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The neurobiology of D-amino acid oxidase (DAO) and its involvement in schizophrenia

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Abstract

D-amino acid oxidase (DAO, DAAO) is a flavoenzyme that metabolises certain D-amino acids, notably the endogenous N-methyl D-aspartate receptor (NMDAR) co-agonist, D-serine. As such, it has the potential to modulate NMDAR function and to contribute to the widely hypothesized involvement of NMDAR signalling in schizophrenia. Three lines of evidence now provide support for this possibility: DAO shows genetic associations to the disorder in several, though not all, studies; the expression and activity of DAO are increased in schizophrenia; and DAO inactivation in rodents produces behavioural and biochemical effects suggestive of potential therapeutic benefits. However, several key issues remain unclear. These include the regional, cellular and subcellular localization of DAO, the physiological importance of DAO and of its substrates other than D-serine, and the causes and consequences of elevated DAO in schizophrenia. Here we critically review the neurobiology of DAO, its involvement in schizophrenia, and the therapeutic value of DAO inhibition. The review also illuminates issues that have a broader relevance beyond DAO itself: how should we weigh up convergent and cumulatively impressive, but individually inconclusive, pieces of evidence regarding the role that a given gene may play in the aetiology, pathophysiology, and pharmacotherapy of schizophrenia?

Keywords

D-amino acid; DAO; DAAO; NMDA receptor; schizophrenia; glutamate; D-serine

Introduction

The enzyme D-amino acid oxidase (DAO, DAAO) was discovered in the porcine kidney almost 75 years ago,1 and has since been extensively studied as a model flavin-dependent oxidase. DAO is now of interest for psychiatry (Table 1)1-12 because its major substrate in brain is D-serine, a co-agonist of the N-methyl D-aspartate type of ionotropic glutamate receptor (NMDAR): DAO therefore has the capability to regulate NMDAR function via D-serine breakdown and might contribute to NMDAR hypofunction in schizophrenia, or be relevant to its remediation. Here we review the biology of DAO in the brain, the evidence for its involvement in schizophrenia, and its therapeutic potential in the disorder.

The neurobiology of DAO

The DAO gene and its products

The human DAO gene is located at chromosome 12q24 and comprises eleven exons (Figure 1). The full length transcript is 1595bp4,13 and shows 78 and 77% nucleotide homology

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with mouse14 and rat15 DAO respectively. The human DAO transcript encodes a ~39kDa protein of 347 amino acids4 and a single major band is detected on western blots.16-20

Although only a single DAO mRNA or protein has been unequivocally demonstrated, there may be isoforms of DAO. The potential for additional DAO transcripts is suggested by the presence of transcription initiation sequences in the first intron,13 which may be relevant to the discovery of a human brain DAO mRNA variant with a 5′ untranslated region (UTR) deletion.21 This is of interest given that the 5′UTR of the rabbit kidney DAO acts as a translational repressor.22 Variants may also arise within the 3′UTR via multiple poly-adenylation signals.15,23 A final transcript variant, lacking exon 9, has been identified from mouse cDNA libraries.24 At the protein level, a DAO immunoreactive band, ~1-1.5 kDa smaller than full length DAO, is detectable in kidney,25 and there are two active isozymes reported in human kidney.26 In brain, Sacchi *et al.,* (2008)20 immunoprecipitated a ~34kDa DAO band, but noted that the extra band(s) could reflect proteolysis, as previously described for DAO,27 or cross-reactivity. Overall, there remains no conclusive evidence for functional isoforms of human DAO, but it is attractive to postulate their existence as an explanation for various unexplained observations suggestive of DAO heterogeneity discussed below.

The actions of DAO in the brain

DAO oxidises D-amino acids through concomitant reduction of its prosthetic group, flavin adenine dinucleotide (FAD), producing the corresponding imino acid; this is then hydrolysed to yield ammonia and the corresponding α-keto acid. Hydrogen peroxide is produced during flavin reoxidation (Figure 2; reviewed in refs. 28 and 29). FAD binding is notably weaker in human DAO than in DAO from other species examined, providing a potential means to regulate DAO activity in humans since FAD-unbound DAO, whilst it still binds substrate, is catalytically inactive.30 DAO is characteristic of flavin-dependent oxidases by displaying stereospecificty to D-amino acids. It selectively oxidises those with small, neutral side chains, notably D-serine, D-alanine, D-proline, and D-leucine, for which human DAO shows affinities (Km) of ~1-10mM.[31,32]

DAO enzyme activity was discovered in the mammalian brain over forty years ago.3,33 However, its significance remained enigmatic until the discovery of D-amino acids in brain tissue, including the DAO substrates D-alanine, D-serine, D-leucine and D-proline, of which D-serine is by far the most abundant (Table 2).18,34-54 A further, key piece of the jigsaw was provided by the discovery of an enzyme enriched in brain that synthesises D-serine from L-serine, called serine racemase (SRR).55,56 While some brain D-serine could also arise from the periphery and the diet,39,57 it is likely that brain D-serine is largely the result of local synthesis from L-serine.58 A peripheral origin may well be greater for, if not the sole source of, the other D-amino acids mentioned, for which synthetic enzymes in brain have not been demonstrated. Consistent with this, levels of D-alanine rise in the brain following oral administration.59

