tone of glutamatergic projection neurons, resulting in the overstimulation of GABAergic interneurons in the ventral tegmental area. These activated GABA neurons in turn blunt the mesocortical dopamine pathway, preventing adequate dopamine release in the PFC, and thus could contribute to the negative and cognitive symptoms (Ellaithy, Younkin, Gonzalez-Maeso, & Logothetis, 2015). Serotonin (5-HT) receptor subtypes 5-HT_{1A} and 5-HT_{2A}, which are important for emotion and cognition, are elevated and reduced, respectively, in the PFC of patients with schizophrenia (Selvaraj, Arnone, Cappai, & Howes, 2014),. These receptors are highly expressed in pyramidal neurons of the PFC (Kia et al., 1996) and regulate NMDAR activity (Yuen, Jiang, Chen, Feng, & Yan, 2008; Yuen et al., 2005). Thus, changes in PFC 5-HT signaling could

contribute to the cognitive and negative symptoms by altering NMDAR activity in the PFC. Another potential consequence of cortical interneuron disinhibition is that the increased firing of cortical glutamatergic projection neurons leads to hyperactivation of the dopamine mesolimbic pathway and ultimately the positive symptoms (Ellaithy et al., 2015). It is also possible that over activation of the hippocampal-ventral tegmental area loop in schizophrenia can lead to increased dopamine release and onset of psychosis (Lisman et al., 2008).

5. AUGMENTING NMDA RECEPTOR FUNCTION TO TREAT SCHIZOPHRENIA

To this day, the major pharmacological treatment strategy for schizophrenia is based on a serendipitous discovery over 50 years ago of the antipsychotic effects of chlorpromazine (Delay & Deniker, 1955), which was initially developed as an antihistamine to reduce intraoperative autonomic stress. The discovery that these antipsychotic drugs increased dopamine turnover and that their clinical potency correlated with D_2 receptor affinity, led to the development of 10 “first-generation” dopamine D_2 blocker antipsychotic medications. It was not until 20 years later when another serendipitous finding that clozapine, a dibenzodiazepine derivative of the tricyclic antidepressant imipramine, was found in clinical trials to possess antipsychotic efficacy superior to that of existing agents (Kane, Honigfeld, Singer, & Meltzer, 1988). This result started an era of intensive research by the pharmaceutical industry to develop additional “second-generation” antipsychotics with a high 5-HT_2/D_2 ratio, as this was believed to be the therapeutic mechanism of action for clozapine (Meltzer, 1989). Unfortunately, a series of second-generation drugs developed on the basis of favorable 5-HT_2/D_2 ratios failed to outperform first-generation drugs in large publicly funded multicenter trials (P. B. Jones et al., 2006; Lieberman et al., 2005; Sikich et al., 2008). Although these second-generation antipsychotics produced fewer extrapyramidal side effects than first-generation compounds, they produced other serious side effects including hyperlipidemia, glucose intolerance, and weight gain. In light of these findings, there has been a shift to focus on other components (i.e. cognitive and negative symptoms) of schizophrenia rather than just the antipsychotic responsive positive symptoms that primarily engage the dopaminergic system. This section will highlight some of the various strategies employed to augment NMDAR function in schizophrenia.

5.1. The glycine modulatory site

Since the GMS of the NMDAR is not saturated *in vivo* (Bergeron et al., 1998), it is therefore a potential therapeutic target, supporting the hypothesis that administration of GMS agonists could benefit patients by enhancing activation of NMDARs. There are several strategies by which the availability or concentration of GMS co-agonists and antagonists can be altered as a means to augment NMDAR function. Thus, targeting the GMS has been a very active area of research in both the pharmaceutical industry and academia.

