Chapter 6
D-Serine Signaling and Schizophrenia

Toru Nishikawa

Abstract It has been widely accepted that the hypofunction of the N-methyl-D-aspartate-type glutamate receptor (NMDAR) may be implicated in the pathophysiology of both positive- and negative-cognitive symptomatologies of schizophrenia because NMDAR antagonists, including phencyclidine (PCP) and anti-NMDAR antibodies, mimic these respective antipsychotic-responsive and antipsychotic-resistant symptoms. D-Serine and other agonists for the glycine modulatory site of the NMDAR, which facilitate the receptor function, are found to not only inhibit behavioral models of schizophrenia and hyperdopaminergic transmission caused by schizophrenomimetics, PCP, and amphetamines, in experimental animals, but also ameliorate the entire extent of the above schizophrenic symptoms. Moreover, D-serine has been revealed to be a brain-enriched endogenous substance displaying an NMDAR-like distribution. At least, in the forebrain areas, the NMDAR function levels are under control of the extracellular D-serine concentrations that are regulated in a different manner from that of classical neurotransmitters by neuronal and glial activities, the calcium-permeable AMPA receptor, the Asc-1 neutral amino acid transporter, and the neuronal serine racemase, a D-serine synthesizing enzyme. These findings raise the possibility that insufficient extracellular D-serine signaling could be a part of a key factor that leads to the presumed hypofunction of the NMDAR in schizophrenia. Further investigations on the molecular and cellular mechanisms of the D-serine metabolism and their alterations in schizophrenia may contribute to the elucidation of the pathophysiology of and development of a novel therapeutic approach to this intractable mental disorder.

Keywords N-Methyl-D-aspartate-type glutamate receptor • Dopaminergic transmission • Schizophrenia • D-Serine

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6.1 Introduction: A Link Between D-Serine and Schizophrenia

Prominent stereoselective effects of D-serine in the central nervous system were first demonstrated on the sodium-independent [3H]glycine binding to the homogenate of the rat cerebral cortex (Kishimoto et al. 1981). At that time, the exact nature of the target substance of D-serine was unknown, while the L-isomer of serine had been described to be as equipotent as or more effective than the D-isomer during interactions with the strychnine-sensitive inhibitory glycine receptor (Kishimoto et al. 1981; Tokutomi et al. 1989; White et al. 1989). In 1988, the potent effects of D-serine were possibly explained by the findings of Kleckner and Dingledine (1988) that D-serine and D-alanine enhanced the ability of N-methyl-D-aspartate (NMDA) to activate the NMDA-type glutamate receptor in neurons or expressed in Xenopus Oocytes much stronger than their enantiomers. They also revealed that D-serine and D-alanine stimulated the strychnine-insensitive glycine site of the NMDAR that was shown to be stimulated by glycine, but different from the inhibitory glycine receptor (Johnson and Ascher 1987). The stimulation of the glycine site was required for activation of the NMDAR although an agonist for the site, such as glycine, D-serine, or D-alanine, alone could not activate the NMDAR. In the light of these unique actions, the three amino acids have been called "coagonists for the NMDAR."

The author noted the stereoselective facilitating effects of the D-amino acids on the NMDAR functions as a tool to develop a novel pharmacotherapy for intractable schizophrenia based on the glutamate hypothesis of schizophrenia. Thus, phencyclidine (PCP: 1-(1-phenyl cyclohexyl)piperidine), which generates an antipsychotic-resistant psychosis displaying both positive and negative symptomatologies indistinguishable from those of schizophrenia, was found to block the NMDAR in 1983 (Anis et al. 1983). These observations have suggested that diminished NMDAR-mediated glutamate neurotransmission might be involved in the pathophysiology of schizophrenia. This hypothesis is further supported by the facts that sub-psychotomimetic doses of the NMDAR antagonists for healthy volunteers produce schizophrenic symptoms in the patients with schizophrenia under remission (Javitt and Zulkin 1991; Petersen and Stillman 1978). Moreover, the S-isomer of ketamine, an NMDAR antagonist, has a higher affinity for the glutamate receptor and a greater schizophrenomimetic effect than the R-isomer. Recent observations that autoantibodies against the NMDAR subunits elicit a psychotic state including symptoms that resemble those of schizophrenia also favor the postulated NMDAR dysfunction in schizophrenia.

Therefore, the NMDAR hypofunction hypothesis has indicated that recovery of the glutamate receptor function by its agonists, allosteric agonists, or indirect positive modulators could be expected to ameliorate the antipsychotic-resistant negative symptoms and cognitive deficits in patients with schizophrenia. To test this possibility, the author started to study the effects of the D-serine and D-alanine

on the drug-induced model of schizophrenia because (1) agonists for the glutamate site, but not the glycine site, of the NMDAR produce neuronal cell injury or death, (2) the selectivity of the actions of these D-amino acids at the glycine site can be verified by using their L-isomers, and (3) the D-amino acids had been believed not to be endogenous substances that would not be easily broken down due to the lack of their specific metabolic pathways. This plan appears to be one of the beginnings for the link between schizophrenia and D-serine and lead to the detection of intrinsic D-serine in the brain.

The purpose of this section is to summarize the behavioral and neurochemical analyses supporting the possible relationship between D-serine and schizophrenia and introduce the studies that clarify the molecular and cellular mechanisms underlying endogenous D-serine metabolism and functions that could be targets for investigation of the pathophysiology of schizophrenia and for the development of a novel pharmacotherapy for this mental disorder.

6.2 Ameliorating Effects of D-Serine on Pharmacological Models of Schizophrenia

6.2.1 Phencyclidine Model

In rodents, the acute or chronic administration of a schizophrenomimetic, PCP, induces abnormal behavior including hyperlocomotion, stereotypy, and ataxia and disturbances in preattentive information processing/gating mechanisms and cognitive and social functions (Javitt and Zukin 1991; Tanii et al. 1994). Because the single and repeated use of PCP causes a schizophrenia-like psychosis resistant to antipsychotic drugs and because the above behavioral changes are refractory to or only partially attenuated by antipsychotic drugs, it has been well accepted that PCP-treated animals provide an experimental and comprehensive model for schizophrenia (Javitt and Zukin 1991).

