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D-serine: a new word in the glutamatergic neuro-glial language

Review Article

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Summary. Gliotransmission is a process in which astrocytes are dynamic elements that influence synaptic transmission and synaptogenesis. The best-known gliotransmitters are glutamate and ATP. However, in the past decade, it has been demonstrated that D-serine, a D-amino acid, acts as a gliotransmitter in glutamatergic synapses. The physiological relevance of D-serine is sustained by the way in which it modulates the action of glutamatergic neurotransmission, neuronal migration and long-term potentiation (LTP). In addition, the synthesis and degradation mechanisms of D-serine have been proposed as potential therapeutic targets for the treatment of Alzheimer's disease, schizophrenia and related disorders. In the present review, detailed information is provided about the physiological and physiopathological relevance of D-serine, including metabolic and regulation aspects.

Keywords: Gliotransmission – D-serine – Glutamate – NMDA – Glycine site

1. Basic aspects about metabolism and actions of D-serine

1.1 Introduction

For a long time, D-amino acids (D-aac) were ignored by researchers, because they belong to the less biologically active conformation of amino acids. Although the existence of D-aac was confirmed in bacteria, worms and other invertebrates (Corrigan, 1969), it was a few years age that they were detected in mammalian tissues in high levels, especially in the brain (Hashimoto et al., 1992; Chouinard et al., 1993; Nagata et al., 1994). Among the first D-aac discovered in high concentrations in the brain was the D-aspartate (Dunlop et al., 1986). Later on, another very important D-aac called D-serine (D-ser) was found in elevated levels in the mammalian brain (Hashimoto et al., 1993b). Since its discovery, data about the functions of D-ser have increased markedly and it has been investigated along many scientific lines. Although this D-aac is found in peripheral tissues, its high content in the brain, especially in astrocytes, makes it an important factor for understanding neuromodulation (Hashimoto et al., 1995). Classically, synapses were considered as polarized elements where neurotransmitter substances are released from the presynaptic cells and bind to their postsynaptic receptors. However, the central nervous system (CNS) is made up of neurons and glial cells, the latter being the most numerous (Nedergaard et al., 2003). Glial cells are tightly located with neurons, allowing a bidirectional communication between neurons and glia (Volterra and Harris, 1999; Haydon, 2001; Volterra and Meldolesi, 2005). The complex produced by synaptic cells and the surrounding glia is the basis for an emerging concept that reflects on the synapses as tripartite elements and proposes glia as dynamic components that control synaptogenesis (Pfrieger, 2002) and synaptic transmission (Oliet et al., 2004). These functions carried out by astrocytes are mediated by neuromodulators and gliotransmitters released by them. Although glutamate (glu) and ATP are the best-known gliotransmitters, it is now clear that D-ser can be added to the list (Wolosker et al., 1992).

1.2 Synthesis and distribution of D-ser

D-ser is synthesized from L-serine (L-ser) via one enzymatic step catalyzed by the enzyme serine racemase (SR) (Schell, 2004). This enzyme is proposed as the main endogenous source, if not the only one, of D-ser. The SR

catalyses the conversion of D-ser into L-ser, albeit with lower affinity (Wolosker et al., 1999; Konno, 2003). The SR distribution is analoguous to D-ser sharing the highest levels in the forebrain (Wolosker et al., 1999; Xia et al., 2004). In the CNS, SR is an almost exclusive enzyme of glial fibrillary acidic protein (GFAP) positive astrocytes (Wolosker et al., 1999; Xia et al., 2004; Williams et al., 2006), but is also found in several cortical neurons and in hindbrain glutamatergic neurons (Williams et al., 2006). In the peripheral nervous system, SR is mainly located in Schwann cells (Wu and Barger, 2004). The level of D-ser varies during brain development. In the adult stage, the highest level of this D-aac is in the forebrain, while in neonates it is found in the cerebellum (Schell et al., 1995, 1997). Notably, the cerebellar concentrations of D-ser in the adult brain are practically undetectable (Schell et al., 1995). In addition, D-ser distribution resembles that observed for N-methyl-D-aspartate (NMDA) glu receptors. Contrary to this, however, the glycine (gly) distribution, which, like D-ser, is a NMDA coagonist, does not resemble the NMDA receptor distribution, except in the hindbrain, the adult cerebellum and the olfactory bulbs, where D-ser is also present (Schell et al., 1995). In the brain stem, the gly levels are maximal and there is a correspondence between gly distribution and NMDA receptor distribution (Schell et al., 1995). Interestingly, in the pons medulla, spinal cord and cerebellum, where D-ser levels are undetectable, gly levels are elevated (Schell et al., 1997).