DAO has a modest affinity for its substrates in the context of their low concentrations in the brain (Table 2). This has led to some doubt as to the physiological relevance of the enzyme *in vivo,*31,60 but evidence for the functionality of central DAO comes from two main sources. Firstly, the ddY/DAO- mouse, which lacks active DAO due to a point mutation (Gly181Arg).5,61 In these mice, levels of D-serine and other DAO substrates are increased several-fold in most brain areas (see Table 2, right hand column), in keeping with a major role for DAO in their metabolism. Secondly, oral or systemic administration of DAO inhibitors to normal rodents can increase central D-serine levels.10,62 However, the ddY/DAO- data also show some interesting complexities. D-serine and D-proline are either unchanged or only minimally increased in the cerebral cortex in contrast to their marked increases in cerebellum, consistent with the view that DAO plays at most a minor role in the

forebrain (see below). On the other hand, D-alanine and D-leucine levels are elevated in the cerebral cortex of ddY/DAO- mice by a similar magnitude to that in the cerebellum. This pattern of results in the ddY/DAO- mouse illustrates that there is more to the metabolism of brain D-amino acids than just locally acting DAO – potentially including selective D-amino acid uptake into the brain,58,63,64 other enzymes and transporters (which may differ in their selectivity for different D-amino acids, and in their distribution within the brain), and a role for peripheral as well as central actions of DAO.39,50

The role of DAO in NMDAR modulation

The NMDAR requires, in addition to glutamate, binding of a co-agonist at the 'strychnine insensitive glycine modulatory site' in order to open. Several studies have indicated that, as well as glycine, D-serine binds at this site and facilitates NMDAR function.65-67 Moreover, seminal studies which showed enrichment of D-serine to forebrain astrocytes concentrated around NMDAR 2A/B subunits68,69 led to the proposal that D-serine is the endogenous NMDAR co-agonist, at least in the forebrain.70-78 Numerous studies have verified that endogenous as well as exogenous D-serine potentiates NMDAR function.79-87 The evidence that D-serine is the main NMDAR co-agonist in the forebrain, together with its greater abundance compared to other D-amino acids, explains the predominance of studies focusing on D-serine's roles and regulation. In passing, it is worth noting that D-alanine can also act as an NMDAR co-agonist67,88 and that human DAO has a higher affinity for D-alanine than for D-serine (1.3mM vs. 7.5mM).31 However, the low concentration of D-alanine (~10% that of D-serine; Table 2), and the absence of a known synthetic enzyme, cast doubt on whether it is a physiological NMDAR co-agonist.

In light of these considerations, it is possible that DAO could influence physiological NMDAR function through modulation of D-serine availability in the synapse. Some evidence exists to support this notion. Firstly, exogenously applied DAO reduces NMDAR function.70,89-94 Secondly, ddY/DAO- mice show increased cerebellar NMDAR function17 and enhanced hippocampal NMDAR-dependent long-term potentiation (LTP).9 Thirdly, systemically administered DAO inhibitors produce effects consistent with enhanced NMDAR function (see below). Note that findings in both the latter types of study could reflect the lack or inhibition of peripheral DAO (leading to higher circulating levels of its substrates) rather than central DAO. Direct evidence that local actions of endogenous brain DAO are functional is, to our knowledge, limited to a pharmacological study showing that DAO inhibition localised to the ventral tegmental area augments NMDAR-dependent behaviours.95

Apart from NMDAR modulation, other roles of DAO substrates, and thus of DAO itself, may exist. D-serine antagonizes AMPA glutamate receptors96 suggesting that D-serine and DAO could be involved in both positive and negative modulatory effects at glutamatergic synapses. D-serine is also an endogenous ligand at the GluRδ2 receptor, an ionotropic glutamate-like receptor important in cerebellar development and plasticity.97 D-serine may also modulate glycinergic transmission through antagonizing NR1/NR3A or NR1/NR3B receptors, which are insensitive to glutamate and activated by glycine.98,99 D-serine also binds to human platelet 5-HT_3 receptors.100 D-proline does not act at NMDARs but can activate glycine receptors,101 whilst D-leucine is a potent regulator of the blood-brain barrier enkephalin transport system.102 It is not known whether any these various additional actions of D-amino acids have any significance with regard to DAO and its involvement in schizophrenia.

Distribution of DAO in brain and its spatial relationships with its substrates

There are several complexities and controversies regarding the localization of DAO in the brain, in terms of region, cell type, and subcellular compartment, and concerning the relationship between expression and activity.

Regional activity and expression—Based upon activity assays, DAO has traditionally been viewed as a hindbrain enzyme,3,6,33,49,59,68,103,104 although DAO activity has also be detected in the forebrain in some studies, albeit only at a small fraction (~1-5%) of that seen in cerebellum.3,12,103,105 Notwithstanding these barely detectable levels of enzyme activity, DAO mRNA is consistently detectable in forebrain regions, both in rodents21,106-109 and in humans.19,21 DAO immunoreactivity is also detectable in cortical homogenates,17,18,20 and by immunohistochemistry in frontal cortex, hippocampus and midbrain.7,19,20 A precedent for these findings exists in the rabbit kidney, where the presence of DAO mRNA (and protein) contrasts with undetectable DAO activity.22 In humans, the presence of inactive forms of DAO protein could be related to the weaker FAD binding of human DAO noted earlier.30 Regardless of the mechanism, the unequivocal expression of DAO but minimal enzyme activity raises the possibility that forebrain DAO might have different and as yet unidentified functions to hindbrain DAO. As an aside, the reciprocal issue concerns how D-serine and other DAO substrates are metabolised in the forebrain if DAO is essentially inactive therein.76 One possibility is that regulation is via transport and recycling (between cells and synapses, and between brain and periphery), rather than by local degradation. Alternatively, D-serine may be regulated by the α,β eliminase or reverse racemase functions of SRR, which convert D-serine to pyruvate and L-serine respectively, although their contributions under physiological conditions remain unclear.110,111 A third possibility is that an additional, unidentified D-serine degrading enzyme exists in the forebrain.