Research groups of the author (Tanii et al. 1990, 1991a, b, 1994) and Contreras (1990) first demonstrated that D-serine possesses an anti-PCP model property by showing the attenuating effects of the D-amino acid given intra-cerebroventricurally on the ability of the systemic administration of PCP to produce increased locomotion, stereotypy, and/or ataxia. These effects of D-serine have been considered to be mediated by the strychnine-insensitive glycine-binding site of the NMDAR on the basis of the following observations: (1) D-serine and D-alanine more potently inhibited the PCP-induced abnormal behavior than L-serine and L-alanine, respectively, coinciding the stereoselectivity of the serine and alanine isomers as agonists for the glycine site (Tanii et al. 1991a, 1994), (2) the decreasing effects of D-serine and D-alanine on PCP-induced hyperactivity were antagonized by intraventricular application of 7-chlorokynurenate and 5,7-dichlorokynurenate, respectively, which

are selective antagonists of the glycine modulatory site (Tanii et al. 1994), and (3) D-serine improved the behavioral abnormalities after administration of another NMDAR antagonist, dizocilpine (MK-801) (Contreras 1990). The detailed mechanisms underlying the anti-PCP or anti-dizocilpine effects of D-serine and other glycine modulatory site agonists including glycine, glycine transporter inhibitor, and D-amino acid oxidase inhibitors that increase the brain concentrations of endogenous D-serine (see Chap. 19) are still unclear. These allosteric agonists could reduce the behavioral effects of noncompetitive antagonists for the NMDAR by increasing the open frequency of the NMDAR ion channel that facilitates liberation of these antagonists from the channel or by activation of the NMDAR that is not occupied by these ion channel blockers (Tanii et al. 1991a, 1994). Furthermore, the NMDAR antagonist induction of disturbances in information processing, sensorimotor gating, and/or attentional processes, which can be evaluated by the prepulse inhibition and lateral inhibition test, respectively, has been found to be ameliorated by direct and indirect agonists of the glycine modulatory site (Depoortere et al. 1999; Hashimoto et al. 2009; Kanahara et al. 2008; Lipina et al. 2005).

The previously mentioned data support the ideas that stimulating agents of the NMDAR glycine site may have a broader therapeutic efficacy for various symptoms of schizophrenia than current antipsychotic drugs and that behavioral disturbances evoked by the NMDAR antagonists could be useful indices for screening such agents.

6.2.2 Amphetamine Model

Another pharmacological model for schizophrenia is the amphetamine or dopamine agonist model that is presumed to mimic the pathophysiology of enhanced dopaminergic transmission, at least, the D2-type dopamine receptor underlying positive symptoms of the disorder. This presumption is based upon the facts that the potency of the therapeutic effects of antipsychotics on the hallucinatory and paranoid state of patients with schizophrenia parallels not only that of their inhibiting effects on hyperlocomotion and/or stereotyped behavior induced by acute treatment with a dopamine agonist such as amphetamines but also that of their antagonizing effects on and affinity for the D2-type dopamine receptor. Moreover, hallucinations and delusions easily relapse in remitted patients with schizophrenia following a sub-psychotomimetic dose of a dopamine agonist for healthy volunteers.

Intraventricular infusion of D-alanine and D-serine but not L-alanine (Hashimoto et al. 1991) also attenuated the methamphetamine production of hyperlocomotion in rats without affecting the stereotypy and catalepsy, suggesting that stimulation of the NMDAR glycine modulatory site could improve the positive symptoms of

schizophrenia and produce minimal extrapyramidal symptoms. In line with these results, the attenuating influence of a large dose of D-serine given systemically on amphetamine-induced psychomotor activity was observed in the rats by Smith et al. (2009).

6.3 Dopaminergic Transmission and D-Serine

Acute application of schizophrenomimetic NMDAR antagonists, PCP or dizocilpine, given either systemically or locally has been demonstrated to increase the tissue dopamine metabolism and the extracellular dopamine concentrations in the discrete brain regions of experimental animals including the prefrontal cortex; the nucleus accumbens; the limbic forebrain area consisting of the septum, olfactory tubercle, and nucleus accumbens; and the striatum (Deutch et al. 1987; Kashiwa et al. 1995; Nishijima et al. 1996; Rao et al. 1989; Tanii et al. 1990; Umino et al. 1998). The magnitude of the enhancement of dopamine transmission after PCP or dizocilpine application was most prominent in the prefrontal cortical areas (Deutch et al. 1987; Nishijima et al. 1996; Rao et al. 1989; Umino et al. 1998). In the medial prefrontal cortex of the rat, the facilitating effects of PCP on the dopamine metabolism were attenuated by an intra-prefrontal infusion of D-alanine, but not L-alanine, in a dose-dependent fashion (Umino et al. 1998). Furthermore, a similar augmented dopamine metabolism was elicited by local injection of competitive antagonists for the NMDAR, but not for the non-NMDA ionotropic glutamate receptors, into the prefrontal cortex in an NMDA-reversible manner (Hata et al. 1990; Nishijima et al. 1994). These data indicate that the prefrontal NMDAR exerts a tonic facilitatory control over the terminals of dopamine neurons projecting to the prefrontal cortex from the ventral tegmental area.

While the accurate neuron setups of the NMDAR-dopamine interaction are still unclear, the over-liberation of the prefrontal extracellular dopamine following the NMDAR antagonists appears to result from a reduced inhibitory GABAergic tone that is provoked by the interruption of the tonic facilitation by the NMDAR expressed on the GABA interneurons. This possibility was substantiated by the following results obtained by in vivo dialysis experiments of Yonezawa et al. (1998): (1) systemic administration of PCP or dizocilpine leads to an increase and a decrease in the extracellular dopamine and GABA concentrations, respectively, (2) local infusion of a $GABA_A$ receptor agonist, muscimol, reversed the elevated levels of the extracellular dopamine, and (3) a $GABA_A$ receptor antagonist, bicuculline, augmented the extracellular dopamine contents. In agreement with this view, ketamine-induced acceleration of the frontal dopamine metabolism was normalized by the systemic administration of diazepam, an allosteric agonist of the $GABA_A$ receptor (Irifune et al. 1998).

It was also demonstrated by Balla et al. (2003, 2012) that repeated blockade of the NMDAR by the daily systemic administration of PCP caused augmentation of

an increase in the extracellular dopamine release in response to a challenge dose of amphetamine in the prefrontal cortex and striatum. Such augmentation of the amphetamine-provoked dopamine release was seen in the caudate-putamen of the patients with schizophrenia as revealed by in vivo studies using positron-emission tomography measuring the rate of displacement of radioligand binding to the D2 dopamine receptor by endogenous dopamine (Abi-Dargham et al. 2009; Laruelle et al. 1996). Balla et al. (2003, 2012) further reported that the subchronic daily co-administration of an agonist for the glycine modulatory site with PCP lowered the hyperresponsiveness of the prefrontal dopamine release to an amphetamine challenge.

Finally, an in vivo dialysis study in freely moving rats (Smith et al. 2009) pointed out that an elevation of the extracellular dopamine levels in the nucleus accumbens by amphetamine was reduced by the systemic injection of a high dose of D-serine. The reducing effect could be related to the attenuation by D-alanine and D-serine of methamphetamine induction of hyperactivity in the rats (Hashimoto et al. 1991; see the previous Sect. 6.2).

6.4 Clinical Treatment Trials with D-Serine of Patients with Schizophrenia

As indicated in Fig. 6.1, the aforementioned studies of the PCP model or NMDAR dysfunction model and the amphetamine model or hyperdopaminergic transmission model extrapolate that, at least in a group of schizophrenia, the NMDAR hypofunction could elicit positive symptoms by hyperdopaminergic activity subsequent to the reduced GABAergic tone and negative symptoms and cognitive defects by disturbances of non-dopaminergic systems. Accelerated serotonergic transmission would lead to the part of the positive and/or negative symptoms by composing the pathophysiological consequences of the NMDAR dysfunction, because (1) the NMDAR antagonists produce an increase in the extracellular serotonin concentrations in the prefrontal cortex, hippocampus, nucleus accumbens, and striatum (López-Gil et al. 2007; Martin et al. 1998; Whitton et al. 1992; Yan et al. 1997) and (2) a selective agonist, dimethyltryptamine, provokes a type of formal thought disorder (Gouzoulis-Mayfrank et al. 2005) (Fig. 6.1). The presumed mechanisms underlying the schizophrenic symptoms suggest that facilitation of the NMDAR function by a direct or indirect agonist could ameliorate both antipsychotic-responsive dopamine-related symptoms and antipsychotic-resistant dopamine-unrelated symptoms (Fig. 6.1).