1.3 Regulation of D-serine synthesis

The levels of D-ser are controlled by the activity of the SR. This enzyme is regulated by multiple factors (Cook et al., 2002; Dunlop and Neidle, 2005; Strisovsky et al., 2005). Pyridoxal 5′-phosphate (PLP) is the main glial cofactor that stimulates the SR activity. In addition to PLP, other compounds, such as Mg^{2+} and ATP, are capable of stimulating the synthesis of D-ser by increasing the rate of activity of SR (de Miranda et al., 2002; Neidle and Dunlop, 2002; Foltyn et al., 2005). The ion Ca^{2+} is another cofactor that positively modulates this enzyme in astrocytes (Cook et al., 2002). SR can also be regulated by protein–protein interactions. SR binds to glutamate receptor interacting protein (GRIP), which acts as scaffolding protein for the α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors. GRIP contains six PDZ domains, a motif associated with protein–protein interactions. SR selectively binds to the PDZ-6 domain through its C-terminal extreme which contains the PDZ-binding consensus sequence VSV (valine-serine-valine). The interaction between SR and GRIP leads to an increase in the rate of D-ser synthesis (Kim et al., 2005). These authors observed two transfected groups of C6 glioma cells, which express GRIP endogenously, with wild type SR and with a mutant variant in the consensus sequence VSV of the C-terminal extreme of SR. They found that the production of D-ser was reduced by 65% in the cells transfected with the mutant variant of SR, suggesting that the activation of this enzyme depends on its interaction with GRIP (Kim et al., 2005). The physiologic relevance of this observation is based on the stimulation of AMPA receptors, which leads to a strong increase in D-ser synthesis (Kim et al., 2005). AMPA activation promotes the phosphorylation of this receptor with the consequent dissociation from it of GRIP. This allows GRIP to bind to SR. On the other hand, gly and certain L-aspartic acid metabolites (L-aspartic acid, L-asparagine and α, β-threo-3-hydroxy aspartic acid) competitively inhibit SR activity (Dunlop and Neidle, 2005; Strisovsky et al., 2005). Notably, it was found that nitric oxide (NO) decreases the enzymatic activity of SR (Shoji et al., 2006). A summarized view of the different modulators of SR is detailed in Table 1.

1.4 D- and L-serine metabolic cycle

SR constitutes the pathway of an important metabolic machinery. As mentioned above, SR converts D-ser into L-ser and vice versa. However, this enzyme can also promote the elimination of water from either L- or D-ser, producing pyruvate and ammonia (de Miranda et al., 2002; Neidle and Dunlop, 2002; Strisovsky et al., 2003; Foltyn et al., 2005). Interestingly, the ability of SR to form pyruvate by eliminating water is greater than the ability to racemize L-ser. In fact, only one molecule of four of L-ser attacked by SR is converted into D-ser, while the other three are converted into pyruvate (Strisovsky et al., 2003, 2005; Foltyn et al., 2005). Pyruvate can enter to the Krebs cycle via different pathways, promoting ATP synthesis or being converted into lactate by the enzyme lactate dehydrogenase (LDH). If pyruvate gains access to the Krebs cycle, the ATP obtained closes a positive metabolic cycle, stimulating SR, which originally synthesized the

Table 1. Regulation factors of serine racemase

Positive regulators	Negative regulators
PLP, ATP, Mg^{2+}, Ca^{2+}, GRIP, AMPA stimulation	Gly, L-aspartic acid metabolites, NO

pyruvate. In addition, the course of pyruvate through the Krebs cycle supports the generation of several important amino acids for glia and neurons (GABA, glutamate, glutamine), from α- to ketoglutarate. The conversion of pyruvate into lactate provides a metabolic coupling between neurons and glia due to lactate serving as an energetic precursor for neurons, especially during periods of synaptic hyperactivity, oxidative stress or Zn^{2+}-induced neurotoxicity (Foltyn et al., 2005).

In mammals, D-ser is metabolized by the peroxisomal flavoprotein D-amino acid oxidase (DAAO), an enzyme located in astrocytes of the hindbrain and cerebellum (Schell et al., 1995; Moreno et al., 1999; Urai et al., 2002), converting it into pyruvate. DAAO, has shown to be stereoselective, because it has no effect on L-amino acids or dicarboxylic amino acids (Pilone, 2000). In agreement with these findings, studies have been carried out using knock-out mice lacking the DAAO gene. They showed a significant increase in D-ser levels, especially in the brain stem and cerebellum, two regions containing low D-ser levels in wild type animals (Morikawa et al., 2001). This could suggest a constitutive activation of DAAO in the mentioned regions of wild type mice. On the contrary, D-ser levels did not change significantly in the forebrain of knock-out animals, suggesting that in this region, D-ser levels are regulated by another mechanism (Morikawa et al., 2001). The main degradation process in this area would be the water elimination to form pyruvate, catalyzed by the SR, as explained previously (Foltyn et al., 2005).