Cellular expression—It is also controversial as to the cell types that express DAO in the brain. DAO is conventionally described as being a glial enzyme, based upon histochemical studies which show cerebellar DAO activity localised in astrocytes and Bergmann glia.6,33,104 The presence of DAO in these cells is supported by immunohistochemistry in the rat7 and in humans19 as well as by *in situ* hybridization detection of DAO mRNA.19 DAO is also present in glia of the hippocampus and cerebral cortex.7,19,20

There is increasing evidence that DAO is not solely glial. DAO immunoreactivity has been reported in both Golgi and Purkinje cells in the rat,7 In the hippocampus and cerebral cortex, pyramidal neurons show DAO immunoreactivity7,19 and express DAO mRNA.19 DAO also localizes to neurons in dopaminergic midbrain nuclei.7,19 A well-conducted recent study, however, with a novel antibody, conspicuously failed to demonstrate neuronal DAO immunoreactivity in human cortical or diencephalic tissue.20 In total, the evidence that DAO is expressed by neurons as well as glia is strong but not compelling. Clarification will be helped by more detailed cellular mRNA studies (with in situ hybridization and single-cell type approaches) and by the availability and application of more anti-DAO antibodies.

The issue of which cell types contain DAO is important with regard to D-serine uptake. A largely glial localization of DAO would appear to contrast with the fact that Asc-1, the primary means of synaptic D-serine transport,112 is expressed predominantly, if not exclusively, by neurons.113-115 Furthermore, a second D-serine transporter, ASCT2,116-118 thought to be glial,119 is now also reported to be localised to neurons.120 These data suggest that a substantial portion of synaptic D-serine is taken up into neurons, thus indirectly supporting the possibility that DAO is functional in neurons as well as in glia.

Subcellular localization—Ultrastructural and biochemical studies show that DAO is a peroxisomal enzyme.7,104,121-124 It is targeted to peroxisomes as a partially folded inactive intermediate, which exposes a C-terminal peroxisomal targeting sequence encoded by the eleventh exon.23,125 Transport of an inactive form of DAO is presumably beneficial since production of hydrogen peroxide by DAO in other cellular compartments may be deleterious;125 indeed, DAO over-expression in glial cells is cytotoxic through hydrogen peroxide production.126 However, complicating matters, DAO may also occur in other cell compartments. The C-terminal sequence of DAO is prone to proteolysis127,128 and conceivably, if proteolysis occurred outside of peroxisomes, DAO might not be targeted to the organelle and may function elsewhere. Consistent with this, cleavage of the C-terminal 2kDa of porcine DAO yields a fully active DAO protein,129 and yeast mutants that express DAO lacking the peroxisomal targeting sequence have active cytosolic DAO.130 Notably, a detailed co-localization study found that a large proportion of DAO in human astrocytes does not overlap with peroxisomal markers.20 This non-peroxisomal form of DAO was suggested to relate to an electrophoretically more mobile form of DAO – possibly related to proteolytic cleavage events – and might relate to earlier data suggestive of DAO in other cellular compartments, including non-peroxisomal cytoplasmic granules131 and the plasma membrane.132

The subcellular distribution of DAO is relevant to the question of how it ‘sees’ its substrates. For DAO located outside of the peroxisome, accessibility of DAO to its substrates would likely not be an issue. However, in its classical peroxisomal location, presumably a transport mechanism for the D-amino acids from the cytosol into the peroxisome is required. Possible candidates include *dsr-1*, a gene that is expressed in the brain, is up-regulated by D-serine, and is predicted to encode a membrane-spanning transport protein,133 and *dsm-1*, which is expressed by neurons, affects D-serine transport, and shows a punctuate, cytoplasmic localisation when expressed in COS-7 cells.134

In summary, the view that DAO is a peroxisomal, glial, hindbrain enzyme is too simplistic: DAO is likely neuronal as well as glial, may be localised outside of as well as within peroxisomes, and may be present in the forebrain even if its significance therein remains ambiguous (Figure 3). The relative importance and functionality of DAO in these various locations is unclear, and it is unknown whether there are associated differences in the activity or regulation of the enzyme. Nevertheless, the more nuanced situation that recent data reveal provides both a challenge and an opportunity to better understand the physiological and pathophysiological role of DAO. Parenthetically, comparable unforeseen complexities have recently emerged regarding SRR. Initially viewed as being glial and cytosolic,56 SRR is now thought to be partially if not largely neuronal,135,136 and to be prominently associated with the plasma membrane.137,138 Moreover, redistribution between cytosol and membrane plays a crucial role in the determination of SRR activity and its regulation by glutamate signalling.137,138 It remains to be shown whether these findings impact on DAO, or are indicative of a spatially co-ordinated process of D-serine synthesis and degradation, but they do illustrate that there could be many complexities in the expression, activity, and regulation of DAO that await discovery.

The role of DAO in schizophrenia

Glutamate dysfunction in schizophrenia was first suggested from observations that the NMDAR antagonist phencyclidine (PCP) produces a schizophrenia-like phenotype.139 Subsequently, converging pharmacological, genetic, neuropathological and other data have led to the widely supported NMDAR hypofunction model of schizophrenia.140-149 A more specific variant of this hypothesis envisages that a deficiency of D-serine signalling contributes to NMDAR hypofunction, a view supported by the following lines of evidence:

(1) Decreased D-serine levels have been reported in schizophrenia. Hashimoto and colleagues demonstrated significant reductions in serum D-serine,150 and subsequently lower D-serine as a proportion of total (D+L)- serine in cerebrospinal fluid (CSF),151 a finding replicated by the same group in serum152 and by an independent group in CSF.18 (2) Therapeutic effects have been observed in some clinical trials with D-serine, the partial agonist D-cycloserine, and with D-alanine, when added to antipsychotic medication,153-157 and a meta-analysis concluded that D-serine is beneficial for negative symptoms, with a trend effect on cognitive symptoms.158 (3) In animal models, D-serine produces behavioural and neurochemical alterations consistent with these clinical effects.88,159-163

These factors suggest that DAO, through its role in the metabolism of D-serine – and perhaps D-alanine - may be a potential contributor to, and treatment target for, the proposed NMDAR involvement in schizophrenia. We now review evidence that DAO may be a schizophrenia susceptibility gene, that DAO expression and activity are increased in the disorder, and that DAO inhibition may be a novel therapeutic approach.