There have been more than 70 placebo-controlled clinical trials of GMS agonists in schizophrenia, including D-serine, glycine, D-cycloserine (DCS), and D-alanine. Taken as a whole, the results have been mixed. Many studies reported significant improvements over multiple symptom domains while others did not. Intrinsic differences in efficacy between

GMS co-agonists (Goff, Tsai, Manoach, & Coyle, 1995; Quartermain, Mower, Rafferty, Herting, & Lanthorn, 1994), and methodological factors, most notably small sample sizes, subject compliance, and differences in concurrent antipsychotic use, likely contributed to the variability among these trials. Unfortunately, an NIMH funded large, multi-center, placebo controlled clinical trial of glycine and DCS added on to antipsychotic drugs in schizophrenic patients reported no effects of either drug on negative symptoms or cognition (Buchanan et al., 2007). Recent meta-analysis of 17 double-blind randomized placebo-controlled trials testing whether glutamate positive modulators (GMS modulators: D-serine, D-cycloserine, benzoate, Org25935; AMPA receptor: Minocyclin, CX516; NMDAR: N-acetyl cysteine, pregnenelone, L-carnosine) improve cognitive deficits (overall cognitive function and eight specific cognitive domains) in schizophrenia found that these types of drugs were not superior to placebo as an adjunctive therapy to antipsychotics (Iwata et al., 2015). It should be noted that earlier meta-analyses found that GMS agonists were able to improve multiple symptom domains in conjunction with antipsychotic treatment (Choi, Wykes, & Kurtz, 2013; Tsai & Lin, 2010). However, this most recent meta-analysis by Iwata et al., 2015 included more studies, subjects, and drugs than the previous studies (Choi et al., 2013; Tsai & Lin, 2010).

All of the aforementioned studies tested whether augmenting NMDAR function could improve symptoms in patients with established schizophrenia. It is possible that pharmacologic intervention in the earlier stages of the disorder might produce more robust effects. A recent double-blind, placebo-controlled, parallel-group randomized pilot trial in the United States found that D-serine improved negative symptoms in clinical high-risk teenage patients (Kantrowitz et al., 2015). Even though a larger sample size and replication is needed, this study suggests that D-serine could be effective in treating the prodromal symptoms of schizophrenia.

An alternative approach to directly targeting the GMS is to block reuptake of co-agonist. Research has focused on inhibiting glycine reuptake via GlyT1 blockade because the uptake and release mechanisms for D-serine are poorly understood. Sarcosine (*N*-methylglycine), an intermediate and byproduct in glycine synthesis and degradation, is an endogenous and competitive GlyT1 antagonist. The (Tsai & Lin, 2010) meta-analysis found it effective on total psychopathology, negative symptoms, and general psychopathology. However, sarcosine-derived GlyT1 inhibitors produce undesirable side effects, such as hypoactivity and ataxia, and have therefore prompted the development of non-sarcosine-based GlyT1inhibitors. Unfortunately, the noncompetitive GlyT-1 antagonist, bitopertin, which significantly reduced negative symptoms in a Phase-II trial in schizophrenia, failed to reach its endpoints to improve negative symptoms in multicenter Phase II/III trials (Bugarski-Kirola, Wang, Abi-Saab, & Blattler, 2014). One reason for the poor clinical outcomes with this class of drugs could be that inhibiting GlyT1 augments NMDAR function primarily at extra-synaptic receptors as suggested by recent electrophysiological studies (Li et al., 2013; Papouin et al., 2012), thereby undercutting therapeutic effects.

GMS agonist availability can also be increased by inhibiting DAAO, the enzyme that catabolizes D-amino acids, like D-serine and D-alanine. The expression and activity of DAAO are increased in patients with schizophrenia, and early candidate gene association

studies suggested that DAAO was a schizophrenia risk gene (Verrall, Burnet, Betts, & Harrison, 2010). Benzoate is a naturally occurring DAAO inhibitor that is considered a generally safe food preservative by the FDA. In a small randomized, double-blind, placebo-controlled trial, sodium benzoate significantly improved positive, negative, and cognitive symptoms in patients with schizophrenia stabilized on antipsychotics (Lane et al., 2013). However, this study did not measure plasma D-serine levels following benzoate treatment. There is also an effort to determine whether more potent DAAO inhibitors would increase the bioavailability of D-serine for uptake into the brain. Interestingly, co-administration of novel DAAO inhibitors (much more potent than benzoate at inhibiting enzyme activity) with D-serine does not significantly increase peripheral D-serine levels in dogs and baboons compared to D-serine alone, even though these drugs were effective in doing so in rodents (Rojas et al., 2015). This study raises concerns about the viability of inhibiting peripheral DAAO in humans and suggests that the therapeutic effects seen with benzoate in patients with schizophrenia (Lane et al., 2013) were due to mechanisms other than DAAO inhibition.