1.5 D-serine in the glutamatergic neurotransmission

The general aspects for an understanding of how D-ser acts as a gliotransmitter are the same that control classical chemical neurotransmission (cellular depolarization, release of the transmitter, receptor activation and signal termination). It is known that the stimulation of non-NMDA (AMPA, kainate-KA-) receptors is the main stimulus that promotes the efflux of D-ser from astrocytes (Schell et al., 1995). Mothet et al. (2005) demonstrated via in vitro studies that the activation of AMPA/KA and even metabotropic glu receptors triggers the release of D-ser in a Ca^{2+}-dependent manner. Notably, inhibition of the vesicular proton ATPase decreases the levels of released D-ser. This finding suggests the inhibition of vesicular storage of the gliotransmitter by a transporter protein which has yet to be identified. Recent studies showed that astrocytes can release D-ser and other gliotransmitters by Ca^{2+}-dependent exocytosis (Coco et al., 2003; Bezzi et al., 2004; Volterra and Meldolesi et al., 2005). However, D-ser can be released by a Ca^{2+}-independent mechanism because most cytoplasmatic D-ser is not stored (Kim et al., 2005). In agreement, in conditions of low osmolarity or poor extracellular concentration of divalent cations, D-ser is released through hemichannels, anionic channels or P2X7 receptors, impulsed by a chemical gradient (Volterra and Meldolesi et al., 2005). In addition, D-ser can also be released through the alanine-serine-cysteine transporter (ASCT), commonly by countertransport with L-ser in a Na^{+}-dependent manner (Ribeiro et al., 2002) (Fig. 1). Although glial cells are the primary source of D-ser release, some neurons release it after NMDA stimulation (Kartvelishvily et al., 2006). Interestingly, it is suggested that neuronal release of D-ser would occur through a Ca^{2+}-independent mechanism, opposite to glial release, that would be mainly Ca^{2+}-dependent (Kartvelishvily et al., 2006). Neurophysiological studies of NMDA receptors suggest that with a certain combination of the NR1 and NR2 subunits, D-ser, after being released, binds to the NMDA gly site with threefold potency in comparison to gly binding (Matsui et al., 1995; Priestley et al., 1995). In addition, it has been demonstrated that D-ser binds to the gly site through the same kind of interaction as gly (Furukawa and Gouaux, 2003). The NMDA receptor has unique properties. It consists of a tetramer of two distinct subunits (Kemp and McKernan, 2002; Prybylowski and Wenthold, 2004). Up to date, three different subunits for this receptor have been cloned: NR1, NR2 (mentioned above) and NR3 (Cull-Candy et al., 2001). Most NMDA receptors are formed by combinations of NR1 and NR2 subunits, containing the recognition sites for coagonist and for glu, respectively. The NR3 subunit, less common, can be assembled with either NR1 or NR2 to depress the NMDA activation (Das et al., 1998). Despite all these data, is there enough evidence for the importance of D-ser as a glutamatergic coagonist?

Indeed, the hippocampus provides an excellent model for studying the function of D-ser in the glutamatergic neurotransmission, because it expresses a high density of D-ser and NMDA receptors, especially in the areas CA1 and CA3 (O'Brien et al., 2005). The hippocampus is one of the brain sites where long-term potentiation (LTP) takes place through NMDA activation (Nicoll, 2003). Considering that D-ser is an endogenous ligand for the NMDA receptor, it is not surprising that the release of D-ser from astrocytes is implicated in the induction of LTP in the pyramidal synapses of the area CA3 (Yang et al., 2003). In fact, administration of DAAO inhibits this LTP, suggesting that D-ser, more than gly, is the endogenous

NMDA coagonist in this brain area (Barnes, 2003). In agreement with this, it was found that the deficit of LTP is not associated with low levels of gly, supporting the role of D-ser as the main modulator of the NMDA gly site (Mothet et al., 2006).