Genetic association of DAO with schizophrenia

The landmark study of Chumakov *et al.,* (2002)8 identified DAO and G72 as putative risk genes for schizophrenia. G72 was a previously unidentified gene shown to overlap with markers within the chromosome 13q34 region associating with schizophrenia. Biochemical analysis revealed DAO as a binding partner of the G72 protein product, and the investigators therefore examined single nucleotide polymorphisms (SNPs) within DAO for association with schizophrenia in their French-Canadian case-control sample. They identified four DAO SNPs, all intronic, called MDAAO4-7 (Figure 1), which showed association as well as marginal evidence for epistasis with G72. These and other DAO SNPs have subsequently been examined in a number of case-control and family-based studies of schizophrenia, providing the usual mixture of positive164-168 and negative152,169-173 results. Additionally, one study reported association of a DAO SNP with depressive and anxiety symptoms in schizophrenia.174

The data (other than refs. 168 and 173) have been included in three meta-analyses, all of which used the same ‘SzGene’ database (www.schizophreniaforum.org/res/sczgene), albeit with differing inclusion criteria. Allen et al (2008)175 meta-analysed the case-control data frozen at 30 April 2007. A SNP in DAO, rs4623951 (MDAAO-1; Figure 1), showed significant ($P<0.026$) association across all ethnicities, with a protective effect of the T allele (Odds ratio [OR] =0.88, 95% CI 0.79-0.98); however, using standard ‘Venice’ epidemiological criteria,176 it ranked as only ‘weak’ (category C) evidence, because although the amount and replication of evidence was considered strong (category A), the odds ratio was low. Sun et al (2008)177 used the database as at 3 August 2007 and also limited their analysis to the case-control data. They adopted a conceptually and statistically different approach – a survey and gene ranking rather than a formal meta-analysis, with a P value derived from the combined odds ratio method. Of the 75 genes that met a nominal $P<0.05$ overall significance, DAO was eighth in the list, with a combined odds ratio of 1.31, $P=1.1\times10^{-6}$. Shi et al (2008)178 included DAO in their meta-analysis of twelve ‘top’ genes, using the data in SzGene as at 1 March 2008. Unlike the other two meta-analyses, Shi and colleagues combined case-control and family-based studies (although only one family study152 was actually included) and applied a gene-wide corrected significance. The same DAO SNP as in Allen et al (2008),175 rs4623951, showed significant association to schizophrenia (OR=0.84, 95% CI 0.75-0.94; P=0.002), with the result virtually unaffected by exclusion of the family-based study, and with no evidence for publication bias. Three other DAO SNPs (rs2111902, rs3918346, and rs3741775 [i.e.MDAAO4, 5 and 6]) showed no evidence for association with schizophrenia (all $P>0.3$).

The three meta-analyses provide a moderate degree of support for an association between DAO and schizophrenia, specifically for rs4623951. However, some studies or SNPs were omitted for various reasons (e.g. the way the data had been presented in the original study) and so the meta-analyses do not capture all the available datasets. Additionally, neither have haplotype analyses been conducted, nor has a causal variant been identified. Nevertheless, DAO may be considered to be in the category of schizophrenia susceptibility genes for which there are reasonable grounds to defend, and continue to investigate, its candidacy.

The mechanism underlying any genetic association of DAO with schizophrenia remains unclear. Since the associated SNPs in the DAO gene are non-coding, being either in non-coding regions or synonymous, any pathophysiological functionality is likely exerted through an effect on DAO expression. In turn, altered DAO expression could affect D-serine or other DAO substrate levels. However, Burnet *et al.,* (2008)11 found no effect of two DAO tag SNPs (rs2070587 in intron 1, and rs3741775 in intron 4) on DAO expression or activity, and Yamada *et al.,* (2005)152 found no effect of DAO genotype (six of the SNPs studied by Chumakov et al [2002],8 including rs4623951) on serum D-serine. Thus, there is no evidence to support the proposed molecular basis for DAO's association with schizophrenia, although these negative studies are not definitive in terms of SNP coverage nor sample size. One study has assessed potential SNP functionality in terms of their impact on cognitive endophenotypes related to schizophrenia, but found no association of three DAO SNPs (MDAAO5-7) with performance on a broad range of cognitive tasks.179

DAO was originally identified as a candidate gene by virtue of its biochemical and genetic interaction with G72.8 However, neither interaction has been well replicated. Corvin *et al.,* (2007)167 failed to confirm the multiplicative effect between the same SNPs in DAO and G72 although they did report epistasis between two others SNPs, while another study165 found no epistatic interactions between DAO and G72. Biochemically, the evidence is also conflicting. G72 was originally reported to activate DAO's oxidization of D-serine.8 Sacchi *et al.* (2008)20 found that G72 and DAO do co-immunoprecipitate from human cortex, however, G72 reduced rather than increased DAO activity. On the other hand, Kvajo *et al.,* (2008)180 could not co-immunoprecipitate DAO and G72 when expressed in the same cells, nor co-localize to the same subcellular compartments, and that G72 expression does not modulate DAO activity. Moreover, a comprehensive recent study could not identify G72 expression in human brain,181 in contrast to an earlier report,182 casting doubt on the potential for an interaction between G72 and DAO *in vivo*. Thus, despite continuing evidence that G72 may itself be a schizophrenia gene177,183 and that G72 transgenic mice display a relevant behavioural phenotype,184 it is not established that G72 activates, or even interacts with, DAO, and suggests that the renaming of G72 as D-amino acid oxidase activator (DAOA) was premature.