Allosteric agonists for the NMDAR acting at the glycine modulatory site including glycine, D-serine (Table 6.1), D-alanine, glycine transporter inhibitor sarcosine, and D-cycloserine have indeed been reported to improve the rating scores of the antipsychotic-refractory negative and cognitive symptoms of patients with

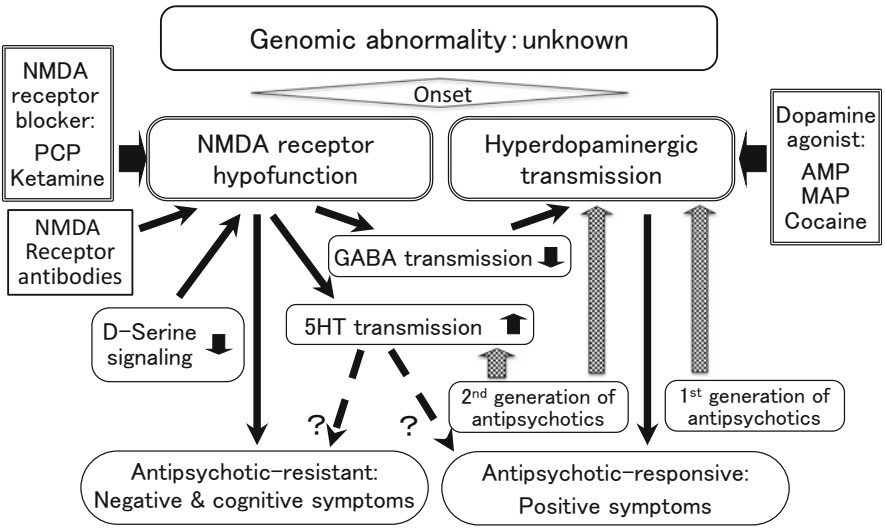

Fig. 6.1 Schematic representation of a pharmacological analysis of the molecular basis of schizophrenic symptoms. Mainly based on the clinical and experimental pharmacological data, the hypothetical pathological changes and their relationships among the neurotransmitter and neuromodulator systems in schizophrenia and substance-induced schizophrenia-like psychoses are depicted. Abbreviations: *AMP* amphetamine, *GABA* γ-aminobutyric acid, *5HT* serotonin, *MAP* methamphetamine, *PCP* phencyclidine

schizophrenia treated with non-clozapine antipsychotics but not with clozapine. The therapeutic efficacy of glycine, D-serine, and/or sarcosine has been confirmed by meta-analyses of their double-blind clinical trials (Singh and Singh 2011; Tsai and Lin 2010; Tuominen et al. 2006;). Recent dose-related investigations of D-serine (Kantrowitz et al. 2010; Weiser et al. 2012) revealed that significant improvement of rating scores of the negative and cognitive symptoms was found after treatment of D-serine at more than 60 mg/kg/day, but not at 30 mg/kg/day and 2 g/day. It is also noteworthy that the results of pilot double-blind studies showed that monotherapy by D-serine reduced the total and negative symptom PANSS scores of patients with schizophrenia (Ermilov et al. 2013) or negative symptoms of individuals at clinical high risk of schizophrenia as estimated by the scale of prodromal symptoms (Kantrowitz et al. 2015).

Consequently, the ameliorating efficacy of the exogenous application of D-serine and other glycine site agonists on schizophrenic symptoms is fitted with the hypofunction of the NMDAR in a group of schizophrenia. However, the effect size of these agents is rather small, which could be due to insufficiencies in their potency or selectivity for the NMDAR and/or their permeability of the blood-brain barrier (BBB).

Table 6.1 Clinical trials of D-serine treatment for patients with schizophrenia or individuals at high risk of schizophrenia

D-serine dosage	Period (weeks)	N	Method (control drug)	Combined antipsychotics	Positive symptoms	Negative symptoms	Cognitive disturbances	Year	Authors
30 mg/kg/day	6	31	Double blind (placebo)	Various (except clozapine)	Improved	Improved	Improved	1998	Tsai et al.
30 mg/kg/day	6	20	Double blind (placebo)	Clozapine	Unchanged	Unchanged	Unchanged	1999	Tsai et al.
30 mg/kg/day	6	39	Double blind, crossover (placebo)	Risperidone or olanzapine	Improved	Improved	Improved	2005	Heresco-Levy et al.
2 g/day (sarcosine or D-ser)	6	44	Double blind (placebo)	Various (except clozapine)	Improved	Improved	Improved	2005	Lane et al.
30, 60, 120 mg/kg/day	4	42	Open label	Various (except clozapine)	Improved	Improved	Improved (≥60 mg)	2010	Kantrowitz et al.
2g/day	6	40	Double blind (placebo)	Various (except clozapine)	Unchanged	Unchanged	Unchanged	2010	Lane et al.
2g/day	16	195	Double blind (placebo)	Various (except clozapine)	Unchanged	Unchanged	Unchanged	2012	Weiser et al.
1.5 (1 week) ~3.0 (9 weeks) g/day	10	8[a]	Double blind (olanzapine)	None	Unchanged[c]	Improved[c]	Unchanged[c]	2013	Ermilov et al.
60 mg/kg/day	16	44[b]	Double blind (placebo)	None	(–)	Improved	(–)	2015	Kantrowitz et al.

[a]Inpatients with a documented history of treatment resistance according to Kane et al. (1988)
[b]Individuals at high risk of schizophrenia
[c]As compared to the scores at the start of the trial but not after the high-dose olanzapine treatment

6.5 Endogenous D-Serine and the Pathophysiology of Schizophrenia

6.5.1 Detection of Brain Endogenous D-Serine

In the initial behavioral study for the development of a novel therapy for intractable schizophrenic symptoms, the author considered the use of D-serine and D-alanine to facilitate the NMDAR function (see the Sect. 6.1) together with a way to overcome their low permeability to the brain. In response to the request of the author, Dr. Hibino from the Nippon Oil & Fat Company synthesized N-myristoyl-D-serine and N-myristoyl-D-alanine as fatty acid derivatives of these amino acids with improved permeability across the BBB. These compounds could be predicted to decompose to their respective fatty acid and free D-amino acid that stimulate the glycine site of the NMDAR (Tanii et al. 1991b). As expected, similar to D-serine and D-alanine, N-myristoyl-D-serine and N-myristoyl-D-alanine inhibited the PCP-induced hyperactivity, stereotypy, and ataxia in a glycine site antagonist-reversible manner (Tanii et al. 1991b), suggesting their action at the NMDAR regulation site. The possible emergence of assumed "non-intrinsic compounds" of the two free D-amino acids in the rats treated by their N-myristic acid derivatives was tested by gas chromatography (GC) and GC-mass spectrometry under cooperation of Dr. Fujii (Tasukuba University, presently Kyoto University) and the late Dr. Hayashi (National Institute of Neuroscience), and endogenous free D-serine was detected at high concentrations in the forebrain, low in the kidney, and non-detectable levels in the liver and serum in the control rats without injections of the lipid-modified D-amino acids (Hashimoto et al. 1992a).