Like other neurotransmitters, the actions of D-ser must be finished by its clearance from the synaptic cleft by transporter proteins expressed in the membranes of neurons and glial cells (Hayashi et al., 1997; Yamamoto et al., 2001; Javitt et al., 2002; O'Brien et al., 2005). Astrocytes express an Na^+-dependent transporter with low affinity for D- and L-ser (Hayashi et al., 1997). The properties of this transporter are correlated with that observed for the ASCT system, which uptakes D-ser in astrocytes and the retina (Ribeiro et al., 2002; O'Brien et al., 2005). Another transporter of neutral amino acids, Asc-1, which is Na^+-independent, shows high affinity for D-ser and is expressed in presynaptic terminals, dendrites and neuronal bodies (Helboe et al., 2003; Matsuo et al., 2004). The Asc-1 system was shown to be important for the CNS development. Knock-out mice lacking the Asc-1 gene had normal appearance at birth, but their brains and other key organs showed a 30% reduction in their weights compared with wild type mice (Xie et al., 2005). In addition, knock-out animals developed spontaneous convulsive seizures and periodic tremors. Both abnormalities are reduced by administrating the NMDA antagonist MK-801 (3 mg/kg) or by high doses of diazepam (10 mg/kg) (Xie et al., 2005). Taken together, these data suggest an increased synaptic excitability in the Asc-1-lacking mice and that NMDA activation could be one of the main causes of it, because D-ser levels in these animals would be higher than in control mice. On the other hand, the effect obtained after administration of diazepam indicates that in knock-out animals, the GABAergic neurotransmission is intact and that an increase of the inhibitory activity could overcome the neuronal hyperactivity (Xie et al., 2005).

2. Physiological and physiopathological relevance of D-serine functions in the glutamatergic neurotransmission

2.1 D-serine as a neuronal migration factor

It is well known that glu has an important role as a neuronal migration factor during CNS development (Yacubova and Komuro, 2003; Kim et al., 2005). One of the best characterized models, where glutamatergic participation through NMDA activation is observed, corresponds to the radial migration of the granule cells of the developing cerebellum (Hatten, 1999). Recent studies have demonstrated that glu is crucial for promoting the mobility of granule cells through the molecular layer by stimulating NMDA receptors (Yacubova and Komuro, 2003). However, the mechanism by which glu causes the migration of granule cells by NMDA activation is controversial, due to the fact that neurons do not form mature synapses until their migration into the inner granular cell layer. A recent hypothesis proposes that glu released by Bergmann glia (BG) activates immature NMDA receptors in a non-synaptic paracrine mode (Yacubova and Komuro, 2003). In addition, there is well-documented literature that elicits the importance of BG in the cerebellar development. Indeed, BG play a relevant role in the growth of Purkinje cells, serving them as the main source of L-ser, which acts as a neurotrophic factor (Altman and Bayer, 1996; Yamada et al., 2000). In fact, BG express SR during cerebellar development, and the D-ser levels released by the BG peak at postnatal day 14 (intense cell migration period) and then decrease markedly (Boehning and Snyder, 2003). Apparently, BG-derived D-ser promotes the granule cells' migration by stimulation of NMDA receptors (Kim et al., 2005). In agreement with this, it was found that the inhibition of SR or the administration of DAAO blocks the cellular migration by reduction of the Ca^{2+} efflux induced by NMDA activation (Kim et al., 2005). Similar results are observed in cerebellar slices, after administration of fenazine ethosulphate, which strongly reduces the intracellular Ca^{2+} level. This effect is reversed by removing the drug from the medium (Kim et al., 2005). This shows the importance of the intracellular Ca^{2+} in the neuronal migration. It is probable that D-ser promotes synaptogenesis of cerebellar neural networks because its ontogeny in BG parallels the expression of the NR2A and NR2B subunit of the NMDA receptor in Purkinje cells (Schell et al., 1997). Considering that NMDA blockade during neocorticogenesis promotes an abnormal cortical development (Gressens, 2000; Reiprich et al., 2005), it is possible that the disruption of D-ser metabolism at early life stages might lead to similar disorders.

2.2 D-serine, a neuronal death promoter

There is no doubt that NMDA receptors trigger neuronal death in some neuropathological conditions where they are overstimulated or are chronically activated (Kemp and McKernan, 2002; Hardingham and Bading, 2003; Lipton, 2004). Increased extracellular levels of glu due to an enhanced release (Takano et al, 2001) or a decrease in the uptake rate of this amino acid are the commonest