DAO expression and activity in schizophrenia

The possibility that DAO may be involved pathophysiologically in schizophrenia is advanced by recent findings that its expression and activity are increased in the disorder. Table 3 summarises these data, together with those concerning SRR and Asc-1 (ASCT2 has not been measured), since alterations in these might compound or ameliorate DAO changes. In a small study, Kapoor *et al.* (2006)21 reported elevated DAO mRNA and enzyme activity in the cerebellum, with no change in DAO mRNA in the cerebral cortex. The cortical and cerebellar mRNA findings were replicated in a larger study,19 and DAO immunoreactivity showed a trend increase in the cerebellum, but could not be quantified in the prefrontal cortex.19 A third study, in a separate and larger cohort, confirmed elevated cerebellar DAO mRNA and activity in schizophrenia.11 Increased DAO activity has also been found in the parietal cortex12 while Bendikov et al (2007)18 found unchanged DAO protein in the prefrontal cortex and hippocampus. Taken together, these data provide clear evidence of

increased cerebellar DAO in schizophrenia, while the data in the other regions are more ambiguous, perhaps reflecting the uncertainties regarding the levels, activity and function of DAO in the forebrain (see above). Studies of SRR in schizophrenia are inconsistent (Table 3), but overall do not suggest that there is a compensatory increased synthesis of D-serine; however, since only SRR expression and not enzyme activity has been measured, this conclusion is tentative.

Increased cerebellar DAO activity in schizophrenia may arise for one of several reasons. The fact that DAO mRNA is increased (and correlates with DAO activity)11 indicates that the mechanism is likely to involve transcriptional regulation. However, as noted, it does not appear related to DAO genotype;11 in any event, since DAO risk alleles are carried by only a minority of cases and by some control subjects, this could not explain the observed differences between diagnostic groups. G72 mRNA is reportedly increased in schizophrenia,182 and if it is a DAO activator, then this might be a contributory factor; however, the uncertainties noted above about the relationship between G72 and DAO, and regarding the expression of G72 in the brain, make this speculative. Another possibility is antipsychotic medication. One study19 found a non-significant ~10% increase of DAO immunoreactivity in rats administered two weeks' haloperidol, and another12 found higher DAO activity in medicated patients with schizophrenia or bipolar disorder compared to antipsychotic-free cases. However, the latter effect may reflect illness features or severity, not medication, since DAO expression and activity do not correlate with lifetime or recent antipsychotic exposure in patients11,12 and DAO activity is unaffected in rats administered haloperidol.11,12 Together, these data imply that elevated DAO expression in schizophrenia is unlikely to be due to antipsychotic medication. Instead, it is tempting to argue that it is part of the glutamatergic pathophysiology of the disorder, downstream of the various genetic and environmental factors and their interactions that appear to converge upon NMDAR signalling. Further research however is necessary if this notion is to be replaced by a more specific and falsifiable proposal. One clue may come from the fact that there is a correlation between duration of illness and DAO expression and activity in the hippocampus18 and in the cerebellum.11 This might reflect a progression of the aspects of the illness that are being affected (or at least indexed) by DAO. However, no such correlations have been seen in the neocortex.12,18

Not only is the cause of increased DAO in schizophrenia unknown, but neither are its implications straightforward. Firstly, because the increase is established only in the cerebellum, a region not usually associated with the core pathophysiology or phenomenology of the disorder. However, there is diverse evidence for cerebellar involvement in schizophrenia, particularly in its cognitive and motor domains.185-188 There are also data showing cerebellar modulation of forebrain function, including dopamine release.189 As such, an increase in DAO activity in schizophrenia may be pathophysiologically significant even if it does prove to be limited to the cerebellum., Secondly, it is not clear whether D-serine is functional in the cerebellum since levels in the adult cerebellum are very low (Table 2) - presumably because DAO activity is high. Moreover, adding exogenous DAO has no effect on cerebellar NMDAR activity,70 supporting the view that glycine and not D-serine serves as the NMDAR co-agonist in the cerebellum.68 In this light, it could be argued that increasing cerebellar DAO activity further (as in schizophrenia) will have little or no effect. On the other hand, D-serine may have a spatially limited role within the cerebellum. In particular, Bergmann glia contain D-serine68,69,190 and, as noted earlier, express abundant DAO.6,7,19,33,104 These cells envelop and regulate synaptic inputs to Purkinje cells,191-193 and thus D-serine released from Bergmann glia may modulate Purkinje cell NMDAR194 and GluRδ297 signalling, and thence cerebellar output. By the same token, elevated DAO in schizophrenia could indirectly contribute to cerebellar dysfunction. As a final suggestion, increased DAO in schizophrenia,

in any brain region, could be pathophysiological through an increased production of hydrogen peroxide, leading to apoptosis,126,195,196 a process proposed to be involved in schizophrenia, though with limited evidence.197,198

In total, the increased expression and activity of DAO in schizophrenia supports a role for the enzyme as a pathophysiological factor. Whether this is a major or minor role, and how it relates to any genetic involvement of DAO in the disorder, remains unclear. Constitutive and conditional DAO over-expressing mice, as well as further human brain studies, will help clarify these issues.