Endogenous D-serine shows a brain-preferring and NMDAR-associated distribution pattern in the rats, mice, and humans (Hashimoto et al. 1992a, b, 1993a, b, 1993c, 1995b; Kumashiro et al. 1995). The author's research group revealed the synthesis (Takahashi et al 1997), extracellular release (Hashimoto et al. 1995a), binding (Matsui et al. 1995; Matoba et al. 1997), uptake (Hayashi et al. 1997; Yamamoto et al. 2001), and breakdown (Hashimoto et al. 1993c) processes of D-serine. Serine racemase and D-amino acid oxidase are believed to catalyze the synthesis of D-serine from L-serine (see Sect. 6.5.1) and the degradation of D-serine to β-hydroxypyruvate and ammonia (see Sect. 6.5.1) in mammals, respectively. However, the molecular machineries specific to the uptake and extracellular release for D-serine are still unclear. In addition, the cell types that contain D-serine and each D-serine metabolic pathway need further elucidation (Nishikawa 2011).

Interestingly, the distribution pattern and the levels of the tissue D-serine concentrations in the discrete brain portions dramatically change during postnatal development, and these changes also resemble those of the GRIN2B (NR2B) subunit mRNA of the NMDAR (Hashimoto et al. 1993a, 1995b). The neuroanatomical features of D-serine suggest that D-serine may be an intrinsic coagonist for the NMDAR (Hashimoto et al. 1993a; Nishikawa 2011). Consistent with this view, the elimination of D-serine without reduction in the tissue and/or extracellular

concentration of another NMDAR coagonist, glycine, from brain slice preparation (Kim et al. 2005; Mothet et al. 2000; Panatier et al. 2006) or in vivo (Ishiwata et al. 2015) by application of D-amino acid oxidase or neuron-selective deletion of the gene for a D-serine-synthesizing enzyme, serine racemase, respectively, produces a hypoactivity of the NMDAR.

Despite the D-serine action at a receptor site, regulation mechanisms of the extracellular levels of D-serine differ from those of classical neurotransmitters including glutamate, glycine, and dopamine in the medial frontal cortex of rodents: (1) depolarization by a potassium channel opener evokes a considerable elevation of the extracellular levels of glutamate and glycine but a significant diminution in those of D-serine (Hashimoto et al. 1995a), (2) cessation of nerve impulse traffic by a sodium channel blocker results in a almost complete loss of the extracellular dopamine (Nishijima et al. 1996) but an increase in the extracellular D-serine contents (Hashimoto et al. 1995a), and (3) chelation of the extracellular contents of calcium ion leads to a drastic decrease in those of dopamine, but rather to an upregulation of those of D-serine (Hashimoto et al. 1995a), although some researchers report that maintenance of the extracellular D-serine levels requires calcium ions (Mothet et al. 2005). No reduction in the extracellular D-serine contents by the calcium ion depletion appears to fit with the demonstration by Pan et al. (2015) that calcium ion-independent D-serine release occurs through the pannexin-1 hemichannel in the astroglia.

6.5.2 *Possible Involvement of Disturbed D-Serine Signaling in the Pathophysiology of Schizophrenia*

The accumulating lines of evidence indicating that D-serine plays a critical role as an endogenous coagonist for the tNMDAR display improving actions against PCP, and amphetamine models for schizophrenia and therapeutic effects on non-clozapine antipsychotic-refractory symptoms of schizophrenia agree with the assumption that aberrant D-serine signaling could be a causative mechanism of the hypofunction of the NMDAR in a group of schizophrenia. While there are so far no findings directly proving the disturbed D-serine metabolism in the pathogenesis or pathophysiology of schizophrenia, a lot of observations in both human and animal studies concur with the implication.

In the postmortem brain tissues, no differences in the D-serine concentrations have been detected between patients with schizophrenia and control subjects without neuropsychiatric disorders (Bendikov et al. 2007; Kumashiro et al. 1995). The results of case-control studies on the quantitative measurement of the D-serine levels in the blood and cerebrospinal fluid (see Brouwer et al. 2013 for a review) are controversial, and meta-analysis of these data indicates no significant changes in the D-amino acid levels in schizophrenia (Brouwer et al. 2013).

It should be noted that the density of [^{3}H]glycine binding to the glycine modulatory site of the NMDAR, which is a target of D-serine, was upregulated in the various cerebral cortical areas of the postmortem brains of patients with schizophrenia as compared to the controls (Ishimaru et al 1994). This upregulation could be explained by a compensatory phenomenon for diminished signaling of the endogenous glycine site agonists, glycine, and /or D-serine. The hypothetical reduced stimulation of the glycine site appears to accord with the in vivo study using single photon emission tomography demonstrating that the drug-naive patients with schizophrenia showed the loss of radioligand ([^{123}I]CNS-1261) binding to the PCP site within the ion channel of the NMDAR in the hippocampus (Pilowsky et al. 2006), because the binding loss could reflect decreased channel open frequencies due to insufficient signals to the NMDAR coagonist site.

These data could be related to the plausible disturbed D-serine metabolism in schizophrenia that is suggested by postmortem brain studies reporting the expressional changes in the transcripts or proteins of genes for D-serine synthesis and degradation enzymes, serine racemase, and D-amino acid oxidase, respectively, in the various brain portions (Madeira et al. 2008; Shinkai et al. 2007; Steffek et al. 2006; Verrall et al. 2007). The plasma levels of protein products of the D-amino acid oxidase activator that was identified from chromosome 13q34, a linkage region for schizophrenia, have been observed to be higher in patients with schizophrenia than in the healthy controls (Lin et al. 2014). In terms of the controversial data (Detera-Wadleigh and McMahon 2006; Li and He 2007; Yamada et al. 2005) or no ratification research, the reproducibility, specificity, and functional significance of these data are still open to argument.

Some results of genetic investigations also agree with the possible deficits in the D-serine signaling system. Single nucleotide polymorphisms and/or haplotypes of the genes for serine racemase (Goltsov et al. 2006; Morita et al. 2007), D-amino acid oxidase (Chumakov et al. 2002), and D-amino acid oxidase activator (G72) (Chumakov et al. 2002) have been found to be significantly associated with schizophrenia. Moreover, a meta-analysis (Shi et al. 2008) or genome-wide association study (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014) has confirmed the genetic association of serine racemase or G72 with schizophrenia, respectively.