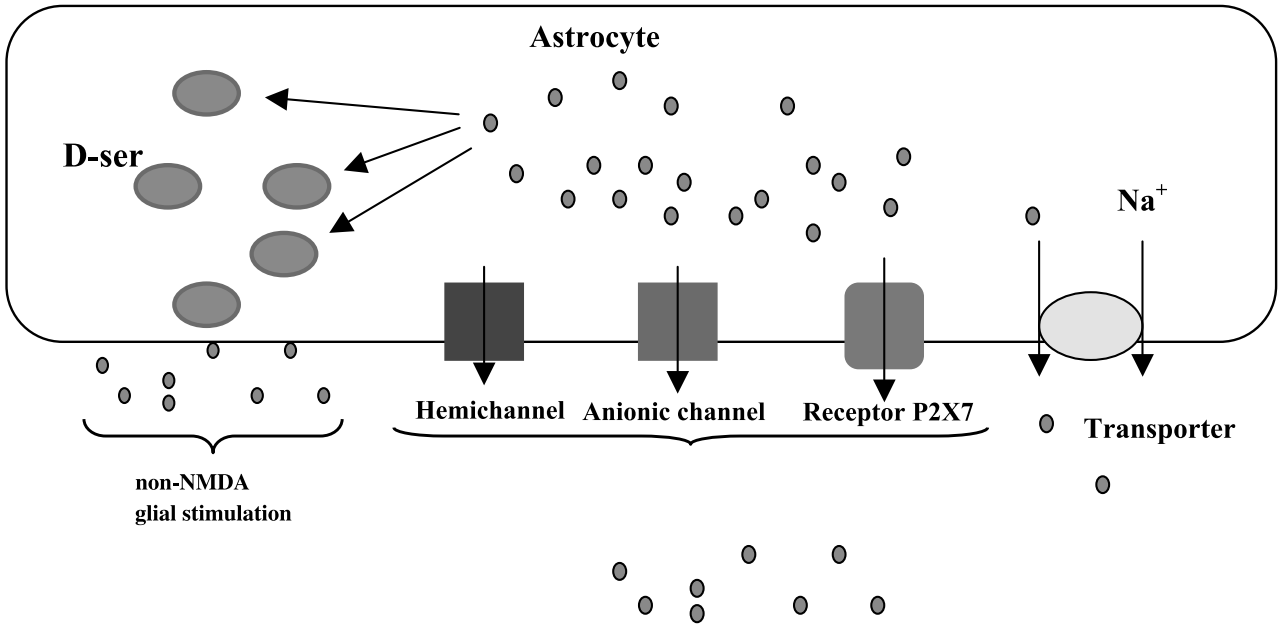

Fig. 1. Mechanism of release of D-ser from astrocytes. Big dots denote glial vesicules, small dots correspond to D-ser. See text for details

causes by which NMDA activation induces neuronal death (Lipton, 2004). In several stress models, excitotoxic cell death mediated by NMDA receptors was observed (Moghaddam, 1993). Olney (1971) defined excitotoxicity as an acute process in which glu or its excitatory structural analogs trigger nerve cell death in the CNS of rodents. The excitotoxic action of glu, via NMDA activation, as a result of its increased release or low uptake, in addition to the excitotoxicity potentiation by glucocorticoids, has been involved in the pathogenesis of stress-induced cerebral damage (Sapolsky et al., 1990; Moghaddam, 1993; Magariños and McEwen, 1995; Kim et al., 1996). In addition, intense NMDA activation produces an increase in the expression of inducible nitric oxide synthase, an enzyme that produces high amounts of NO, which promotes oxidative neuronal damage by forming reactive oxygen species and nitrosilation of diverse proteins (Olivenza et al., 2000). Considering that D-ser acts as the major NMDA coagonist and that NO inhibits the SR activity, it could be thought that NO has double but opposite modulating roles in the excitotoxicity process. On the one hand, it synergies the neuronal damage induced by NMDA stimulation (Olivenza et al., 2000), and on the other, it reduces the coagonist actions of D-ser on this receptor (Shoji et al., 2006). This fact establishes the exciting possibility of the existence of NO-mediated modulating actions on glutamatergic transmission, destined to equilibrate the NMDA activation; this awaits assessment. Oxidative damage is also potentiated by the disruption of glu uptake, because low glial glu levels are correlated with a reduced glutathione production, a well-known endogenous antioxidant (Tan et al., 1998). Glu uptake is mediated by high affinity transporters placed in the plasma membrane of neurons and astrocytes (Danbolt, 2001) developing an essential function in the excitatory neurotransmission and preventing excitotoxicity (Nicholls and Attwell, 1990). These membrane transporters possess redox-sensing properties, due to the existence of sulphidryle groups in its structure. Oxidation of these groups following an oxidative insult might lead to a reduced glu uptake (Trotti et al., 1996). Due to the fact that D-ser modulates the NMDA activity and that it is suspected that glia is involved in excitotoxicity (Aschner et al., 1999; Swanson et al., 2004), it is possible that D-ser threatens neurons' survival, exacerbating the action of glu when there are altered levels of it. D-ser-promoted neurodegeneration is probably caused by an increased AMPA glial activation induced by glu which determines the SR activation by increasing the intracellular Ca^{2+}.

Alzheimer's disease (AD) is a pathology where the excitotoxic effect of D-ser is observed. The amyloid-β-peptide (Aβ) is proposed as the main physiopathological factor of AD (Butterfield and Boyd-Kimball, 2004). Aβ causes an inflammatory reaction in microglia, which triggers excitotoxic neuronal death (Barger and Basile, 2001; Wu and Barger, 2004; Butterfield and Boyd-Kimball, 2004).