Another strategy to restore the NMDAR hypofunction observed in schizophrenia could be to reduce the levels of the endogenous GMS antagonist, kynurenic acid. Preclinical studies in normal rodents demonstrate that cognition is impaired by the administration of either kynurenic acid or kynurenine, the immediate precursor to kynurenic acid (Herman, Bubser, Conn, & Jones, 2012). Kynurenine aminotransferase II inhibitors, which block the formation of kynurenic acid, prevent the cognitive and auditory-gating deficits in rodents and nonhuman primates caused by drugs such as, ketamine and amphetamine (Kozak et al., 2014; Schwarcz, Bruno, Muchowski, & Wu, 2012). These findings suggest that modulation of the kynurenine pathway could be a novel mechanism by which to attenuate the cognitive symptoms in schizophrenia. It should be noted that kynurenic acid is also a potent non-competitive antagonist of the α-7-nicotinic acetylcholine receptor (α7nAChR) and that the cognitive impairments produced by kyurenic acid could be mediated in part by its interaction with the α7nAChR (Albuquerque & Schwarcz, 2013).

In sum, there has been a great effort made to design novel compounds aimed at enhancing NMDAR activity, particularly by targeting the GMS. An optimistic interpretation of the studies conducted so far that directly or indirectly target the NMDAR GMS, is that they provide a proof of principle for the therapeutic effects of augmenting NMDAR function in schizophrenia, but not strong evidence for a feasible long-term treatment. For example, D-serine and glycine have poor pharmacokinetics and brain penetrance, exogenous glycine may preferentially act at extra-synaptic NMDARs, and chronic DCS results in receptor desensitization.

5.2. Allosteric modulation of the NMDA receptor

Although neuroactive steroids can directly regulate NMDAR activity, certain neurosteroids have low potency and poor selectivity, thus making them poor candidates for therapeutic agents. It was recently found that the major brain-derived cholesterol metabolite, 24(S)-hydroxycholesterol, is a very potent and selective NMDAR positive allosteric modulator (PAM) with a distinct mechanism that does not overlap with other allosteric modulators (Paul et al., 2013). Furthermore, synthetic oxysterol derivatives (i.e., SGE-201 and

SGE-301) had desirable *in vivo* drug-like properties and reversed NMDAR antagonist-induced cognitive and social deficits (Paul et al., 2013). Although the exact mechanism by which activating this novel oxysterol site augments NMDAR function is unknown, these findings suggest that it could serve as a therapeutic drug target.