DAO as a target for the treatment of schizophrenia

As noted above, both D-serine and D-alanine show some effectiveness as add-on treatment in schizophrenia, in particular for the amelioration of negative and possibly cognitive symptoms. There are also comparable approaches and data regarding glycine augmentation. 154,157 Since enzymes represent viable drug targets, DAO is receiving attention as a potential alternative therapeutic means to enhance NMDAR function in schizophrenia. 10,62,199-204 The fact that DAO activity appears to be increased in schizophrenia provides another reason to propose that its inhibition might be beneficial. It is also intriguing that the original antipsychotic, chlorpromazine, was shown to be a DAO inhibitor *in vitro* over fifty years ago,2 confirmed recently205 and also found to apply to risperidone;206 whether these observations are relevant clinically are unknown, but they do provide a precedent for the potential therapeutic benefits of selective DAO inhibitors.

To date there have been no clinical trials of DAO inhibitors in schizophrenia, but several preclinical studies which, although findings remain preliminary, show that inactivation of DAO, either in ddY/DAO- mice or after pharmacological DAO inhibition in rats and mice, produces behavioural, electrophysiological and neurochemical effects suggestive of a pro-cognitive profile (Table 4). The Table includes the three DAO inhibitors for which functional data have been published thus far: AS057278,10 CBIO,201,203 and Compound 8.202 Several other small molecule DAO inhibitors have been patented but their behavioural effects have yet to be reported.62,204

The ddY/DAO- mice have improved spatial working memory in the Morris water maze9,207 and enhanced learning in fear-based tasks207 supporting a role for DAO in modulating cognitive processes. Complementing these data, DAO inhibition can correct NMDAR antagonist-induced deficits in pre-pulse inhibition10,201,203 and possibly other behaviours (Table 4). Moreover, SRR genetically modified mice, which have a ~90% depletion of D-serinehave impaired spatial memory,208 and reduced prepulse inhibition and sociability,209 indirectly supporting the possibility that restoring D-serine levels may be therapeutic against deficits of this kind in schizophrenia. A pertinent question is whether there are potential advantages to doing so using a DAO inhibitor rather than by D-serine administration. There are two reasons to propose this. Firstly, a DAO inhibitor will also raise levels of D-alanine and its other substrates, which might be beneficial. Secondly, a DAO inhibitor will avoid the potential for nephrotoxicity which might emerge from the renal oxidation of administered D-serine,210-214 since kidney DAO will be inhibited.

However, despite the data summarised in Table 4 and the rationale for DAO inhibitors, there remain substantial hurdles, of which the first two also apply to other strategies to elevate D-serine levels. (1) Part of the case for the use of DAO inhibitors is the evidence that D-serine is reduced in schizophrenia, yet levels of D-serine in the *brain* (as opposed to plasma and CSF) are not decreased18,41,51 and even the reductions in plasma and CSF have not been replicated in recent studies.215,216 (2) If DAO inhibition were to markedly increase brain D-serine, it would not be without risks, because of the potential for oxidative damage217

and neurotoxicity.85,218.219 It might also lead to NMDAR internalisation, limiting its therapeutic value.220 (3) The existing data show that DAO inhibitors can ameliorate some NMDAR antagonist-induced deficits. However, this is not seen across all behaviours, nor is there evidence for an antipsychotic-like profile (Table 4). Also, biochemical and behavioural effects are sometimes seen only when the inhibitor is given in conjunction with systemic D-serine or D-alanine.201,203 Although these limitations may reflect the poor brain penetration and modest potency of the drugs tested so far, it may transpire that DAO inhibition alone cannot achieve the desired range and robustness of efficacy, especially since the negative findings of Smith *et al202* occurred despite a substantial (80%) inhibition of brain as well as peripheral DAO. (4) Female ddY/DAO- mice exhibit increased anxiety,53 suggesting a possible anxiogenic side-effect of DAO inhibition.

These various issues highlight that the complex and poorly understood interplay between DAO, D-serine, and NMDAR regulation, noted repeatedly in this review, complicate our understanding of the mechanism(s) via which DAO inhibition might, or might not, prove to be therapeutic.157,204

Conclusions and future directions

DAO, as the enzyme which degrades the NMDAR co-agonist D-serine, has the potential to modulate NMDAR function and to contribute to NMDAR hypofunction in schizophrenia. Both genetic and biochemical data support an involvement of DAO in the disorder, however the processes involved are difficult to interpret. This is due to the many questions left unanswered concerning the neurobiology of DAO and its physiological roles. Notably there is still much that is unclear as to its localization and activity within the brain, and its spatial and functional relationships with its substrates. In addition, D-serine and thus DAO may have roles other than NMDAR modulation, whilst other DAO substrates, especially D-alanine, may also be relevant to any involvement of DAO in schizophrenia. Similarly, although recent preclinical data hint at potential therapeutic benefits of DAO inhibitors, extensive further study is required to establish their efficacy, tolerability, and mechanism.

Finally, we note that many of the issues covered here are relevant to other molecules that are being investigated in schizophrenia which are both possible susceptibility genes and drug targets, such as nicotinic α7 receptors,221 DISC-1,222 and catechol-O-methyl transferase.223 For example, to what extent does their candidacy as a risk gene influence therapeutic considerations, and vice versa? When contemplating the gene product as a target, how important is evidence that there is altered expression or function of the gene in the disease? Group II metabotropic glutamate receptors also come into the category of having diverse yet inconclusive evidence for an aetiopathogenic involvement in schizophrenia, and with a neurobiological and pharmacological rationale to propose them as drug targets.224-226 The randomised clinical trial showing that an agonist of these receptors is an effective antipsychotic in a provides an important precedent,227 and gives impetus to continue to address these questions with regard to DAO. Equally, the failure yet to replicate this result is testament to the hurdles faced by the field.228