In addition, increased NMDA activity has been found in the brains of individuals affected by AD, and memantine, an NMDA antagonist, has been found to have neuroprotective actions (Lipton, 2004). In contrast, the hippocampus of patients with AD shows increased levels in SR activity, and Aβ stimulates, in vitro, the release of excitotoxic levels of D-ser from microglia (Wu et al., 2004). The Aβ-peptide increases the levels of D-ser by two possible mechanisms. First, it promotes the stimulation of an activator protein-1 (AP-1) binding sequence located in the first intron of the SR gene, increasing its transcription rate (Wu and Barger, 2004). Second, Aβ regulates SR post-transcriptionally by causing increases in the microglial Ca^{2+} levels (Silei et al., 1999), which up-regulates the enzymatic activity (Cook et al., 2002). These roles of D-ser provide new pharmacological insights for the treatment of neurodegenerative diseases or disorders characterized by significant neuronal damage.

2.3 D-serine and schizophrenia: beyond dopamine and glutamate

Schizophrenia is a complex mental disorder that commonly emerges during adolescence, but its onset is earlier in males that in females (Castle et al., 1998). Although Carlsson postulated the dopaminergic hypothesis in the 1980s (Carlsson, 1988), more recently there has been the suggestion that schizophrenia might be related to glutamatergic hypofunction in the limbic system and forebrain (Coyle et al., 2001). It was found that NMDA receptor blockade by drugs such as phencyclidine and ketamine causes schizophrenic-like symptoms in primates and humans and exacerbates the symptoms of patients with schizophrenia (Lahti et al., 1995). In spite of antipsychotic drugs improving the positive symptoms of the disease (hallucinations, delirium, paranoia and others), they have poor effects on the negative symptoms (cognitive damage, social retreat, etc.). For this reason, researchers began to consider glutamatergic neurotransmission as a possible therapeutic target. In an attempt to counteract the NMDA hypofunction, several pharmacological approaches for the treatment of schizophrenia were tested, administrating modulators of the gly site of the receptor, together with antipsychotic drugs. Among the modulators evaluated were gly (Javitt et al., 1994), D-ser (Tsai et al., 1998) and D-cycloserine (Cascella et al., 1994). Although this approach had moderate success, it was observed that D-ser was nephrotoxic (Carone and Ganote, 1975) and that D-cycloserine, initially used as an antibiotic to treat tuberculosis (Epstein et al., 1955), has a central secondary effect after a year of treatment (Lewis et al., 1957). Despite the observations made by Carone and Ganote (1975) about the nephrotoxic actions of D-ser, Levy and colleagues evaluated the efficacy of gly at high doses (2004) and of D-ser (2005), added to the treatment of schizophrenic patients administrated with olanzapine and risperidone. Even though, in both cases, positive, negative and cognitive symptoms of the disease were improved (Levy et al., 2004, 2005), the doses required of D-ser where much smaller than the doses of gly (30 mg/kg/day and 800 mg/kg/day, respectively), due to the fact that D-ser passes through the blood brain barrier (BBB) more easily than gly (Olendorph, 1971). On the other hand, gly affects inhibitory synapses of the brain stem and spinal cord, by activating its strychnine sensitive receptors (Levy et al., 1999). On the contrary, D-ser did not demonstrate the ability to stimulate the known neurotransmission systems, but it was well tolerated by patients and was efficient in improving the schizophrenic symptoms, which makes it a useful therapeutic tool for the treatment of the disease (Levy et al., 2005). However, in patients treated with clozapine, none of the modulators mentioned, including D-ser (in a dose of 30 mg/kg/day), improves the schizophrenic symptoms, when administrated simultaneously with clozapine (Tsai et al., 1999). Finally, it was observed that a dietary supplement containing L-ser, which enhances the cerebral D-ser levels in rats when administrated systemically, provided an alternative pharmacological strategy (Takahashi et al., 1997; Hashimoto, 2002). As expected, the efficacy of the treatment with antipsychotics and L- or D-ser depends on the ability of these amino acids to pass through the BBB. Contrary to what has been observed for most L-amino acids, Bauer et al. (2005) demonstrated that D-ser has access to the CNS in higher quantity than L-ser. Considering that D- and L-ser have common transport systems, Bauer et al. (2005) proposes a preferred stereoselective transport for D-ser through the BBB. Although this transport system is not elucidated, it is known that subtype 1 of the Na^+-independent system L is the predominant uptake mechanism of D- and L-ser in the BBB (Yamamoto et al., 2005) and could be one of the candidates for supplying exogenous D-ser to the CNS. Actually, it is postulated that schizophrenia could have an important genetic component (Lin et al., 1997; Chumakov et al., 2002). Genetic linkage studies have involved DAAO in some forms of schizophrenia, which suggests that changes in the activity of this enzyme could alter the levels of D-ser and consequently the NMDA activation (Chumakov, 2002). A 50 million base pair region on hu-