5.3. Metabotropic glutamate receptors 2 and 3

Group II metabotropic glutamate receptors (mGlu) are widely expressed throughout the rodent and human brain. The mGlu subtype 2 ($mGlu_2$) is expressed in many of the brain regions implicated in schizophrenia, including the hippocampus, striatum, prefrontal cortex, and amygdala (Herman et al., 2012). These receptors are found presynaptically, functioning as autoreceptors to inhibit glutamate release, and are also found postsynaptically. There is evidence for crosstalk between $mGlu_2$ and 5-HT_{2A} and for the formation of $mGlu_2$-5-HT_{2A} receptor heterocomplexes (Ellaithy et al., 2015). The mGlu subtype 3 ($mGlu_3$) shows a more diffuse expression pattern than $mGlu_2$,, being expressed presynaptically and in astrocytes (Herman et al., 2012). Although preclinical evidence and initial clinical trials showed promise for $mGlu_{2/3}$ agonists (orthosteric agonists lack subtype specificity) as novel treatments for schizophrenia, subsequent and larger clinical trials with the Lily $mGlu_{2/3}$ prodrug were inconclusive (Kinon et al., 2011) and failed to demonstrate improvements compared to placebo (Hopkins, 2013). Positive allosteric modulators (PAMs) of type II mGlu receptors might hold more promise than traditional agonists. PAMs are unlike traditional agonists because they do not directly activate the receptor, but rather enhance signaling in the presence of endogenous agonist. These types of compounds may be better than traditional agonists because they are less likely to cause receptor internalization and have a safer side effect profile. These types of compounds are better than traditional agonists because they do not cause receptor internalization and have a safer side effect profile. Two $mGlu_2$ PAMs have so far reached clinical trials. A Phase IIa study with ADX71149 (Addex and Janssen) identified patients with residual negative symptoms as those most likely to benefit from adjunctive treatment with ADX71149 (Ellaithy et al., 2015). Potentiation of $mGlu_3$ might also be a therapeutic target to treat the cognitive symptoms of schizophrenia, as $mGlu_3$ negative allosteric modulators impair synaptic plasticity and learning in mice (Walker et al., 2015).

5.4. Metabotropic glutamate receptor 5

The mGlu subtype 5 ($mGlu_5$) is expressed throughout the brain, but is enriched in cortico-limbic regions that are important for affect and memory (Herman et al., 2012). It is primarily located postsynaptically in both excitatory and inhibitory neurons (Biber et al., 1999; Herman et al., 2012). In particular, $mGlu_{5,}$ via its physical interaction with the NMDAR in the postsynaptic density, can enhance NMDAR function. This enhancement is independent of $G_{\alpha q}$ signaling and is facilitated by adaptor proteins, such as Shank and Homer (C. Gao, Tronson, & Radulovic, 2013). $mGlu_5$ is a leading target for novel therapeutics to treat schizophrenia and cognitive disorders, especially since the development of subtype specific PAMs. One newly developed PAM, VU0409551, was found to reverse the deficits in NMDAR function, synaptic plasticity, and memory in SR−/− mice, a genetic model relevant to schizophrenia (Balu et al., 2013). VU0409551 also produced robust antipsychotic-like and cognitive enhancing effects in pharmacologically induced animal models of schizophrenia

(Rook et al., 2015). These results support positive allosteric modulation of $mGlu_5$ as a promising mechanism by which to treat schizophrenia.

5.5. Cholinergic receptors

Muscarinic acetylcholine receptors (mAChRs) are G-protein coupled metabotropic receptors that are widely distributed throughout the neocortex and five isoforms (M1–M5) (Caulfield & Birdsall, 1998). The M1 mAChR is the predominant subtype in the brain, being expressed throughout the striatum, cortex, and postsynaptically on the cell bodies and dendrites of hippocampal pyramidal neurons and granule cells (Marino, Rouse, Levey, Potter, & Conn, 1998). Importantly, M1 mAChR activation in the hippocampus and other forebrain regions potentiates NMDAR currents (Marino et al., 1998). Thus, there has been interest in determining whether M1 mAChRs can alleviate some of the psychotic and cognitive deficits observed in schizophrenia through enhancement of NMDAR neurotransmission. Consistent with this hypothesis, was a small clinical trial in schizophrenia that demonstrated the antipsychotic efficacy of the putative M1/M4 selective mAChR agonist xanomaline (Shekhar et al., 2008). However, current cholinergic therapeutics are limited in their applicability because of aversive side-effect profiles that are attributed to peripheral activation of M2 and M3 mAChRs (Wess, Eglen, & Gautam, 2007). Thus, there has been an effort to generate novel and selective M1 mAChR PAMs (C. K. Jones, Byun, & Bubser, 2012). One such example is VU0453595, which was recently found to reverse the electrophysiological and behavioral deficits in PCP-treated mice (Ghoshal et al., 2015).