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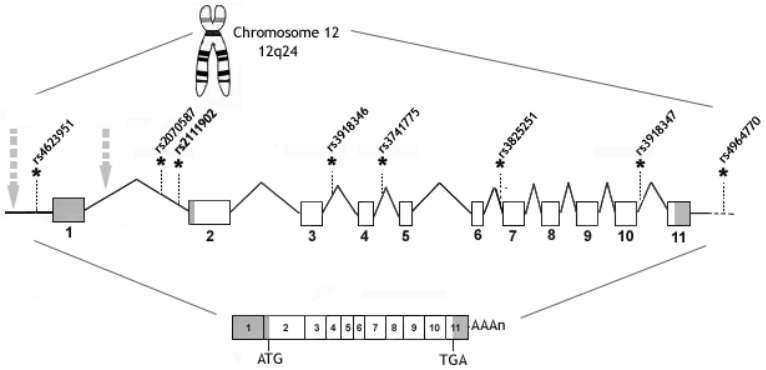

Figure 1. The D-amino acid oxidase (DAO) gene and transcript

The DAO gene on 12q24 comprises 11 known exons (numbered). Exon 1 plus 9 base pairs of exon 2 encode the 5′ untranslated region (shaded gray) of the DAO transcript, exons 2-11 encode the open-reading frame (start codon ATG, stop codon TGA), and exon 11 encodes the 3′ untranslated region (shaded gray). The transcriptional start site is in exon 1 and the 5′ flanking sequence contains GC box, cAMP-responsive element, and sterol-dependent repressor sequences (long grey dashed arrow). Intron 1 contains additional regulatory sequences, three TATA boxes and a transcription-enhancing CAAT box (short grey dashed arrow). The position of several single nucleotide polymorphisms (SNPs) associated with schizophrenia in the original study8 are shown: rs211902 (MDAAO4); rs3918346 (MDAAO5); rs3741775 (MDAAO6), and rs3918347 (MDAAO7). In addition, rs4623951 (MDAAO11) was significantly associated with schizophrenia in two meta-analyses,175,179 and rs3825251 and rs4964770 are part of a haplotype associated with schizophrenia in a recent Japanese study.168 rs4964770 is located in the region downstream of DAO. Finally, rs2070587 is a tag SNP studied for a potential effect on DAO expression and activity.11

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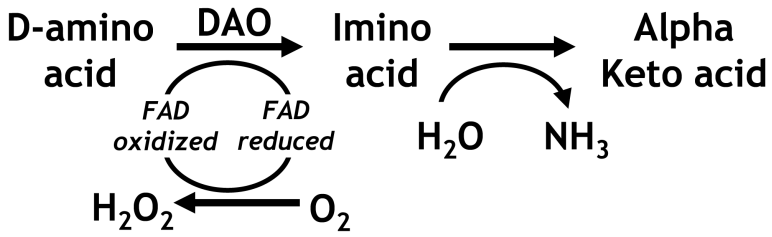

Figure 2. The enzymatic reaction catalyzed by DAO

As described in the text, only certain D-amino acids are substrates for DAO, of which the NMDAR co-agonist D-serine is the most abundant in brain, and the one which has been most studied.

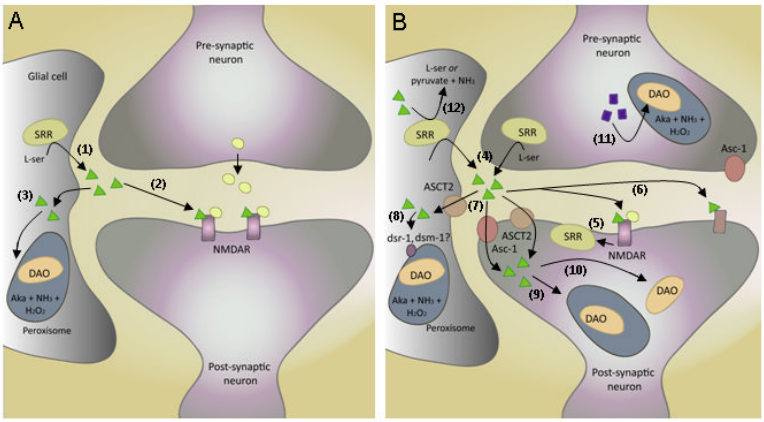

Figure 3. Synaptic regulation and DAO catabolism of D-serine

(A) Schematic showing a simplified, traditional view of synaptic D-serine and its breakdown by DAO. (1) Glial SRR synthesizes D-serine (green triangles) from L-serine. (2) D-serine is released at tripartite synapses to facilitate the action of synaptic glutamate (yellow circles) at NMDARs. (3) Synaptic D-serine is then taken up into glia and broken down within glia by peroxisomal DAO, forming the alpha keto acid (Aka), ammonia and hydrogen peroxide. (B) Schematic incorporating additional players and pathways that may be involved in DAO function and D-serine regulation., as discussed in this review. (4) SRR may also be localized in neurons, allowing neuronal formation and release of D-serine (5) SRR, translocates to the plasma membrane (of neurons or glial cells) following NMDAR activation, regulating D-serine synthesis. (6) Synaptic D-serine can have actions additional to potentiating NMDARs, including antagonism at NR1/NR3 and AMPA receptors and binding to the GluRδ2 receptor. (7) D-serine is removed from the synapse into glia by ASCT2 (and potentially other transporters), and into neurons predominantly via Asc-1 and also via ASCT2. (8) Intracellular D-serine may enter peroxisomes via a transporter, for which *dsr-1* and *dsm-1* are potential candidates. (9) D-serine taken up into neurons may be broken down by neuronal DAO. (10) DAO may also exist, and be functional, outside of peroxisomes. (11) In addition to D-serine, DAO also breaks down certain other D-amino acids, including D-alanine (dark blue squares). (12) D-serine may be catabolised via DAO-independent mechanisms including SRR mediated eliminase or reverse racemase functions. It is unclear how many of steps (4) – (12) exist *in vivo*, and their relative importance in different cellular and synaptic populations. However, the schematic emphasises the likely complexities involved in understanding the neurobiology of DAO and its relationships with other components of D-serine regulation.