In animal experiments, serine racemase gene knockout mice that deplete the brain tissue and extracellular D-serine concentrations to approximately 10 % compared to those of the wild-type controls (Balu et al. 2013; Horio et al. 2011; Labrie et al. 2009) exhibit hypofunction of the NMDAR and behavioral, molecular, and morphological abnormalities that are considered to be models of schizophrenia (Balu et al. 2013; Labrie et al. 2009; see Chap. 7 for details). These reports reinforce the notion drown from the abovementioned biochemical analysis of human brain tissues that a decrement in the synaptic D-serine concentrations could yield certain portions of schizophrenic symptomatologies, whereas no significant changes in the tissue contents of D-serine in the postmortem schizophrenic brains seem to deny a critical drop in the brain serine racemase activity.

6.5.3 Regulation Mechanisms of D-Serine Signaling in Mammalian Brains

From the viewpoint of the coagonist nature of D-serine for the NMDAR, the extracellular concentrations of D-serine require exceedingly precise control systems to maintain adequate levels for physiological activation of the glutamate receptor that is essential for higher-order brain functions. The lack of a depolarization-induced elevation and of a nerve impulse cessation-dependent diminishment of the extracellular D-serine concentrations indicates the possibility that glial cells could participate in their modulation. As expected, our in vivo dialysis experiments revealed that a local infusion of a reversible glia toxin, fluorocitrate, via the dialysis tubing caused a significant reduction in not only the extracellular concentrations of glutamine, a glial activity marker, but also those of D-serine in the medial frontal cortex of the rat (Kanematsu et al. 2006). Subsequent studies by Oliet group (Henneberger et al. 2010; Panatier et al. 2006) added the data denoting the substantial role of astroglia in the regulation of the extracellular release of D-serine.

The extracellular liberation of brain D-serine has been pointed out to be under the influence of the ionotropic glutamate receptors. Snyder's research group found that the kainate-type glutamate receptor facilitates the release of the [3H]D-serine preloaded to the primary culture of the astroglia from the rat cortex (Schell et al. 1995). The α-amino-3-hydroxy-5-methyl-4-isoxazolepropioinic acid (AMPA)-type glutamate receptor has also been described to play a phasic stimulatory role in the control of the extracellular release of preloaded radiolabeled or intrinsic D-serine from the in vitro preparations including the primary culture of the rat cortical astroglia (Mothet et al. 2005; Rosenberg et al. 2010; Schell et al. 1995) or neurons (Kartvelishvily et al. 2006; Rosenberg et al. 2010), C6 glioma cells (Mothet et al. 2005), and isolated retinal tissues (Sullivan and Miller 2010, 2012). In contrast, our in vivo studies have demonstrated that the calcium-permeable-type GRIA2 subunit-lacking AMPA receptor exerts a phasic inhibitory regulation of the extracellular levels of D-serine in the medial frontal cortex of the rat (Ishiwata et al. 2013a). This discrepancy could be attributed to the differences in the cellular interactions (i.e., neuron-glia and glia-glia) and neuronal circuits between the in vitro and in vivo experimental conditions. The calcium-permeable AMPA receptor-connected inhibitory influence is considered to be a specific interaction because an AMPA receptor agonist-induced decrease in the extracellular taurine contents is insensitive to a selective antagonist for the calcium-permeable AMPA receptor (Ishiwata et al. 2013a).

Neutral amino acid transporters containing sodium-dependent ASCT1 and ASCT2 (Gliddon et al. 2009; Hayashi et al. 1997; O'Brien et al. 2005; Ribeiro et al. 2002), sodium-independent Asc-1 (Fukasawa et al. 2000; Rutter et al. 2007), and proton-dependent PAT1 (Metzner et al. 2005) have been documented to provide an uptake capacity of D-serine with low to relatively high affinity (IC_{50} of approximately 10–50 μM for Asc-1) and to be expressed in neurons or astroglia in

the brain tissues. The pharmacological and neuroanatomical features of these transporters suggest their plausible involvement in the physiological uptake of D-serine in mammalian brains. In fact, we have found using an in vivo dialysis technique that an Asc-1 inhibitor, S-methyl-L-cysteine, augments the extracellular D-serine levels in the medial frontal cortex of the rat (Ishiwata et al. 2013b).

A profound loss of the extracellular and tissue amounts of D-serine and disturbances in the NMDAR-mediated formation of the long-term potentiation (LTP) by genetic total depletion of serine racemase in the mice seems to endow the D-serine-synthesizing enzyme with a role in the setting of the extracellular levels of D-serine (Benneyworth et al. 2011). CamKIIα-expressing neuron-specific deficits in the serine racemase lead to an NMDAR hypofunction with a significant diminution in the extracellular D-serine contents in the hippocampus (Benneyworth et al. 2011; Ishiwata et al. 2015).

Although the data indicating the molecules that modulate the extracellular D-serine concentrations have been accumulated as already mentioned, the exact machinery that directly liberates D-serine from the intracellular site to the extracellular fluid and the precise intracellular storage site of the releasable D-serine are mostly unknown. The SNARE proteins (Mothet et al. 2005), the hemichannel of connexin-43 (Stehberg et al. 2012) or pannexin-1 (Pan et al. 2015), the Asc-1 transporter (Rosenberg et al. 2013), or Dsm-1 (PAPST-1) (Shimazu et al. 2006) have been proposed to be involved in the extracellular release of D-serine and need further elucidation regarding their detailed functions in the release process and cellular localization.

6.6 Conclusions

Experimental and clinical investigations have indicated that the antipsychotic-responsive and antipsychotic-resistant symptoms of schizophrenia and their pharmacological models are ameliorated by D-serine through facilitation of the NMDAR functions. Since D-serine has been demonstrated to be an endogenous coagonist for the NMDAR, the molecular cascades and cellular setups for the brain D-serine signaling may be suitable targets for analyses of the pathophysiology of the NMDAR hypofunction and generation of a novel pharmacotherapy of schizophrenia and related psychoses.

References

Abi-Dargham A, van de Giessen E, Slifstein M et al (2009) Baseline and amphetamine-stimulated dopamine activity are related in drug-naïve schizophrenic subjects. Biol Psychiatry 65 (12):1091–1093

Anis NA, Berry SC, Burton NR et al (1983) The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurons by N-methyl-aspartate. Br J Pharmacol 79:565–575

Balla A, Sershen H, Serra M (2003) Subchronic continuous phencyclidine administration potentiates amphetamine-induced frontal cortex dopamine release. Neuropsychopharmacology 28 (1):34–44

Balla A, Schneider S, Sershen H et al (2012) Effects of novel, high affinity glycine transport inhibitors on frontostriatal dopamine release in a rodent model of schizophrenia. Eur Neuropsychopharmacol 22(12):902–910

Balu DT, Li Y, Puhl MD et al (2013) Multiple risk pathways for schizophrenia converge in serine racemase knockout mice, a mouse model of NMDA receptor hypofunction. Proc Natl Acad Sci U S A 110(26):E2400–E2409

Bendikov I, Nadri C, Amar S et al (2007) A CSF and postmortem brain study of D-serine metabolic parameters in schizophrenia. Schizophr Res 90(1–3):41–51

Benneyworth MA, Basu AC, Coyle JT (2011) Discordant behavioral effects of psychotomimetic drugs in mice with altered NMDA receptor function. Psychopharmacology (Berlin) 213 (1):143–153

