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INVITED REVIEW

D-Amino acids in brain neurotransmission and synaptic plasticity

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Abstract Far from our initial view of D-amino acids as being limited to invertebrates, they are now considered active molecules at synapses of mammalian central and peripheral nervous systems, capable of modulating synaptic communication within neuronal networks. In particular, experimental data accumulated in the last few decades show that through the regulation of glutamatergic neurotransmission, D-serine influences the functional plasticity of cerebral circuitry throughout life. In addition, the modulation of NMDA-R-dependent signalling by D-aspartate has been demonstrated by pharmacological studies and after the targeted deletion of the D-aspartate-degrading enzyme. Considering the major contribution of the glutamatergic system to a wide range of neurological disorders such as schizophrenia, Alzheimer's disease and amyotrophic lateral sclerosis, an improved understanding of the mechanisms of D-amino-acid-dependent neuromodulation will certainly offer new insights for the development of relevant strategies to treat these neurological diseases.

Keywords D-Serine · D-Aspartate · Glutamate · NMDA receptor · Synaptic plasticity · Long-term potentiation · Serine racemase · D-Amino acid oxidase · D-Aspartate oxidase

Introduction

A major characteristic of scientific thinking is that it constantly challenges what is accepted as dogma, helping to increase, and sometimes overturn, our knowledge of the complexity of biological functions. This is particularly the case with the role of free D-amino acids in the nervous system. For a long time, these compounds were thought to occur only in lower organisms (Lamzin et al. 1995), and their presence in the tissues of eukaryotes was considered unnatural (Corrigan 1969). Thus, while it was known that D-alanine and a derivative of D-glutamine constituted a peptidoglycan within the cell walls of bacteria and D-serine controlled the rate of growth of these organisms (Smith and Higuchi 1960; Whitney and Grula 1968), the prevalent idea was that D-amino acids in mammals were provided by diet or derived from the metabolism of endogenous microbial flora. However, the presence in higher species of several flavoproteins responsible for the oxidative deamination of neutral and dicarboxylic D-amino acids, enzymes characterized as early as the mid-1930s (Krebs 1935; Still et al. 1949), strongly suggested that mammals, including humans, could also possess specific D-amino acid-dependent pathways with defined biological functions.

It was only with the advent of refinements in chromatographic and in vivo microdialysis techniques together with immunohistochemical experiments using stereospecific antibodies that the presence of free D-amino acids at significant amounts, sometimes exceeding those of the L-enantiomers (Hashimoto et al. 1993b, 1995b; Schell et al. 1995), was definitively demonstrated in the brain of rodents and humans. Finally, the localization of these D-amino acids in specific cell types and the characterization of their uptake, biosynthesis and release processes in primary cultures of glial and neuronal cells were decisive stages in ascertaining their role in cellular communications in the brain of higher organisms (Drejer et al. 1983; Dunlop et al. 1986; Man et al. 1987).

This review focuses on the available evidence indicating that the amino acids D-serine and D-aspartate are involved

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in the modulation of neurotransmission and functional plasticity at glutamatergic synapses of the central nervous system. Deciphering the mechanisms underlying this modulation is now a major challenge for neuroscientists interested in characterizing new therapeutic targets in glutamate-related neurological diseases.

D-Serine: an endogenous neuromodulator at glutamatergic synapses

The first report of significant levels of free D-serine in the brain came in the early 1990s from the Hashimoto group, which used a modified high-performance liquid chromatography technique to distinguish between the D- and L-enantiomers (Hashimoto et al. 1993b, 1995a). Their work shows that the acid isoform is not quasi-ubiquitous in the central and peripheral nervous systems; it is detected in some brain regions at fairly high levels (up to 500 μM), suggesting a significant influence on neurotransmission and related processes. Several interesting results obtained with complementary technical approaches are consistent with this hypothesis: using specific antibodies raised against the amino acid and adequate perfusion of cerebral tissues, D-serine is found to concentrate in the vicinity of *N*-methyl-D-aspartate receptors (NMDA-R) (Hashimoto et al. 1993b; Schell et al. 1997), which are critically involved in brain development, learning and memory and cellular excitotoxicity.

NMDA-Rs are a class of ionotropic glutamate receptors composed of GluN1 subunits combined with the different four GluN2 subunits, where the functional properties of each heteromeric assembly depend on its subunit composition (Paoletti 2011; Traynelis et al. 2010). Binding studies have revealed that D-serine selectively binds to the strychnine-insensitive glycine-binding site present on the GluN1 subunit (Fletcher et al. 1989; Matsui et al. 1995; McBain et al. 1989; Furukawa and Gouaux 2003), while electrophysiological analyses indicate that D-serine differentially activates purified recombinant NMDA-Rs expressed on oocytes depending on the subunit composition of the receptor, the amino acid being more potent than glycine at binding to GluN2A-containing NMDA-Rs but less potent with GluN2B-containing (Matsui et al. 1995; Priestley et al. 1995; but see Wafford et al. 1995). Taken together, these data suggest that D-serine is a full agonist of NMDA-Rs, and recordings from ex vivo brain preparations confirm that exogenous application of the amino acid enhances NMDA-R-mediated synaptic currents in a large range of cerebral structures (Fig. 1a), including the hippocampal CA1 area (Haxaire et al. 2012; Henneberger et al. 2010; Junjaud et al. 2006; Martina et al. 2003; Mothet et al. 2006; Yang et al. 2003; Zhang et al. 2008), layer V/VI of the prefrontal cortex (Fossat et al. 2012), layer II/III of the visual cortex (Ito and