nAChRs, a family of receptors that is comprised of 16 different subunits, are widely expressed in the brain, mediate fast synaptic signaling, and modulate the release of other neurotransmitters. Although most nAChRs subunits assemble only into heteropentameric receptor ion channel combinations, the α7 subunits are able to generate functional homomeric nAChRs (Dani & Bertrand, 2007). These receptors have distinct characteristics due to their homopentameric composition that distinguishes them from the other nAChR subtypes including: rapid desensitization, less sensitivity to nicotine as an agonist, and a higher permeability to calcium (Dani & Bertrand, 2007). The majority of the nAChRs in the brain are composed of either α4β2 or α7 subunits. α7 nAChRs are abundantly expressed in the hippocampus and cortex, and play an important role in cognitive functions in both rodents and humans (Dani & Bertrand, 2007). Activation of α7 nAChRs increases cholinergic neurotransmission, the release of glutamate and dopamine, and is pro-cognitive. For these reasons, the α7 nAChR has been a therapeutic target for cognitive impairments in schizophrenia and Alzheimer's disease. One new promising drug that engages the α7 nAChR is encenicline (EVP-6124; [(R)-7-chloro-N-quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide]), a high-affinity partial agonist that potentiates the response to the natural agonist acetylcholine (Prickaerts et al., 2012). Encenicline appears to work as a neuromodulator, with its pro-cognitive effects mediated in part by modulating multiple neurotransmitter systems including glutamate, dopamine, and acetylcholine in the prefrontal cortex and other brain regions (Huang et al., 2014). A recent phase 2, study found that encenicline was generally well tolerated and significantly improved cognition and function in patients with schizophrenia (Keefe et al., 2015). Efforts are also being made to design α7

nAChR PAMs and α4β2 agonists in hopes of ameliorating the cognitive symptoms in schizophrenia (C. K. Jones et al., 2012).

Schizophrenia is a highly heterogeneous disorder that is clinically defined based only on phenomenology, and not yet based on biology. Thus, it is possible that some of the variability in pharmacological responses reported in the above clinical trials could be due to variations in the pathology across schizophrenia patients. As we begin to better understand the neurobiological and genetic underpinnings of schizophrenia, mechanistically novel drugs could be potentially be tested in selected populations that will most likely benefit from that type of intervention.

6. CONCLUSION

Data from clinical, genetic, and animal model studies strongly implicate the NMDAR as a central hub for many of the pathological brain processes that occur in schizophrenia. It has been long known that the dissociative anesthetics and NMDAR antagonists, PCP and ketamine, produce the full range of schizophrenia symptoms and cognitive deficits in healthy subjects (Javitt & Zukin, 1991; Krystal et al., 1994), while ketamine exacerbates symptoms in stabilized schizophrenia patients (Lahti, Weiler, Tamara Michaelidis, Parwani, & Tamminga, 2001). Patients with NMDAR autoimmune encephalitis that produce antibodies against the GluN1 subunit, initially present with psychiatric symptoms similar to schizophrenia. Furthermore, evidence suggests that a certain population of patients with schizophrenia produce antibodies against the NMDAR. Data from patients and human *post-mortem* brains also suggests that the NMDAR is hypofunctional in schizophrenia. The recent explosion of large-scale GWAS and sequencing studies has provided significant evidence for disturbances in genes related to glutamatergic signaling, the postsynaptic density, and dendritic spines. Finally, there is a vast literature on pharmacologic and genetic animal models of NMDAR hypofunction that recapitulate the various neuropathological, electrophysiological, and behavioral abnormalities observed in schizophrenia. It should be noted, however, that this review is an oversimplification of an extremely complex disease. In schizophrenia, there are also disturbances to the GABAergic, cholinergic, and dopaminergic neurotransmitter systems (Coyle, Balu, Benneyworth, Basu, & Roseman, 2010; Lisman et al., 2008), as well as disruptions to astrocytes and white matter integrity (Mighdoll, Tao, Kleinman, & Hyde, 2015). Furthermore, there is convincing evidence that the immune system and oxidative stress play key roles in the pathophysiology of schizophrenia (Leza et al., 2015). Thus, schizophrenia likely results from various combinations of environmental disruptions in brain development and numerous genetic vulnerabilities. These etiological complexities imply that no single pharmacological approach will treat all aspects of the illness nor be effective for all patients with schizophrenia.