Brouwer A, Luykx JJ, van Boxmeer L et al (2013) NMDA-receptor coagonists in serum, plasma, and cerebrospinal fluid of schizophrenia patients: a meta-analysis of case-control studies. Neurosci Biobehav Rev 37(8):1587–1596

Chumakov I, Blumenfeld M, Guerassimenko O et al (2002) Genetic and physiological data implicating the new human gene G72 and the gene for D-amino acid oxidase in schizophrenia. Proc Natl Acad Sci U S A 99(21):13675–13680

Contreras PC (1990) D-serine antagonized phencyclidine- and MK-801-induced stereotyped behavior and ataxia. Neuropharmacology 29(3):291–293

Depoortere R, Perrault G, Sanger DJ (1999) Prepulse inhibition of the startle reflex in rats: effects of compounds acting at various sites on the NMDA receptor complex. Behav Pharmacol 10 (1):51–62

Detera-Wadleigh SD, McMahon FJ (2006) G72/G30 in schizophrenia and bipolar disorder: review and meta-analysis. Biol Psychiatry 60(2):106–114

Deutch AY, Tam SY, Freeman AS et al (1987) Mesolimbic and mesocortical dopamine activation induced by phencyclidine: contrasting pattern to striatal response. Eur J Pharmacol 134 (3):257–264

Ermilov M, Gelfin E, Levin R et al (2013) A pilot double-blind comparison of d-serine and high-dose olanzapine in treatment-resistant patients with schizophrenia. Schizophr Res 150 (2–3):604–605

Fukasawa Y, Segawa H, Kim JY et al (2000) Identification and characterization of a Na(+)-independent neutral amino acid transporter that associates with the 4F2 heavy chain and exhibits substrate selectivity for small neutral D- and L-amino acids. J Biol Chem 275 (13):9690–9698

Gliddon CM, Shao Z, LeMaistre JL et al (2009) Cellular distribution of the neutral amino acid transporter subtype ASCT2 in mouse brain. J Neurochem 108(2):372–383

Goltsov AY, Loseva JG, Andreeva TV et al (2006) Polymorphism in the 5′-promoter region of serine racemase gene in schizophrenia. Mol Psychiatry 11:325–326

Gouzoulis-Mayfrank E, Heekeren K, Neukirch A et al (2005) Psychological effects of (S)-ketamine and N, N-dimethyltryptamine (DMT): a double-blind, cross-over study in healthy volunteers. Pharmacopsychiatry 38(6):301–311

Hashimoto A, Nishikawa T, Oka T et al (1991) D-Alanine inhibits methamphetamine-induced hyperactivity in rats. Eur J Pharmacol 202:105–107

Hashimoto A, Nishikawa T, Hayashi T et al (1992a) The presence of free D-serine in rat brain. FEBS Lett 296:33–36

Hashimoto A, Nishikawa T, Oka T et al (1992b) Determination of free amino acid enantiomers in rat brain and serum by high performance liquid chromatography after derivatization with N-tert.-butyloxycarbonyl-L-cysteine and o-phthaldialdehyde. J Chromatogr 582:41–48

Hashimoto A, Nishikawa T, Oka T et al (1993a) Endogenous D-serine in rat brain: N-Methyl-D-aspartate receptor-related distribution and aging. J Neurochem 60:783–786

Hashimoto A, Kumashiro S, Nishikawa T et al (1993b) Embryonic development and postnatal changes in free D-aspartate and D-serine in the human prefrontal cortex. J Neurochem 61:348–351

Hashimoto A, Nishikawa T, Konno R et al (1993c) Free D-serine, D-aspartate and D-alanine in central nervous system and serum in mutant mice lacking D-amino acid oxidase. Neurosci Lett 152:33–36

Hashimoto A, Oka T, Nishikawa T (1995a) Extracellular concentration of endogenous free D-serine in the rat brain as revealed by in vivo microdialysis. Neuroscience 66(3):635–643

Hashimoto A, Oka T, Nishikawa T (1995b) Anatomical distribution and postnatal changes in endogenous free D-aspartate and D-serine in rat brain and periphery. Eur J Neurosci 7:1657–1663

Hashimoto K, Fujita Y, Horio M et al (2009) Co-administration of a D-amino acid oxidase inhibitor potentiates the efficacy of D-serine in attenuating prepulse inhibition deficits after administration of dizocilpine. Biol Psychiatry 65(12):1103–1106

Hata N, Nishikawa T, Umino A et al (1990) Evidence for involvement of N-methyl-D-aspartate receptor in tonic inhibitory control of dopaminergic transmission in rat medial frontal cortex. Neurosci Lett 120(1):101–104

Hayashi F, Takahashi K, Nishikawa T (1997) Uptake of L- and D-serine in C6 glioma cells. Neurosci Lett 239:85–88

Henneberger C, Papouin T, Oliet SH et al (2010) Long-term potentiation depends on release of D-serine from astrocytes. Nature 463(7278):232–236

Heresco-Levy U, Javitt DC, Ebstein R et al (2005) D-serine efficacy as add-on pharmacotherapy to risperidone and olanzapine for treatment-refractory schizophrenia. Biol Psychiatry 57 (6):577–585

Horio M, Kohno M, Fujita Y et al (2011) Levels of D-serine in the brain and peripheral organs of serine racemase (Srr) knock-out mice. Neurochem Int 59(6):853–859

Irifune M, Sato T, Kamata Y et al (1998) Inhibition by diazepam of ketamine-induced hyperlocomotion and dopamine turnover in mice. Can J Anaesth 45(5 Pt 1):471–478

Ishimaru M, Kurumaji A, Toru M (1994) Increases in strychnine-insensitive glycine binding sites in cerebral cortex of chronic schizophrenics: evidence for glutamate hypothesis. Biol Psychiatry 35:84–95

Ishiwata S, Ogata S, Umino A et al (2013a) Increasing effects of S-methyl-L-cysteine on the extracellular D-serine concentrations in the rat medial frontal cortex. Amino Acids 44 (5):1391–1395

Ishiwata S, Umino A, Umino M et al (2013b) Modulation of extracellular d-serine content by calcium permeable AMPA receptors in rat medial prefrontal cortex as revealed by in vivo microdialysis. Int J Neuropsychopharmacol 16(6):1395–1406

Ishiwata S, Umino A, Balu DT et al (2015) Neuronal serine racemase regulates extracellular D-serine levels in the adult mouse hippocampus. J Neural Transm 122(8):1099–1103

Javitt DC, Zukin SR (1991) Recent advances in the phencyclidine model of schizophrenia. Am J Psychiatry 148(10):1301–1308

Johnson JW, Ascher P (1987) Glycine potentiates the NMDA response in cultured mouse brain neurons. Nature 325(6104):529–531

Kanahara N, Shimizu E, Ohgake S et al (2008) Glycine and D: −serine, but not D: −cycloserine, attenuate prepulse inhibition deficits induced by NMDA receptor antagonist MK-801. Psychopharmacology (Berlin) 198(3):363–374

Kane JM, Honigfeld G, Singer J et al (1988) Clozapine in treatment-resistant schizophrenics. Psychopharmacol Bull 24(1):62–67