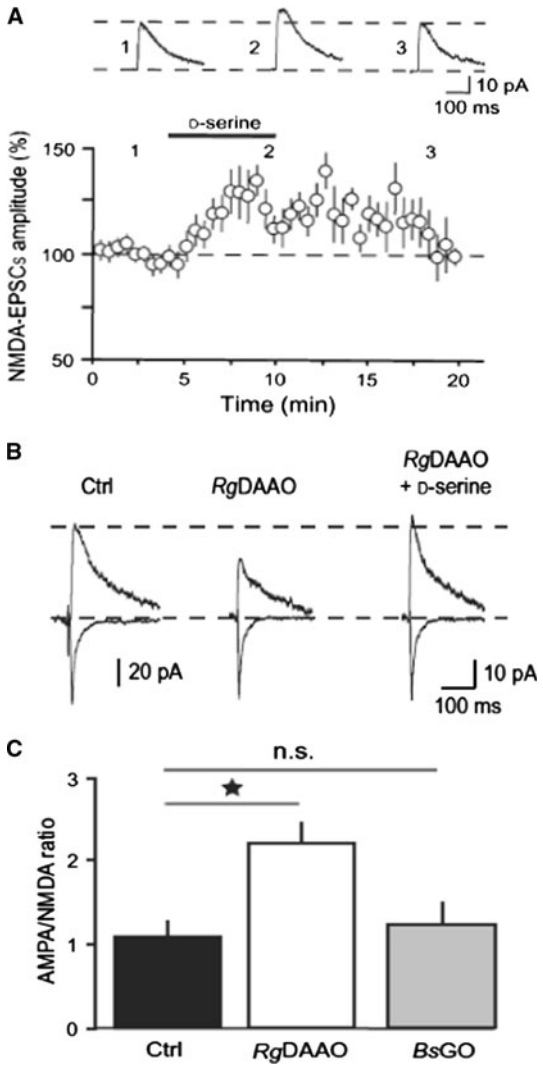

Fig. 1 D-Serine is an endogenous co-agonist of NMDA-R at synapses of the medial prefrontal cortex (mPC). **a** Time-course of the increase in NMDA-R-mediated excitatory postsynaptic currents (EPSCs) induced by the exogenous application of D-serine. Numbers in the upper panel are examples of EPSCs recorded before, during and after D-serine application. **b** Examples of NMDA-R- (*upper trace*) and AMPA-R-mediated EPSCs (*lower trace*) recorded in a control mPC slice (*Ctrl*), in a slice pre-treated with recombinant D-amino acid oxidase (*RgDAAO*), and in a slice pre-treated with DAAO and supplemented with D-serine. **c** *Bar graph* comparing the mean (±SEM) AMPA-EPSC/NMDA-EPSC ratio (AMPA/NMDA radio) calculated from control slices, slices pre-treated with DAAO and slices pre-treated with recombinant glycine oxidase (BsGO) (*$p < 0.05$). Modified from Fossat et al. (2012)

Hicks 2001), the anterior cingulate and olfactory cortices (Collins 1991; Guo et al. 2005), the nucleus of the tractus solitarius (Baptista and Varanda 2005), the dorsolateral striatum (Chapman et al. 2003), the medial nucleus of the trapezoid body (Reyes-Haro et al. 2010) and the supraoptic nucleus of the hypothalamus (Panatier et al. 2006), but not cerebellar mossy-fibre/granule-cell synapses (Billups and Attwell 2003). Regarding the cellular populations

responsive to the amino acid, it is interesting to note the larger increase in NMDA-R activation by D-serine in hippocampal CA1 pyramidal cells than in neighbouring GABAergic interneurons (Martina et al. 2003), probably reflecting differences in NMDA-R subunit composition between these cells. In addition to its primary role in activating NMDA-Rs, therefore, D-serine may also modulate the excitation–inhibition balance of neuronal networks.

Despite the wide consensus regarding the excitatory modulation of NMDA-R activation by D-serine, evidence that the amino acid is a true endogenous co-agonist of NMDA-R in the brain was missed for a while. This question was first resolved using the specific enzymatic degradation of D-serine by D-amino acid oxidase (DAAO). This enzyme is a peroxisomal FAD-containing flavo-oxidase that catalyses the oxidative deamination of the amino acid (Krebs 1935; Pollegioni et al. 2007; Pollegioni and Sacchi 2010). Indeed, Mothet et al. (2000) were the first to show that a pre-treatment with DAAO decreases spontaneous and agonist-evoked NMDA-R-mediated currents in cultured hippocampal neurons. The same enzymatic procedure also reduces electrically evoked NMDA-R-mediated excitatory postsynaptic currents (EPSCs) in the hippocampal CA1 area (Yang et al. 2003) as well as in the hypothalamic supraoptic nucleus (Panatier et al. 2006) and the medial prefrontal cortex (Fossat et al. 2012) (Fig. 1b, c). Interestingly, in the two latter cerebral structures, pre-treatment with glycine oxidase (GO) to deplete endogenous glycine does not alter NMDA-R-dependent EPSCs, indicating that D-serine could be the major endogenous co-agonist of NMDA-R at mature excitatory synapses in these structures. Very recently, the development of conditional null mutations of the D-serine synthesizing enzyme serine racemase (SR) in forebrain neurons has confirmed that D-serine acts as an endogenous NMDA-R co-agonist since this procedure decreases the miniature EPSCs (mEPSCs) specifically generated by the activation of these receptors (Benneyworth et al. 2012). Surprisingly, the irreversible targeted disruption of SR, which induces a ~90 % decrease in forebrain D-serine content (Basu et al. 2009; Horio et al. 2011; Inoue et al. 2008), does not significantly affect the magnitude of NMDA-R-synaptic currents in the hippocampal CA1 area but only the decay kinetics of the EPSCs, which is slightly slowed, although the level of occupancy of the NMDA-R glycine-binding site is significantly reduced (Basu et al. 2009). Although a modification in NMDA-R subunit composition is postulated to account for these changes in kinetics in SR null mice (Basu et al. 2009), the absence of a clear-cut decrease in EPSC magnitude rather suggests the involvement of another co-agonist, most probably glycine, acting on NMDA-R in the absence of D-serine. Interestingly, it has recently been reported that glycine could contribute to NMDA-R-mediated EPSCs only if the slices are pre-treated with DAAO, i.e., when competition with D-serine to reach binding sites is eliminated (Fossat et al. 2012), thus explaining why NMDA-R-mediated EPSCs remain robust in SR KO mice.

It is worth noting that endogenous D-serine is also found to modulate extracerebral NMDA-R activation, although it would be beyond the scope of this review, which focuses on D-amino acids in the brain, to discuss this in detail. Briefly, in retinal preparations, D-serine enhances NMDA-R-mediated calcium increases in ganglion cells (Daniels and Baldridge 2012), while pre-treatment with DAAO or D-serine deaminase (DsdA), an enzyme at least three orders of magnitude more efficient than DAAO in degrading D-serine, or with the SR inhibitor phenazine ethosulfate, diminishes the NMDA-R component of light-evoked synaptic responses in these cells (Gustafson et al. 2007; Stevens et al. 2003, 2010). In the spinal cord, larger NMDA-R-mediated EPSCs occur in dorsal horn neurons of mutant mice with a genetic deletion of DAAO (Wake et al. 2001). These results emphasize a major role for D-serine in the encoding of sensory inputs.

The study of NMDA-R subunit architecture has increased in complexity these past decades after the discovery of a third component, the GluN3 subunit, distributed widely throughout the CNS (Ciabarra et al. 1995; Wee et al. 2008; Wong et al. 2002). This component, which has been divided into GluN3A and GluN3B subtypes, possesses specific pharmacological and functional properties, since GluN1–GluN3 heterodimers require only glycine but not glutamate for activation (see Low and Wee 2010 for a review). In oocytes, D-serine induces only a very weak or no inward current when GluN1–GluN3A or GluN1–GluN3B receptors are expressed, but does inhibit the glycine-evoked currents generated by these receptors (Williams et al. 1996). On the other hand, functional GluN1–GluN3 receptors gated both by glycine and by D-serine have recently been characterized in brain oligodendrocyte-myelin, with the currents evoked being suppressed in GluN3A-deficient mice (Pina-Crespo et al. 2010). Although the impact on brain functionality of these D-serine-dependent effects on GluN3-containing receptors remains to be determined, these results emphasize the multiplicity and the complexity of the modulation exerted by the amino acid at glutamatergic synapses (Fig. 2).