man chromosome 13, located between q24 and q34, has been associated with schizophrenia in a number of studies (Lin et al., 1997; Blouin et al., 1998; Shaw et al., 1998). Chumakov et al. (2002) focused their investigations on this region and identified two putative transcripts, called G72 and G30. The G72 transcript was detected in the amygdala, caudate nucleus and spinal cord. In vitro transcription/translation studies of the G72 transcript demonstrated that this produces a polipeptidic molecule formed by 153 amino acids, while similar analysis for the G30 transcript showed that this does not produce proteic molecules (Chumakov et al., 2002). Surprisingly, it was found that the translation product of G72 transcript was able to interact with DAAO, by protein-protein interactions. In fact, when the protein derived from G72 is added to an excess of DAAO, the activity of this enzyme increases threefold over the basal levels. Relating to this data, Chumakov (2002) proposes a model in which the expression of G72 in schizophrenia produces an enhanced activity of DAAO leading to a decrease in D-ser levels and promoting the NMDA hypofunction. However, the model proposed by Chumakov has disparities with the distribution of DAAO in the mammalian brain. This is due to the fact that this enzyme is almost exclusively found in the cerebellum, the spinal cord and the brain stem (Volpe et al., 1970; Morikawa, 2001), while schizophrenia involves a deficit in the prefrontal cortex and the limbic system (Harrison, 1999). In spite of that, Moreno et al. (1999) reported that DAAO is present in all brain regions. This finding supports the hypothesis that an enhanced DAAO activity could be involved in the glutamatergic hypofunction witnessed in schizophrenia.

2.4 L-ser or D-ser? A conformational contest

Although L-ser and D-ser are only differentiated by their atomic spatial disposition, they carry out very different functions in the CNS (Altman and Bayer, 1996; Yamada et al., 2000; Acosta et al., 2005). L-ser acts as a glia-derived neurotrophic factor (Savoca et al., 1995; Furuya et al., 2000; Acosta et al., 2005), while D-ser is an NMDA coagonist (Hashimoto et al., 1993a; Wolosker et al., 1999), a neuronal migration factor (Kim et al., 2005) and a cell death promoter (Aschner et al., 1999; Swanson et al., 2004).

While the main source of D-ser is through the action of SR on L-ser (Schell, 2004), L-ser is obtained from four different sources: from the diet, from 3-phosphoglycerate, by conversion of glycine through the action of the enzyme serine hydroxymethyltransferase (SHMT) and from the degradation of proteins and phospholipids (de Koning et al., 2003). Two biosynthetic pathways of L-ser from glucose have been identified: the phosphorilated pathway and the non-phosphorilated pathway (Sallach, 1956; Ichihara and Greenberg, 1957), the first being the main source of endogenous L-ser (Neidle and Dunlop, 2002). With reference to this data, it is not difficult to conclude that the body has greater facility to obtain L-ser than to obtain D-ser. In view of the fact that D-ser levels are tightly regulated by multiple factors (de Miranda et al., 2002; Neidle and Dunlop, 2002; Cook et al., 2002; Dunlop and Neidle, 2005; Foltyn et al., 2005; Kim et al., 2005; Strisovsky et al., 2005) because it could be excitotoxic when its extracellular levels are elevated (Aschner et al., 1999; Swanson et al., 2004), it is not surprising that it is much less available than L-ser. Although L-ser and other amino acids, such as L-alanine, can act as an NMDA coagonist (Kleckner and Dingledine, 1988; Thomson, 1990; Hashimoto et al., 1993a, b; Cotman et al., 1995), their potency is 20–30 times weaker than that observed for D-ser, lacking its ability to induce excitotoxicity. Then again, the L- and D-ser distribution in the adult brain, is similar, being in the cerebral cortex, the hippocampus and the corpus callosum, the regions where both amino acids are expressed in their highest levels (Schell et al., 1995, 1997; Wolosker et al., 1999; Yasuda et al., 2001). However, D-ser is also found at high concentration in the olfactory bulbs, the hypothalamus and the corpus striatum, but, unlike L-ser, its cerebellar levels are undetectable in the adult animal (Hashimoto et al., 1995; Yasuda et al., 2001). Additionally, it is known that the D-ser levels in the brain areas cited are parallel with the expression of the NMDA receptor (Schell et al., 1997).