Kanematsu S, Ishii S, Umino A et al (2006) Evidence for involvement of glial cell activity in the control of extracellular D-serine contents in the rat brain. J Neural Transm 113:1717–1721
Kantrowitz JT, Malhotra AK, Cornblatt B et al (2010) High dose D-serine in the treatment of schizophrenia. Schizophr Res 121(1–3):125–130
Kantrowitz JT, Woods SW, Petkova E et al (2015) D-serine for the treatment of negative symptoms in individuals at clinical high risk of schizophrenia: a pilot, double-blind, placebo-controlled, randomised parallel group mechanistic proof-of-concept trial. Lancet Psychiatry 2(5):403–412
Kartvelishvily E, Schleper M, Balan L et al (2006) Neuron-derived D-serine release provides a novel means to activate N-Methyl-D-aspartate receptors. J Biol Chem 281:14151–14162
Kashiwa A, Nishikawa T, Nishijima K et al (1995) Dizocilpine (MK-801) elicits a tetrodotoxin-sensitive increase in extracellular release of dopamine in rat medial frontal cortex. Neurochem Int 26(3):269–279
Kim PM, Aizawa H, Kim PS et al (2005) Serine racemase: activation by glutamate neurotransmission via glutamate receptor interacting protein and mediation of neuronal migration. Proc Natl Acad Sci U S A 102(6):2105–2110
Kishimoto H, Simon JR, Aprison MH (1981) Determination of the equilibrium dissociation constants and number of glycine binding sites in several areas of the rat central nervous system, using a sodium-independent system. J Neurochem 37(4):1015–1024
Kleckner NW, Dingledine R (1988) Requirement for glycine in activation of NMDA-receptors expressed in Xenopus oocytes. Science 241(4867):835–837
Kumashiro S, Hashimoto A, Nishikawa T (1995) Free D-serine in post-mortem brains and spinal cords of individuals with and without neuropsychiatric diseases. Brain Res 681:117–125
Labrie V, Fukumura R, Rastogi A et al (2009) Serine racemase is associated with schizophrenia susceptibility in humans and in a mouse model. Hum Mol Genet 18(17):3227–3243
Lane HY, Chang YC, Liu YC et al (2005) Sarcosine or D-serine add-on treatment for acute exacerbation of schizophrenia: a randomized, double-blind, placebo-controlled study. Arch Gen Psychiatry 62(11):1196–1204
Lane HY, Lin CH, Huang YJ et al (2010) A randomized, double-blind, placebo-controlled comparison study of sarcosine (N-methylglycine) and D-serine add-on treatment for schizophrenia. Int J Neuropsychopharmacol 13(4):451–460
Laruelle M, Abi-Dargham A, van Dyck CH et al (1996) Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. Proc Natl Acad Sci U S A 93(17):9235–9240
Li D, He L (2007) G72/G30 genes and schizophrenia: a systematic meta-analysis of association studies. Genetics 175(2):917–922
Lin CH, Chang HT, Chen YJ et al (2014) Distinctively higher plasma G72 protein levels in patients with schizophrenia than in healthy individuals. Mol Psychiatry 19(6):636–637
Lipina T, Labrie V, Weiner I et al (2005) Modulators of the glycine site on NMDA receptors, D-serine and ALX 5407, display similar beneficial effects to clozapine in mouse models of schizophrenia. Psychopharmacology (Berlin) 179(1):54–67
López-Gil X, Babot Z, Amargós-Bosch M et al (2007) Clozapine and haloperidol differently suppress the MK-801-increased glutamatergic and serotonergic transmission in the medial prefrontal cortex of the rat. Neuropsychopharmacology 32(10):2087–2097
Madeira C, Freitas ME, Vargas-Lopes C et al (2008) Increased brain D-amino acid oxidase (DAAO) activity in schizophrenia. Schizophr Res 101(1–3):76–83
Martin P, Carlsson ML, Hjorth S (1998) Systemic PCP treatment elevates brain extracellular 5-HT: a microdialysis study in awake rats. Neuroreport 9(13):2985–2988
Matoba M, Tomita U, Nishikawa T (1997) Characterization of 5, 7-dichlorokynurenate-insensitive [3H] D-serine binding to synaptosomal fraction isolated from rat brain tissues. J Neurochem 69:399–405
Matsui T, Sekiguchi M, Hasimoto A et al (1995) Functional comparison of D-serine and glycine in rodents: the effects on cloned NMDA receptors and the extracellular concentration. J Neurochem 65:454–458

Metzner L, Kottra G, Neubert K et al (2005) Serotonin, L-tryptophan, and tryptamine are effective inhibitors of the amino acid transport system PAT1. FASEB J 19(11):1468–1473

Morita Y, Ujike H, Tanaka Y et al (2007) A genetic variant of the serine racemase gene is associated with schizophrenia. Biol Psychiatry 61(10):1200–1203

Mothet JP, Parent AT, Wolosker H et al (2000) D-serine is an endogenous ligand for the glycine site of the N-methyl-D-aspartate receptor. Proc Natl Acad Sci U S A 97(9):4926–4931

Mothet JP, Pollegioni L, Ouanounou G et al (2005) Glutamate receptor activation triggers a calcium-dependent and SNARE protein-dependent release of the gliotransmitter D-serine. Proc Natl Acad Sci U S A 102(15):5606–5611

Nishijima K, Kashiwa A, Nishikawa T (1994) Preferential stimulation of extracellular release of dopamine in rat frontal cortex to striatum following competitive inhibition of the N-methyl-D-aspartate receptor. J Neurochem 63(1):375–378

Nishijima K, Kashiwa A, Hashimoto A et al (1996) Differential effects of phencyclidine and methamphetamine on dopamine metabolism in rat frontal cortex and striatum as revealed by in vivo dialysis. Synapse 22(4):304–312

Nishikawa T (2011) Analysis of free D-serine in mammals and its biological relevance. J Chromatogr B Anal Technol Biomed Life Sci 879:3169–3183

O'Brien KB, Miller RF, Bowser MT (2005) D-Serine uptake by isolated retinas is consistent with ASCT-mediated transport. Neurosci Lett 385(1):58–63

Pan HC, Chou YC, Sun SH (2015) P2X7 R-mediated Ca(2+) -independent d-serine release via pannexin-1 of the P2X7 R-pannexin-1 complex in astrocytes. Glia 63(5):877–893

Panatier A, Theodosis DT, Mothet JP et al (2006) Glia-derived D-serine controls NMDA receptor activity and synaptic memory. Cell 125(4):775–784

Petersen RC, Stillman RC (1978) Phencyclidine (PCP) abuse: an appraisal. In: Petersen RC, Stillman RC (eds) NIDA research monograph 21. Superintendent of Documents, US Government Printing Office, Washington, DC, pp 1–17

Pilowsky LS, Bressan RA, Stone JM et al (2006) First in vivo evidence of an NMDA receptor deficit in medication-free schizophrenic patients. Mol Psychiatry 11(2):118–119