One of the most fascinating features of many synapses in the brain is their capacity for functional plasticity. Long-term potentiation (LTP) and depression (LTD) of neurotransmission are long-lasting changes in synaptic strength that are now widely accepted as leading candidates for memory storage mechanisms (Adams et al. 2001; Bear and Malenka 1994; Bliss and Collingridge 1993; Collingridge and Bliss 1995; Izquierdo and Medina 1995; Kim and

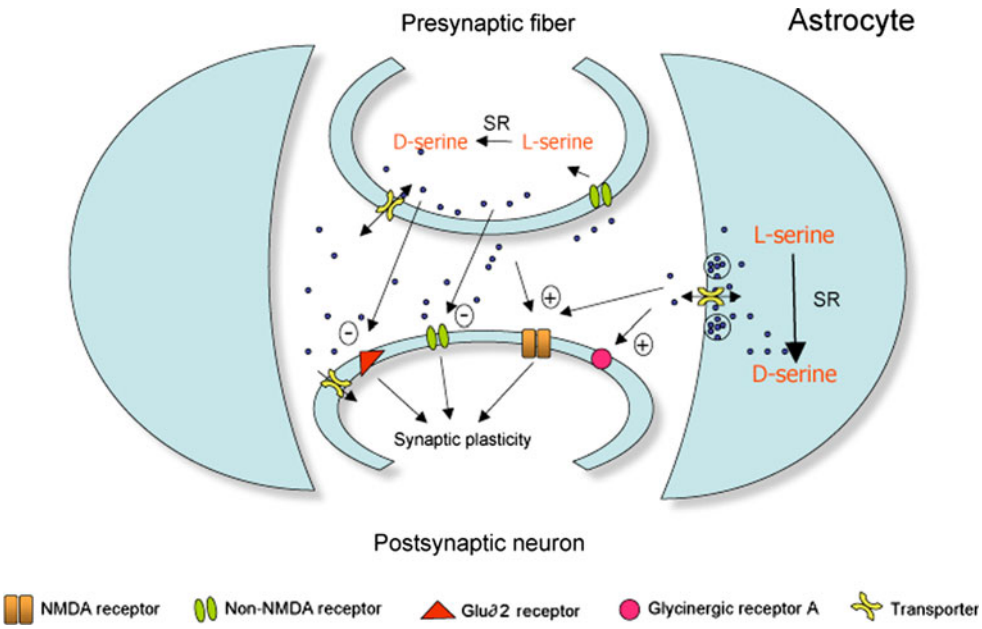

Fig. 2 Schematic representation illustrating possible mechanisms involved in the modulation of neurotransmission and synaptic plasticity (LTP or LTD) by D-serine at glutamatergic synapses. Receptor activation may be positively or negatively regulated depending on the class of glutamate receptor concerned (ionotropic NMDA or non-NMDA receptors or the glutamate-like receptor delta 2), suggesting a complex regulation of synaptic strength by the amino acid. In addition, D-serine could also indirectly control fast neurotransmission by the activation of inhibitory type A glycinergic receptors

Linden 2007; Lynch 2004). Both forms of synaptic plasticity are mainly driven by NMDA-R activation and closely depend on the kinetics of calcium influx through the receptor, which modifies the phosphorylation rate and density of non-NMDA (AMPA/kainate) glutamate receptors at active synapses (Luscher et al. 2000; Martin et al. 2000). Considering that D-serine is critical for NMDA-R activation, it is easy to speculate that the amino acid significantly contributes to the capacity of neuronal networks to express long-lasting functional plasticity. Accordingly, LTP is impaired in hippocampal neuronal cultures containing only traces of D-serine, an impairment overcome by adding the amino acid to the external medium (Yang et al. 2003). Similarly, pre-treatment with DAAO prevents LTP induction in hippocampal neuronal–glial co-cultures and slices (Henneberger et al. 2010; Mothet et al. 2006; Yang et al. 2003) (Fig. 3) as well as in slices of the medial prefrontal cortex (Fossat et al. 2012) and hypothalamic supraoptic nucleus (Panatier et al. 2006). In addition, LTP is greater in hippocampal slices from mice with a deletion of the DAAO gene (Maekawa et al. 2005). On the other hand, impaired LTP expression occurs in SR KO mice, despite the robust NMDA-R-dependent EPSCs displayed by these animals, as well as in animals with conditional null mutations of SR in neurons (Basu et al. 2009; \Benneyworth et al. 2012). Finally, there is now compelling evidence that the age-related impairment of LTP is mainly due to the weaker activation of NMDA-R by D-serine, as levels of the co-agonist decrease dramatically with age without compensation by glycine (Haxaire et al. 2012; Junjaud et al. 2006; Mothet et al. 2006; Potier et al. 2010). All these results indicate that D-serine occupancy of

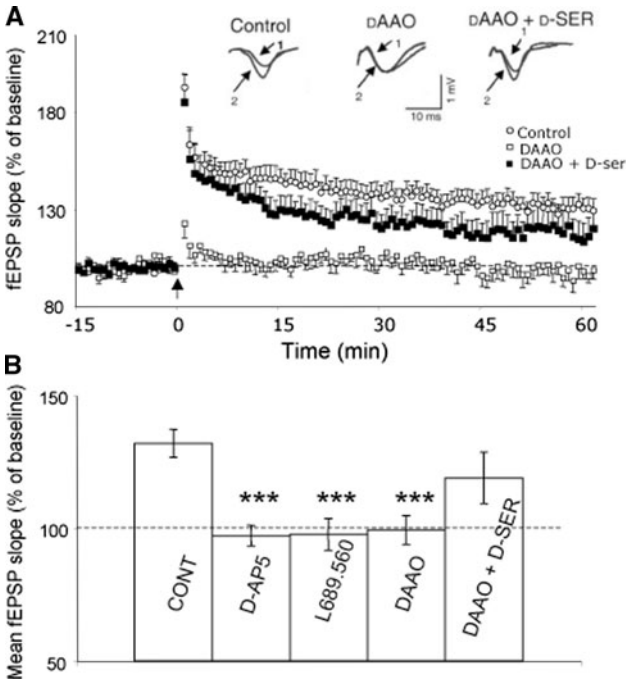

Fig. 3 D-Serine is required for the expression of synaptic plasticity at hippocampal CA3-CA1 synapses. **a** Time-course of theta-burst-stimulation-induced LTP in control slices (*open circles*), in slices pre-treated with the D-serine degrading enzyme D-amino acid oxidase (DAAO) (*open squares*) and in slices pre-treated with DAAO and supplemented with D-serine (*filled squares*). *Insets* are superimposed traces of field excitatory postsynaptic potentials (fEPSPs) recorded in slices of each category before (1) and 60 min after (2) the conditioning stimulation. **b** *Bar graph* indicating the mean potentiation (±SEM) calculated under each condition or after application of the competitive NMDA-R antagonist D-AP5 or the glycine-binding site specific antagonist L689.560, 45–60 min after the stimulation (***$p < 0.001$). Modified from Mothet et al. (2006)

NMDA-R glycine-binding sites closely controls the capacity of synaptic strength to be modified and the extent to which it is modified, in the long term. Accordingly, increasing D-serine levels by supplementing brain tissues with the amino acid significantly enhances LTP or LTD magnitude in hippocampal slices (Duffy et al. 2008; Krasteniakov et al. 2005; Turpin et al. 2011) as well as LTD levels in visual cortex preparations (Yang et al. 2011).