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ABBREVIATIONS

DAAO	D-amino acid oxidase
DCS	D-cycloserine
ERP	evoked related potential
GABA	γ-amino-butyric acid
GCP-II	glutamate carboxypeptidase II
GlyT	glycine transporter
GMS	glycine modulatory site
mAChRs	muscarinic acetylcholine receptors
$mGlu_5$	metabotropic glutamate receptor 5
NAAG	N-acetylaspartylglutamate
nAChR	Nicotinic acetylcholine receptors
NMDAR	NMDA receptor
PAM	positive allosteric modulator
PCP	phencyclidine
PFC	prefrontal cortex
PLP	fold II pyridoxal 5′ phosphate
SR	serine racemase

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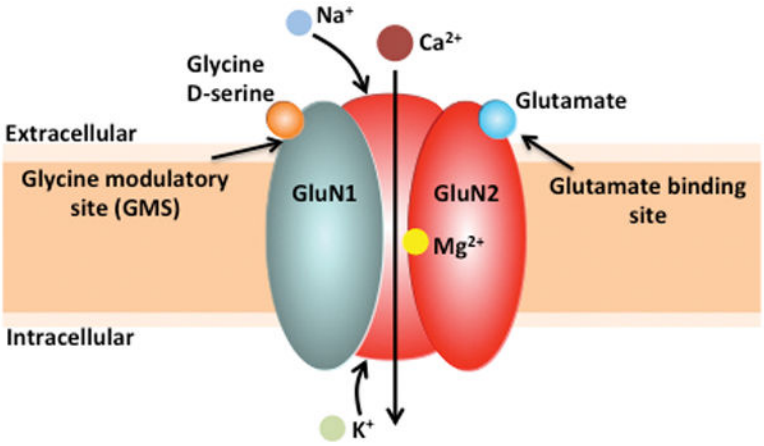

Figure 1. Structure of the NMDA receptor

The conventional NMDAR ion channel is heterotetrameric, consisting of two GluN1 and two GluN2 subunits. These receptors act as molecular coincidence detectors, as in addition to the binding of its agonist glutamate to the GluN2 subunit, activation of the NMDAR requires 1) post-synaptic depolarization, which relieves the Mg^{2+} blockade of the channel and 2) either glycine or D-serine must be bound at the glycine modulatory site (GMS) on the GluN1 subunit. Upon NMDAR channel opening, calcium (Ca^{2+}) and sodium (Na^{+}) enter the neuron, while potassium (K^{+}) exits the neuron.

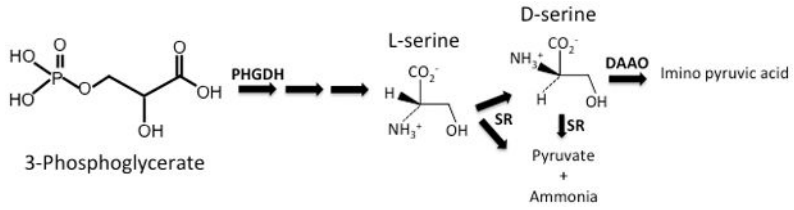

Figure 2. Enzymatic pathways involved in D-serine synthesis and breakdown

Phosphoglycerate 3-dehydrogenase (PGDH), an astrocyte-enriched enzyme, catalyzes the first step in L-serine biosynthesis. L-serine can then be converted to D-serine by the primarily neuronal enzyme serine racemase (SR). SR can also break down L-serine and D-serine (less efficient; smaller arrow) into pyruvate and ammonia. D-serine can be oxidatively deaminated to imino pyruvic acid by D-amino acid oxidase (DAAO).