Rao TS, Kim HS, Lehmann J et al (1989) Differential effects of phencyclidine (PCP) and ketamine on mesocortical and mesostriatal dopamine release in vivo. Life Sci 45(12):1065–1072

Ribeiro CS, Reis M, Panizzutti R et al (2002) Glial transport of the neuromodulator D-serine. Brain Res 929(2):202–209

Rosenberg D, Kartvelishvily E, Shleper M et al (2010) Neuronal release of d-serine: a physiological pathway controlling extracellular d-serine concentration. FASEB J 24(8):2951–2961

Rosenberg D, Artoul S, Segal AC et al (2013) Neuronal D-serine and glycine release via the Asc-1 transporter regulates NMDA receptor-dependent synaptic activity. J Neurosci 33 (8):3533–3544

Rutter AR, Fradley RL, Garrett EM et al (2007) Evidence from gene knockout studies implicates Asc-1 as the primary transporter mediating d-serine reuptake in the mouse CNS. Eur J Neurosci 25(6):1757–1766

Schell MJ, Molliver ME, Snyder SH (1995) D-serine, an endogenous synaptic modulator: localization to astrocytes and glutamate-stimulated release. Proc Natl Acad Sci U S A 92 (9):3948–3952

Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014) Biological insights from 108 schizophrenia-associated genetic loci. Nature 511(7510):421–427

Shi J, Badner JA, Gershon ES (2008) Allelic association of G72/G30 with schizophrenia and bipolar disorder: a comprehensive meta-analysis. Schizophr Res 98(1–3):89–97

Shimazu D, Yamamoto N, Umino A et al (2006) Inhibition of D-serine accumulation to the Xenopus Oocyte by expression of the rat ortholog of human 3′-phosphoadenosine 5′-phosphosulfate transporter gene isolated from the neocortex as D-serine modulator-1. J Neurochem 96:30–42

Shinkai T, De Luca V, Hwang R (2007) Association analyses of the DAOA/G30 and D-amino-acid oxidase genes in schizophrenia: further evidence for a role in schizophrenia. Neuromolecular 9(2):169–177
Singh SP, Singh V (2011) Meta-analysis of the efficacy of adjunctive NMDA receptor modulators in chronic schizophrenia. CNS Drugs 25(10):859–885
Smith SM, Uslaner JM, Yao L et al (2009) The behavioral and neurochemical effects of a novel D-amino acid oxidase inhibitor compound 8 [4H-thieno [3,2-b]pyrrole-5-carboxylic acid] and D-serine. J Pharmacol Exp Ther 328(3):921–930
Steffek AE, Haroutunian V, Meador-Woodruff JH (2006) Serine racemase protein expression in cortex and hippocampus in schizophrenia. Neuroreport 17(11):1181–1185
Stehberg J, Moraga-Amaro R et al (2012) Release of gliotransmitters through astroglial connexin 43 hemichannels is necessary for fear memory consolidation in the basolateral amygdala. FASEB J 26(9):3649–3657
Sullivan SJ, Miller RF (2010) AMPA receptor mediated D-serine release from retinal glial cells. J Neurochem 115(6):1681–1689
Sullivan SJ, Miller RF (2012) AMPA receptor-dependent, light-evoked D-serine release acts on retinal ganglion cell NMDA receptors. J Neurophysiol 108(4):1044–1051
Takahashi K, Hayashi F, Nishikawa T (1997) In vivo evidence for the link between L- and D-serine metabolism in rat cerebral cortex. J Neurochem 69:1286–1290
Tanii Y, Nishikawa T, Umino A et al (1990) Phencyclidine increases extracellular dopamine metabolites in rat medial frontal cortex as measured by in vivo dialysis. Neurosci Lett 112 (2–3):318–323
Tanii Y, Nishikawa T, Hashimoto A et al (1991a) Stereoselective inhibition by D- and L-alanine of phencyclidineinduced locomotor stimulation in the rat. Brain Res 563:281–284
Tanii Y, Nishikawa T, Hibino H et al (1991b) Effects of allosteric agonists for the N-methyl D-aspartate receptor and their derivatives on phencyclidine-induced abnormal behavior in the rat. Brain Sci Ment Disord 2:497–502
Tanii Y, Nishikawa T, Hashimoto A et al (1994) Stereoselective antagonism by enantiomers of alanine and serine of phencyclidine-induced hyperactivity, stereotypy and ataxia in the rat. J Pharmacol Exp Ther 269:1040–1048
Tokutomi N, Kaneda M, Akaike N (1989) What confers specificity on glycine for its receptor site? Br J Pharmacol 97(2):353–360
Tsai GE, Lin PY (2010) Strategies to enhance N-methyl-D-aspartate receptor-mediated neurotransmission in schizophrenia, a critical review and meta-analysis. Curr Pharm Des 16 (5):522–537
Tsai G, Yang P, Chung LC et al (1998) D-serine added to antipsychotics for the treatment of schizophrenia. Biol Psychiatry 44(11):1081–1089
Tsai GE, Yang P, Chung LC (1999) D-serine added to clozapine for the treatment of schizophrenia. Am J Psychiatry 156(11):1822–1825
Tuominen HJ, Tiihonen J, Wahlbeck K (2006) Glutamatergic drugs for schizophrenia. Cochrane Database Syst Rev 19(2):CD003730
Umino A, Takahashi K, Nishikawa T (1998) Characterization of phencyclidine-induced increase in prefrontal cortical dopamine metabolism in the rat. Br J Pharmacol 124:377–385
Verrall L, Walker M, Rawlings N et al (2007) d-Amino acid oxidase and serine racemase in human brain: normal distribution and altered expression in schizophrenia. Eur J Neurosci 26 (6):1657–1669
Weiser M, Heresco-Levy U, Davidson M et al (2012) A multicenter, add-on randomized controlled trial of low-dose d-serine for negative and cognitive symptoms of schizophrenia. J Clin Psychiatry 73(6):e728–e734
White WF, Brown KL, Frank DM (1989) Glycine binding to rat cortex and spinal cord: binding characteristics and pharmacology reveal distinct populations of sites. J Neurochem 53 (2):503–512

Whitton PS, Biggs CS, Pearce BR (1992) MK-801 increases extracellular 5-hydroxytryptamine in rat hippocampus and striatum in vivo. J Neurochem 58(4):1573–1575

Yamada K, Ohnishi T, Hashimoto K et al (2005) Identification of multiple serine racemase (SRR) mRNA isoforms and genetic analyses of SRR and DAO in schizophrenia and D-serine levels. Biol Psychiatry 57(12):1493–1503

Yamamoto N, Tomita U, Umino A et al (2001) Uptake of D-serine by synaptosomal P2 fraction isolated from rat brain. Synapse 42:84–86

Yan QS, Reith ME, Jobe PC et al (1997) Dizocilpine (MK-801) increases not only dopamine but also serotonin and norepinephrine transmissions in the nucleus accumbens as measured by microdialysis in freely moving rats. Brain Res 765(1):149–158

Yonezawa Y, Kuroki T, Kawahara T (1998) Involvement of gamma-aminobutyric acid neurotransmission in phencyclidine-induced dopamine release in the medial prefrontal cortex. Eur J Pharmacol 341(1):45–56