Despite the fact that the majority of studies concerning the functional role of D-serine have focused on the regulation of NMDA-R activation, there is now experimental data indicating that the amino acid could also act on the AMPA/kainate subtype of receptors to alter fast glutamatergic transmission. Indeed, increasing D-serine levels at glutamatergic synapses of the hippocampal CA1 decreases AMPA-R-mediated synaptic potentials (Junjaud et al. 2006; Krasteniakov et al. 2004). This effect may be driven indirectly through the activation of inhibitory strychnine-sensitive glycinergic receptors (Junjaud et al. 2006) or through direct competitive antagonism at the glutamatergic receptor, as demonstrated in acutely isolated hippocampal neurons (Gong et al. 2007). D-Serine also reduces kainate-induced calcium responses as well as AMPA-induced currents in retinal neurons, whereas pre-treatment of the isolated retina with DAAO significantly increases these responses (Daniels et al. 2012). However, whether fast synaptic transmission in the brain is regulated by endogenous D-serine still remains an open question, since pre-treatment with DAAO does not alter AMPA-R-mediated synaptic responses in the hippocampus (Mothet et al. 2006; Yang et al. 2003), the cerebral cortex (Fossat et al. 2012) or the hypothalamic supraoptic nucleus (Panatier et al. 2006), and the conditional disruption of SR does not affect the amplitude of AMPA-R-mediated mEPSCs (Benneyworth et al. 2012). However, one must keep in mind that (Hashimoto and Chiba 2004) have shown that even a single systemic injection of D-serine results in a rapid and massive increase in brain levels of the amino acid, suggesting that a treatment using this procedure could impact fast neurotransmission in the CNS.

In addition to the modulation of the classic ionotropic AMPA and NMDA receptors, D-serine also regulates the activity of the glutamate-like receptor delta 2 (GluRδ2), a receptor that does not form functional homomeric glutamate-gated ion channels in transfected cells (Hansen et al. 2009; Naur et al. 2007). Interestingly, GluRδ2 receptors are selectively localized on the dendritic spines of cerebellar Purkinje cells and are expressed at high levels during the first few postnatal weeks (Kashiwabuchi et al. 1995), the same period in which Bergmann glial cells of the cerebellar cortex are particularly enriched in D-serine due to the weak expression of DAAO (Hashimoto et al. 1993b, 1995a, b). The fact that D-serine binding alters currents in GluRδ2-receptors containing the lurcher mutation by a mechanism that resembles desensitization at AMPA/kainate receptors (Hansen et al. 2009), and that the genetic deletion or naturally occurring mutations of GluRδ2 genes affect cerebellar LTD (Kakegawa et al. 2011; Kashiwabuchi et al. 1995), strongly suggest that the binding of D-serine to GluRδ2 receptors could be a route by which the amino acid regulates functional plasticity in the developing cerebellum.

D-Aspartate: another endogenous neuromodulator of glutamatergic synapses in the brain?

Among the other D-amino acids identified in the brain, such as D-alanine, D-leucine, D-proline and D-glutamate (Hamase et al. 1997; Han et al. 2011; Morikawa et al. 2003), D-aspartate has received significant attention due to its abundant expression during the embryonic phases of brain development (see Errico et al. 2009 for a review). However, although a major function of this amino acid in endocrine systems is now well established (D'Aniello 2007; Huang et al. 2006), its role in modulating brain activity postnatally remains unclear because of its very low levels in adults (Hashimoto et al. 1993a; Sakai et al. 1998; Wolosker et al. 2000). Indeed, as is seen with the correlation between the decrease in D-serine levels and the higher expression of DAAO in the cerebellum after birth (Hashimoto et al. 1995a, b), the postnatal disappearance of D-aspartate from the brain coincides with the onset of the activity of D-aspartate oxidase (DAOX), the sole enzyme determined so far to control D-aspartate levels (Boselli et al. 2007; Negri et al. 1987; Pollegioni et al. 2007). Nevertheless, the possibility that D-aspartate is released in a calcium-dependent manner at the synapse from neurons and astrocytes (Waagepetersen et al. 2001) suggests a putative role for the amino acid in synaptic communication within neuronal networks (D'Aniello et al. 2011). In favour of this hypothesis, D-aspartate binds NMDA-R at the glutamate-binding site (Fagg and Matus 1984; Foster and Fagg 1987; Olverman et al. 1988) and triggers inward currents in hippocampal CA1 pyramidal neurons and striatal neurons from juvenile animals (Errico et al. 2008a, b, 2011b), confirming that the amino acid might interfere with NMDA-R-dependent signalling (Fig. 4a). Interestingly, it should be noted that D-aspartate elicits a detectable current even after the complete antagonization of NMDA-R (Fig. 4a), indicating that the amino acid activates calcium-dependent NMDA-R-independent responses, the origin of which remains to be characterized (Errico et al. 2011a, b, c).

The role of D-aspartate has recently been better estimated by studying the effects of abnormally elevated levels of the amino acid. The targeted deletion of the DAOX gene

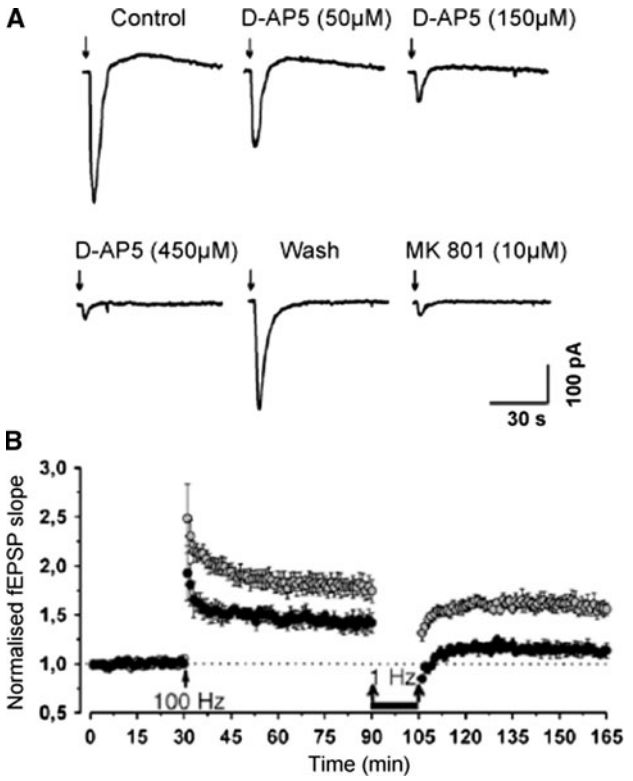

Fig. 4 D-Aspartate gates NMDA-R at glutamatergic synapses. **a** Effects of increasing concentrations of the competitive NMDA-R antagonist D-amino-5-phosphonovalerate (D-AP5) or of the non-competitive antagonist MK801 on inward currents induced in CA1 pyramidal neurons by the local application of D-aspartate. Note that the current is not completely abolished, indicating the involvement of NMDA-R-independent mechanisms. **b** Comparison of the time-course of NMDA-R-mediated LTP and depotentiation induced in slices from control mice (*grey circles*) and from D-aspartate -treated mice (*black circles*). Modified from (Errico et al. 2008a)