Despite the differences mentioned above, the transport system through which glial cells uptake L-ser and D-ser is the same: the ASCT. Although this transporter uptakes both amino acids, it has a higher affinity for L-ser than for D-ser (Hayashi et al., 1997). Regarding the importance of L-ser in the CNS development, we studied, in our laboratory, the uptake of this non-essential amino acid in synaptosomes from the cerebral cortex of rats at different postnatal stages (P5, P7, P13, P21 and adult age) (Cheluja et al., 2006). We found that the uptake profiles of L-ser were similar at each postnatal stage considered, including the adult age, but the kinetic parameters varied with the age. While the maximum velocity of transport was observed at P21, the highest affinity for the substrate was observed at P5 (Cheluja et al., 2006). To date, there is poor information about similar studies carried out for D-ser.

Table 2. Similarities and differences between L-ser and D-ser

	L-ser	D-ser
Biosynthesis and other sources	– Diet – glycine (SHMT) – Glucose – SR	– SR
Degradation	– SR	– SR – DAAO
Distribution	Similar to D-ser	Similar to L-ser
Glial uptake system	ASCT	ASCT
NMDA coagonism	Poor	High
Role in neurodevelopment	Neurotrophic factor	Neuronal migration factor
Implication in neurodegeneration	No	Yes
Related pathologies	– 3-PGDH deficiency – PSP deficiency	– AD – Schizophrenia

Finally, L-ser has been involved in congenital pathologies characterized by a deficit in the expression of enzymes of the phosphorilated pathway of L-ser biosynthesis (de Koning et al., 2003; Acosta et al., 2005). In this context, two disorders were described: 3-phosphoglycerate dehydrogenase (3-PGDH) deficiency and phosphoserine phosphatase deficiency (PSP). Both disorders show severe psychomotor retardation, congenital microcephaly and hypomyelinization (Jaeken et al., 1996; de Koning et al., 2000). Administration of high doses of L-ser, alone or in combination with gly, improved the symptoms of the described disorders (Jaeken et al., 1996; de Koning et al., 1998; Pineda et al., 2000). In an attempt to summarize the main similarities and differences between L- and D-ser, Table 2 was constructed.

Conclusions

Since its discovery, our knowledge about the roles of D-ser in the CNS has markedly increased. It has shown significant relevance in the glutamatergic neurotransmission, but the total mechanisms in which it is involved have not yet been found out. However, many important roles with different objectives were described for D-ser, which increase, even more, the potential of the glutamatergic system as a therapeutic target. It is interesting that the CNS needs two different NMDA receptor modulators, D-ser and gly, with the same molecular target, the glycine site, and that each one has its own distribution (Schell et al., 1997). However, only one of them, gly, possesses a complete neurotransmission system, including receptors and specific transporter proteins (Curtis and Jonhston, 1970; De Feudis et al., 1973; Legendre, 2001; Eulenburg et al., 2005). This creates the exquisite complexity of the CNS, giving a modulator role to a well-known neurotransmitter in a different system to which it belongs, depending on the brain region observed (Schell et al., 1997). Although the gly receptors bind the neurotransmitter in a similar way to the NMDA gly site, the last one does it in a strychnine insensitive profile, unlike the first (Perez-León and Salceda, 1995; Rodríguez-Contreras et al., 1998). Despite the fact that a specific receptor for D-ser has not yet been identified, it could be asked whether the NMDA receptor is the only one that binds it and promotes an effect. Is it possible that D-ser elicited any function on the glycinergic receptors? Considering that the administration of exogenous D-ser does not affect such receptors (Levy et al., 2005), the possibility of the existence of a receptor site, different from NMDA, to which D-ser binds and triggers an effect cannot be discarded. It could be thought that, if such a receptor exists, this small molecule might lead to the proposition of the idea of considering ''hybrid'' neurotransmission systems, where two structurally different molecules are responsible, equally, for the transmission of signals in systems considered, up to now, to have only one transmitter molecule. Because D-ser is the main endogenous NMDA coagonist in many brain areas (Schell et al., 1997; Mothet et al., 2006), D-ser was involved in AD (Silei et al., 1999; Wu et al., 2004) and schizophrenia (Takahashi et al., 1997; Hashimoto, 2002), both pathologies affecting the NMDA transmission.

On the other hand, the importance of D-ser in the CNS development, acting as a neuronal migration factor, has been demonstrated (Kim et al., 2005). In addition, if it is considered that L-ser is an essential glial neurotrophic factor for brain development (Savoca et al., 1995; Furuya et al., 2000; de Koning et al., 2003; Acosta et al., 2004), it could be suggested that the expression levels of SR, the molecular link between L- and D-ser, would be a key factor for the function of the developing neuro-glial circuits. The advances of our knowledge about the glutamatergic system, concerning NMDA modulation, could probably provide a new generation of drugs directed to the gly site of this receptor, to the SR or to the DAAO, all important regulators of glutamatergic neurotransmission.

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