induces a large increase in the amount of D-aspartate and its derivative NMDA in almost all parts of the brain (Errico et al. 2008a, b, 2011b, c). Under these conditions, NMDA-R activation is speculated to be greater because of a significant enhancement in the levels of phosphorylated calcium calmodulin kinase II, a major target of NMDA-R-dependent inward calcium currents (Errico et al. 2011c). In contrast, fast glutamatergic neurotransmission mediated by AMPA/kainate receptors remains unaffected (Errico et al. 2008a). The increase in NMDA-R activity does not reflect a change in receptor density since the expression of GluN1 and GluN2 subunits is not modified in DAOX null animals (Errico et al. 2008a, 2009, 2011a, b, c). As for NMDA-R-dependent synaptic plasticity, the chronic elevation of D-aspartate levels in animals increases theta-burst-induced LTP while the induction of LTD and of depotentiation, a process that clears the way for synaptic activity leading to new cognitive acquisition, are altered in both the hippocampus and the striatum (Errico et al. 2008a, b, 2011a, c). Interestingly, a similar pattern of changes in the expression of LTP and depotentiation is reported after the chronic elevation of D-aspartate levels by oral administration of the amino acid (Fig. 4b). However, it is worth noting that if the magnitude of LTP is increased after a 3-month chronic treatment with D-aspartate, it is decreased after a 12-month treatment (Errico et al. 2011b). In the same way, LTP is higher in young DAOX mutant mice when compared to controls but is weaker in older mutants than controls of the same age (Errico et al. 2011c). Taken together, these results reveal that D-aspartate is a putative endogenous neuromodulator that exacerbates glutamatergic synaptic potentiation (D'Aniello et al. 2011) and, as pointed out by (Errico et al. 2011c), "*unveil a role of DAOX in preventing aberrant NMDA-R stimulation by strictly controlling D-aspartate central levels at low concentrations*". On the other hand, this potentiatory effect suggests that D-aspartate might be a relevant tool to alleviate brain defects due to NMDA-R hypofunction. Accordingly, it has recently been found that increasing D-aspartate levels rescue age-related LTP impairment (Errico et al. 2011b), might attenuate some pharmacologically induced schizophrenia-like symptoms (Errico et al. 2008b) and prevent L-DOPA-induced dyskinesia (Errico et al. 2011a).

Concluding remarks

There is no doubt that our knowledge regarding the presence of D-amino acids in higher species and their interactions with brain function have markedly increased during the last few decades (Fuchs et al. 2005). However, it is also clear that much still remains to be unravelled. In particular, attempting to understand the mechanisms involved in the synaptic turnover of these amino acids is like glimpsing them through a looking glass. For example, D-serine was initially thought to be derived from astrocytes and was therefore considered to be a typical gliotransmitter required for the expression of synaptic plasticity (Fossat et al. 2012; Henneberger et al. 2010; Panatier et al. 2006; Yang et al. 2003). However, the fact that neurons have recently been found to synthesize and release D-serine upon depolarization (Kartvelishvily et al. 2006; Rosenberg et al. 2010) while LTP is abolished after the deletion of the serine racemase gene in neurons but not in astrocytes (Benneyworth et al. 2012) indicates that the mechanisms underlying D-serine-dependent synaptic plasticity are more sophisticated than previously assumed. In this line of reasoning, an elegant hypothesis of a D-serine shuttle between neurons and astrocytes has recently been proposed, suggesting that both cellular components are necessary partners in the action of the amino acid (Wolosker 2011). Also, mechanisms contributing to D-serine and D-aspartate release in the synaptic cleft, including vesicular calcium-dependent

exocytosis, non-vesicular outflow and transporter-mediated hetero-exchange, as well as routes responsible for their elimination from synapses, need to be clarified to better understand the role of D-serine and D-aspartate in neurotransmission dynamics. Considering that the dysregulated turnover of these amino acids is thought to play a pathological role in aging, schizophrenia and acute and chronic neurodegeneration (Billard 2008; Fuchs et al. 2005; Wolosker et al. 2008), these are all important issues.

Conflict of interest The author declares that he has no conflict of interest.

References

Adams MM, Smith TD, Moga D, Gallagher M, Wang Y, Wolfe BB, Rapp PR, Morrison JH (2001) Hippocampal dependent learning ability correlates with *N*-methyl-D-aspartate (NMDA) receptor levels in CA3 neurons of young and aged rats. J Comp Neurol 432(2):230–243

Baptista V, Varanda WA (2005) Glycine binding site of the synaptic NMDA receptor in subpostremal NTS neurons. J Neurophysiol 94(1):147–152

Basu AC, Tsai GE, Ma CL, Ehmsen JT, Mustafa AK, Han L, Jiang ZI, Benneyworth MA, Froimowitz MP, Lange N, Snyder SH, Bergeron R, Coyle JT (2009) Targeted disruption of serine racemase affects glutamatergic neurotransmission and behavior. Mol Psychiatry 14(7):719–727

Bear MF, Malenka RC (1994) Synaptic plasticity: LTP and LTD. Curr Opin Neurobiol 4(3):389–399

Benneyworth MA, Li Y, Basu AC, Bolshakov VY, Coyle JT (2012) Cell selective conditional null mutations of serine racemase demonstrate a predominate localization in cortical glutamatergic neurons. Cell Mol Neurobiol 32(4):613–624

Billard JM (2008) D-Serine signalling as a prominent determinant of neuronal–glial dialogue in the healthy and diseased brain. J Cell Mol Med 12(5B):1872–1884

Billups D, Attwell D (2003) Active release of glycine or D-serine saturates the glycine site of NMDA receptors at the cerebellar mossy fibre to granule cell synapse. Eur J Neurosci 18(11): 2975–2980

Bliss TV, Collingridge GL (1993) A synaptic model of memory: long-term potentiation in the hippocampus. Nature 361(6407): 31–39

Boselli A, Piubelli L, Molla G, Pilone MS, Pollegioni L, Sacchi S (2007) Investigating the role of active site residues of *Rhodotorula gracilis* D-amino acid oxidase on its substrate specificity. Biochimie 89(3):360–368

Chapman DE, Keefe KA, Wilcox KS (2003) Evidence for functionally distinct synaptic NMDA receptors in ventromedial versus dorsolateral striatum. J Neurophysiol 89(1):69–80

Ciabarra AM, Sullivan JM, Gahn LG, Pecht G, Heinemann S, Sevarino KA (1995) Cloning and characterization of chi-1: a developmentally regulated member of a novel class of the ionotropic glutamate receptor family. J Neurosci 15(10): 6498–6508

Collingridge GL, Bliss TV (1995) Memories of NMDA receptors and LTP. Trends Neurosci 18(2):54–56

Collins GG (1991) Pharmacological evidence that NMDA receptors contribute to mono- and di-synaptic potentials in slices of mouse olfactory cortex. Neuropharmacology 30(6):547–555

Corrigan JJ (1969) D-Amino acids in animals. Science 164(876): 142–149

D'Aniello A (2007) D-Aspartic acid: an endogenous amino acid with an important neuroendocrine role. Brain Res Rev 53(2):215–234

D'Aniello S, Somorjai I, Garcia-Fernandez J, Topo E, D'Aniello A (2011) D-Aspartic acid is a novel endogenous neurotransmitter. FASEB J 25(3):1014–1027

Daniels BA, Baldridge WH (2012) D-Serine enhancement of NMDA receptor-mediated calcium increases in rat retinal ganglion cells. J Neurochem 112(5):1180–1189

Daniels BA, Wood L, Tremblay F, Baldridge WH (2012) Functional evidence for D-serine inhibition of non-*N*-methyl-D-aspartate ionotropic glutamate receptors in retinal neurons. Eur J Neurosci 35(1):56–65

Drejer J, Larsson OM, Schousboe A (1983) Characterization of uptake and release processes for D- and L-aspartate in primary cultures of astrocytes and cerebellar granule cells. Neurochem Res 8(2):231–243

Duffy S, Labrie V, Roder JC (2008) D-Serine augments NMDA-NR2B receptor-dependent hippocampal long-term depression and spatial reversal learning. Neuropsychopharmacology 33(5): 1004–1018

Dunlop DS, Neidle A, McHale D, Dunlop DM, Lajtha A (1986) The presence of free D-aspartic acid in rodents and man. Biochem Biophys Res Commun 141(1):27–32

Errico F, Nistico R, Palma G, Federici M, Affuso A, Brilli E, Topo E, Centonze D, Bernardi G, Bozzi Y, D'Aniello A, Di Lauro R, Mercuri NB, Usiello A (2008a) Increased levels of D-aspartate in the hippocampus enhance LTP but do not facilitate cognitive flexibility. Mol Cell Neurosci 37(2):236–246

Errico F, Rossi S, Napolitano F, Catuogno V, Topo E, Fisone G, D'Aniello A, Centonze D, Usiello A (2008b) D-Aspartate prevents corticostriatal long-term depression and attenuates schizophrenia-like symptoms induced by amphetamine and MK-801. J Neurosci 28(41):10404–10414

Errico F, Napolitano F, Nistico R, Centonze D, Usiello A (2009) D-Aspartate: an atypical amino acid with neuromodulatory activity in mammals. Rev Neurosci 20(5–6):429–440

Errico F, Bonito-Oliva A, Bagetta V, Vitucci D, Romano R, Zianni E, Napolitano F, Marinucci S, Di Luca M, Calabresi P, Fisone G, Carta M, Picconi B, Gardoni F, Usiello A (2011a) Higher free D-aspartate and N-methyl-D-aspartate levels prevent striatal depotentiation and anticipate L-DOPA-induced dyskinesia. Exp Neurol 232(2):240–250

Errico F, Nistico R, Napolitano F, Mazzola C, Astone D, Pisapia T, Giustizieri M, D'Aniello A, Mercuri NB, Usiello A (2011b) Increased D-aspartate brain content rescues hippocampal age-related synaptic plasticity deterioration of mice. Neurobiol Aging 32(12):2229–2243

Errico F, Nistico R, Napolitano F, Oliva AB, Romano R, Barbieri F, Florio T, Russo C, Mercuri NB, Usiello A (2011c) Persistent increase of D-aspartate in D-aspartate oxidase mutant mice induces a precocious hippocampal age-dependent synaptic plasticity and spatial memory decay. Neurobiol Aging 32(11): 2061–2074

Fagg GE, Matus A (1984) Selective association of *N*-methyl aspartate and quisqualate types of L-glutamate receptor with brain postsynaptic densities. Proc Natl Acad Sci USA 81(21): 6876–6880

Fletcher EJ, Millar JD, Zeman S, Lodge D (1989) Non-competitive antagonism of *N*-methyl-D-aspartate by displacement of an endogenous glycine-like substance. Eur J Neurosci 1(3):196–203

Fossat P, Turpin FR, Sacchi S, Dulong J, Shi T, Rivet JM, Sweedler JV, Pollegioni L, Millan MJ, Oliet SH, Mothet JP (2012) Glial D-serine gates NMDA receptors at excitatory synapses in prefrontal cortex. Cereb Cortex 22(3):595–606

Foster AC, Fagg GE (1987) Comparison of L-[3H]glutamate, D-[3H]aspartate, DL-[3H]AP5 and [3H]NMDA as ligands for NMDA receptors in crude postsynaptic densities from rat brain. Eur J Pharmacol 133(3):291–300

Fuchs SA, Berger R, Klomp LW, de Koning TJ (2005) D-Amino acids in the central nervous system in health and disease. Mol Genet Metab 85(3):168–180

Furukawa H, Gouaux E (2003) Mechanisms of activation, inhibition and specificity: crystal structures of the NMDA receptor NR1 ligand-binding core. EMBO J 22(12):2873–2885

Gong XQ, Zabek RL, Bai D (2007) D-Serine inhibits AMPA receptor-mediated current in rat hippocampal neurons. Can J Physiol Pharmacol 85(5):546–555

Guo JD, Wang H, Zhang YQ, Zhao ZQ (2005) Alterations of membrane properties and effects of D-serine on NMDA-induced current in rat anterior cingulate cortex neurons after monoarthritis. Neurosci Lett 384(3):245–249

Gustafson EC, Stevens ER, Wolosker H, Miller RF (2007) Endogenous D-serine contributes to NMDA-receptor-mediated light-evoked responses in the vertebrate retina. J Neurophysiol 98(1):122–130

Hamase K, Homma H, Takigawa Y, Fukushima T, Santa T, Imai K (1997) Regional distribution and postnatal changes of D-amino acids in rat brain. Biochim Biophys Acta 1334(2–3):214–222

Han H, Miyoshi Y, Ueno K, Okamura C, Tojo Y, Mita M, Lindner W, Zaitsu K, Hamase K (2011) Simultaneous determination of D-aspartic acid and D-glutamic acid in rat tissues and physiol ogical fluids using a multi-loop two-dimensional HPLC procedure. J Chromatogr B Anal Technol Biomed Life Sci 879(29):3196–3202

Hansen KB, Naur P, Kurtkaya NL, Kristensen AS, Gajhede M, Kastrup JS, Traynelis SF (2009) Modulation of the dimer interface at ionotropic glutamate-like receptor delta2 by D-serine and extracellular calcium. J Neurosci 29(4):907–917

Hashimoto A, Chiba S (2004) Effect of systemic administration of D-serine on the levels of D- and L-serine in several brain areas and periphery of rat. Eur J Pharmacol 495(2–3):153–158

Hashimoto A, Nishikawa T, Konno R, Niwa A, Yasumura Y, Oka T, Takahashi K (1993a) 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(1–2):33–36

Hashimoto A, Nishikawa T, Oka T, Takahashi K (1993b) Endogenous D-serine in rat brain: *N*-methyl-D-aspartate receptor-related distribution and aging. J Neurochem 60(2):783–786

Hashimoto A, Oka T, Nishikawa T (1995a) Anatomical distribution and postnatal changes in endogenous free D-aspartate and D-serine in rat brain and periphery. Eur J Neurosci 7(8):1657–1663

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

Haxaire C, Turpin FR, Potier B, Kervern M, Sinet PM, Barbanel G, Mothet JP, Dutar P, Billard JM (2012) Reversal of age-related oxidative stress prevents hippocampal synaptic plasticity deficits by protecting D-serine-dependent NMDA receptor activation. Aging Cell 11(2):336–344

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

Horio M, Kohno M, Fujita Y, Ishima T, Inoue R, Mori H, Hashimoto K (2011) Levels of D-serine in the brain and peripheral organs of serine racemase (Srr) knock-out mice. Neurochem Int 59(6): 853–859

Huang AS, Beigneux A, Weil ZM, Kim PM, Molliver ME, Blackshaw S, Nelson RJ, Young SG, Snyder SH (2006) D-Aspartate regulates melanocortin formation and function: behavioral alterations in D-aspartate oxidase-deficient mice. J Neurosci 26(10):2814–2819

Inoue R, Hashimoto K, Harai T, Mori H (2008) NMDA- and beta-amyloid1-42-induced neurotoxicity is attenuated in serine racemase knock-out mice. J Neurosci 28(53):14486–14491

Ito K, Hicks TP (2001) Effect of the glycine modulatory site of the *N*-methyl-D-aspartate receptor on synaptic responses in kitten visual cortex. Neurosci Lett 303(2):95–98

Izquierdo I, Medina JH (1995) Correlation between the pharmacology of long-term potentiation and the pharmacology of memory. Neurobiol Learn Mem 63(1):19–32

Junjaud G, Rouaud E, Turpin F, Mothet JP, Billard JM (2006) Age-related effects of the neuromodulator D-serine on neurotransmission and synaptic potentiation in the CA1 hippocampal area of the rat. J Neurochem 98(4):1159–1166

Kakegawa W, Miyoshi Y, Hamase K, Matsuda S, Matsuda K, Kohda K, Emi K, Motohashi J, Konno R, Zaitsu K, Yuzaki M (2011) D-Serine regulates cerebellar LTD and motor coordination through the delta2 glutamate receptor. Nat Neurosci 14(5):603–611

Kartvelishvily E, Shleper M, Balan L, Dumin E, Wolosker H (2006) Neuron-derived D-serine release provides a novel means to activate *N*-methyl-D-aspartate receptors. J Biol Chem 281(20): 14151–14162

Kashiwabuchi N, Ikeda K, Araki K, Hirano T, Shibuki K, Takayama C, Inoue Y, Kutsuwada T, Yagi T, Kang Y et al (1995) Impairment of motor coordination, Purkinje cell synapse formation, and cerebellar long-term depression in GluR delta 2 mutant mice. Cell 81(2):245–252

Kim SJ, Linden DJ (2007) Ubiquitous plasticity and memory storage. Neuron 56(4):582–592

Krasteniakov NV, Martina M, Bergeron R (2004) Subthreshold contribution of *N*-methyl-D-aspartate receptors to long-term potentiation induced by low-frequency pairing in rat hippocampal CA1 pyramidal cells. Neuroscience 126(1):83–94

Krasteniakov NV, Martina M, Bergeron R (2005) Role of the glycine site of the *N*-methyl-D-aspartate receptor in synaptic plasticity induced by pairing. Eur J Neurosci 21(10):2782–2792

Krebs HA (1935) Metabolism of amino-acids: deamination of amino-acids. Biochem J 29(7):1620–1644

Lamzin VS, Dauter Z, Wilson KS (1995) How nature deals with stereoisomers. Curr Opin Struct Biol 5(6):830–836

Low CM, Wee KS (2010) New insights into the not-so-new NR3 subunits of *N*-methyl-D-aspartate receptor: localization, structure, and function. Mol Pharmacol 78(1):1–11

Luscher C, Nicoll RA, Malenka RC, Muller D (2000) Synaptic plasticity and dynamic modulation of the postsynaptic membrane. Nat Neurosci 3(6):545–550

Lynch MA (2004) Long-term potentiation and memory. Physiol Rev 84(1):87–136

Maekawa M, Watanabe M, Yamaguchi S, Konno R, Hori Y (2005) Spatial learning and long-term potentiation of mutant mice lacking D-amino-acid oxidase. Neurosci Res 53(1):34–38

Man EH, Fisher GH, Payan IL, Cadilla-Perezrios R, Garcia NM, Chemburkar R, Arends G, Frey WH 2nd (1987) D-Aspartate in human brain. J Neurochem 48(2):510–515

Martin SJ, Grimwood PD, Morris RG (2000) Synaptic plasticity and memory: an evaluation of the hypothesis. Annu Rev Neurosci 23:649–711

Martina M, Krasteniakov NV, Bergeron R (2003) D-Serine differently modulates NMDA receptor function in rat CA1 hippocampal pyramidal cells and interneurons. J Physiol 548(Pt 2):411–423

Matsui T, Sekiguchi M, Hashimoto A, Tomita U, Nishikawa T, Wada K (1995) Functional comparison of D-serine and glycine in rodents: the effect on cloned NMDA receptors and the extracellular concentration. J Neurochem 65(1):454–458

McBain CJ, Kleckner NW, Wyrick S, Dingledine R (1989) Structural requirements for activation of the glycine coagonist site of *N*-methyl-D-aspartate receptors expressed in *Xenopus* oocytes. Mol Pharmacol 36(4):556–565

Morikawa A, Hamase K, Zaitsu K (2003) Determination of D-alanine in the rat central nervous system and periphery using column-switching high-performance liquid chromatography. Anal Biochem 312(1):66–72

Mothet JP, Parent AT, Wolosker H, Brady RO Jr, Linden DJ, Ferris CD, Rogawski MA, Snyder SH (2000) D-Serine is an endogenous ligand for the glycine site of the *N*-methyl-D-aspartate receptor. Proc Natl Acad Sci USA 97(9):4926–4931

Mothet JP, Rouaud E, Sinet PM, Potier B, Jouvenceau A, Dutar P, Videau C, Epelbaum J, Billard JM (2006) A critical role for the glial-derived neuromodulator D-serine in the age-related deficits of cellular mechanisms of learning and memory. Aging Cell 5(3):267–274

Naur P, Hansen KB, Kristensen AS, Dravid SM, Pickering DS, Olsen L, Vestergaard B, Egebjerg J, Gajhede M, Traynelis SF, Kastrup JS (2007) Ionotropic glutamate-like receptor delta2 binds D-serine and glycine. Proc Natl Acad Sci USA 104(35): 14116–14121

Negri A, Massey V, Williams CH Jr (1987) D-Aspartate oxidase from beef kidney. Purification and properties. J Biol Chem 262(21): 10026–10034

Olverman HJ, Jones AW, Mewett KN, Watkins JC (1988) Structure/activity relations of *N*-methyl-D-aspartate receptor ligands as studied by their inhibition of [3H]D-2-amino-5-phosphonopentanoic acid binding in rat brain membranes. Neuroscience 26(1):17–31

Panatier A, Theodosis DT, Mothet JP, Touquet B, Pollegioni L, Poulain DA, Oliet SH (2006) Glia-derived D-serine controls NMDA receptor activity and synaptic memory. Cell 125(4): 775–784

Paoletti P (2011) Molecular basis of NMDA receptor functional diversity. Eur J Neurosci 33(8):1351–1365

Pina-Crespo JC, Talantova M, Micu I, States B, Chen HS, Tu S, Nakanishi N, Tong G, Zhang D, Heinemann SF, Zamponi GW, Stys PK, Lipton SA (2010) Excitatory glycine responses of CNS myelin mediated by NR1/NR3 "NMDA" receptor subunits. J Neurosci 30(34):11501–11505

Pollegioni L, Sacchi S (2010) Metabolism of the neuromodulator D-serine. Cell Mol Life Sci 67(14):2387–2404

Pollegioni L, Piubelli L, Sacchi S, Pilone MS, Molla G (2007) Physiological functions of D-amino acid oxidases: from yeast to humans. Cell Mol Life Sci 64(11):1373–1394

Potier B, Turpin FR, Sinet PM, Rouaud E, Mothet JP, Videau C, Epelbaum J, Dutar P, Billard JM (2010) Contribution of the D-serine-dependent pathway to the cellular mechanisms underlying cognitive aging. Front Aging Neurosci 2:1

Priestley T, Laughton P, Myers J, Le Bourdelles B, Kerby J, Whiting PJ (1995) Pharmacological properties of recombinant human *N*-methyl-D-aspartate receptors comprising NR1a/NR2A and NR1a/NR2B subunit assemblies expressed in permanently transfected mouse fibroblast cells. Mol Pharmacol 48(5): 841–848

Reyes-Haro D, Muller J, Boresch M, Pivneva T, Benedetti B, Scheller A, Nolte C, Kettenmann H (2010) Neuron–astrocyte interactions in the medial nucleus of the trapezoid body. J Gen Physiol 135(6):583–594

Rosenberg D, Kartvelishvily E, Shleper M, Klinker CM, Bowser MT, Wolosker H (2010) Neuronal release of D-serine: a physiological pathway controlling extracellular D-serine concentration. FASEB J 24(8):2951–2961

Sakai K, Homma H, Lee JA, Fukushima T, Santa T, Tashiro K, Iwatsubo T, Imai K (1998) Emergence of D-aspartic acid in the differentiating neurons of the rat central nervous system. Brain Res 808(1):65–71

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

Schell MJ, Brady RO Jr, Molliver ME, Snyder SH (1997) D-Serine as a neuromodulator: regional and developmental localizations in rat brain glia resemble NMDA receptors. J Neurosci 17(5): 1604–1615

Smith JL, Higuchi K (1960) Studies on the nutrition and physiology of *Pasteurella pestis*. V. Inhibition of growth by D-serine and its reversal by various compounds. J Bacteriol 79:539–543

Stevens ER, Esguerra M, Kim PM, Newman EA, Snyder SH, Zahs KR, Miller RF (2003) D-Serine and serine racemase are present in the vertebrate retina and contribute to the physiological activation of NMDA receptors. Proc Natl Acad Sci USA 100(11):6789–6794

Stevens ER, Gustafson EC, Sullivan SJ, Esguerra M, Miller RF (2010) Light-evoked NMDA receptor-mediated currents are reduced by blocking D-serine synthesis in the salamander retina. NeuroReport 21(4):239–244

Still JL, Buell MV et al (1949) Studies on the cyclophorase system. D-aspartic oxidase. J Biol Chem 179(2):831–837

Traynelis SF, Wollmuth LP, McBain CJ, Menniti FS, Vance KM, Ogden KK, Hansen KB, Yuan H, Myers SJ, Dingledine R (2010) Glutamate receptor ion channels: structure, regulation, and function. Pharmacol Rev 62(3):405–496

Turpin FR, Potier B, Dulong JR, Sinet PM, Alliot J, Oliet SH, Dutar P, Epelbaum J, Mothet JP, Billard JM (2011) Reduced serine racemase expression contributes to age-related deficits in hippocampal cognitive function. Neurobiol Aging 32(8): 1495–1504

Waagepetersen HS, Shimamoto K, Schousboe A (2001) Comparison of effects of DL-threo-beta-benzyloxyaspartate (DL-TBOA) and L-trans-pyrrolidine-2,4-dicarboxylate (t-2,4-PDC) on uptake and release of [3h]D-aspartate in astrocytes and glutamatergic neurons. Neurochem Res 26(6):661–666

Wafford KA, Kathoria M, Bain CJ, Marshall G, Le Bourdelles B, Kemp JA, Whiting PJ (1995) Identification of amino acids in the *N*-methyl-D-aspartate receptor NR1 subunit that contribute to the glycine binding site. Mol Pharmacol 47(2):374–380

Wake K, Yamazaki H, Hanzawa S, Konno R, Sakio H, Niwa A, Hori Y (2001) Exaggerated responses to chronic nociceptive stimuli and enhancement of *N*-methyl-D-aspartate receptor-mediated synaptic transmission in mutant mice lacking D-amino-acid oxidase. Neurosci Lett 297(1):25–28

Wee KS, Zhang Y, Khanna S, Low CM (2008) Immunolocalization of NMDA receptor subunit NR3B in selected structures in the rat forebrain, cerebellum, and lumbar spinal cord. J Comp Neurol 509(1):118–135

Whitney JG, Grula EA (1968) A major attachment site for D-serine in the cell wall mucopeptide of *Micrococcus lysodeikticus*. Biochim Biophys Acta 158(1):124–129

Williams K, Chao J, Kashiwagi K, Masuko T, Igarashi K (1996) Activation of *N*-methyl-D-aspartate receptors by glycine: role of an aspartate residue in the M3–M4 loop of the NR1 subunit. Mol Pharmacol 50(4):701–708

Wolosker H (2011) Serine racemase and the serine shuttle between neurons and astrocytes. Biochim Biophys Acta 1814(11): 1558–1566

Wolosker H, D'Aniello A, Snyder SH (2000) D-Aspartate disposition in neuronal and endocrine tissues: ontogeny, biosynthesis and release. Neuroscience 100(1):183–189

Wolosker H, Dumin E, Balan L, Foltyn VN (2008) D-Amino acids in the brain: D-serine in neurotransmission and neurodegeneration. FEBS J 275(14):3514–3526

Wong HK, Liu XB, Matos MF, Chan SF, Perez-Otano I, Boysen M, Cui J, Nakanishi N, Trimmer JS, Jones EG, Lipton SA, Sucher NJ (2002) Temporal and regional expression of NMDA receptor subunit NR3A in the mammalian brain. J Comp Neurol 450(4): 303–317

Yang Y, Ge W, Chen Y, Zhang Z, Shen W, Wu C, Poo M, Duan S (2003) Contribution of astrocytes to hippocampal long-term potentiation through release of D-serine. Proc Natl Acad Sci USA 100(25):15194–15199

Yang K, Xiong W, Yang G, Kojic L, Wang YT, Cynader M (2011) The regulatory role of long-term depression in juvenile and adult mouse ocular dominance plasticity. Sci Rep 1:203

Zhang Z, Gong N, Wang W, Xu L, Xu TL (2008) Bell-shaped D-serine actions on hippocampal long-term depression and spatial memory retrieval. Cereb Cortex 18(10):2391–2401