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Table 1
Key papers in the biology of DAO with regard to its involvement in schizophrenia

Year	*Finding*[a]
1935	Identification of DAO.1
1956	Chlorpromazine inhibits DAO.2
1966	Discovery of DAO in the brain.3
1988	Cloning of human DAO. 4
1992	Identification of mutation in ddY/DAO- mice.5
1994	Enzyme histochemical localization of DAO in brain.6
1999	Immunocytochemical localization of DAO in brain.7
2002	Genetic association of DAO with schizophrenia.8
2005	ddY/DAO- mice have enhanced spatial learning and LTP.9
2008	DAO inhibition elevates brain D-serine and normalises PCP-induced deficits.10
2008	Increased DAO activity in schizophrenia.11,12

[a] LTP: long-term potentiation; PCP: phencyclidine.

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Table 2

Concentrations of D-amino acids in the adult mammalian brain

Units are nmol/g tissue, converted where necessary from alternative units used in the original publication. Values are mean, ± S.D., 34,35,39,40,42,44,49-52 S.E.M.,37,38,41,43,46-48,54 or unknown.36,45,53 Some values are approximate since they were estimated from graphical data. The right hand column shows the significant fold increases of the D-amino acid in the ddY/DAO$^-$ mouse compared to wild-type mice. Variability in results in the rodent brain likely reflects the assay methods used, and the age, gender, and strain; in the human brain, peri-mortem factors are also relevant.41,51

		Human	Rat	Mouse	Fold-change in ddY/DAO-
D-serine	Cerebral cortex	130±10 (pfc)36 108±6 (pfc gm)41 128±12 (pfc wm)41 66 ± 41 (fc)42 157±49 (fc, m)50 192±68 (fc, f)50 117±30 (pc)18	350±1037 359±7440 210±843 3202±4052	310±1038 353±8339 520±9840 387±7844 423±2147 332±1749 420±2550 285±2053 300±1054	NC39,47,49, 54 1.1338 1.1552
	Hippocampus		280±2037 20840 231±9.743 1470±5051	227±1944 341±2947 340±3049 228±2052 275±2054	NC47,49, 54 1.2952
	Cerebellum	ND41	20±137 ND43	33±2135 ND38 32±2039 28±1640 97±2944 12±247 7.5±0.248 15±149 19±152 3.754	5.239 641 1447 1149 3654.[a]
D-alanine	Cerebral cortex	9.5±2.9 (gm)34 12.3±10.2 (wm)34	ND43 ~448	ND38 3.5±0.839 12±247 12±250 ~5±0.554	3.939 5.147 5.250 1054.[b]
	Hippocampus		ND43	11±3.547 10±347 ~454	5.447 6.150 1054.[b]
	Cerebellum		ND43,48	ND38 11±247 ~1Miy09 2.2±1.139	8.239 7.347 8.950

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		Human	Rat	Mouse	Fold-change in ddY/DAO-
				9±250	~5054.[b]
D-proline	Cerebral cortex			0.31±0.1546	NC46
	Hippocampus			0.11±0.0646	NC46
	Cerebellum			0.29±0.1246	2.446
D-leucine	Cerebral cortex		ND43	0.2545 0.41±0.1146	1046
	Hippocampus		1.6 ± 0.143 0.69 45	0.2845; 0.39±0.0946	946
	Cerebellum		ND43	0.24±0.0446 0.0545 0.2±0.0150	2046

NC: no significant change. ND: not detectable or trace levels. pfc: pre-frontal cortex; fc: frontal cortex; pc: parietal cortex; gm: grey matter; tc: temporal cortex; wm: white matter; m: male; f: female.

[a]With a 2-fold increase in ddY/DAO$^{+/-}$ heterozygotes.

[b]With no change in ddY/DAO$^{+/-}$ heterozygotes.

Table 3
Post-mortem studies of DAO and related molecules in schizophrenia

Study	Cases/ controls	Findings in schizophrenia[a]
D-amino acid oxidase (DAO)		
Kapoor et al, 200621	4/5	Increased DAO mRNA and activity in CB.
Bendikov et al, 200718	15[b]/15	Unchanged DAO in HC and PFC. Hippocampal DAO IR increased in patients ill for >20y (n=5).
Verrall et al, 200719	16/13	Increased DAO mRNA in CB (p=0.004), with trend for DAO IR (p=0.062). DAO mRNA unchanged in PFC.
Burnet et al, 200811	35[b]/35	Increased DAO mRNA (p=0.01) and DAO activity (+37%, p=0.027) in CB.
Madeira et al, 200812	15[b]/15	Increased DAO activity in PC (+~100%; p=0.017).
Serine racemase (SRR)		
Kapoor et al, 200621	4/5	No change in SRR mRNA in PC.[c]
Steffek et al, 2006229	27/23	SRR IR increased in HC (p=0.028), unchanged in PFC, ACC, STG and PVC.
Bendikov et al, 200718	15[b]/15	SRR IR reduced in PFC (p=0.05) and HC (p=0.042).
Verrall et al, 200719	16/13	SRR mRNA unchanged in CB and PFC. SRR IR increased in PFC (p=0.027) but unchanged in CB.
D-serine transporter (Asc-1)		
Burnet et al, 2008230	18/20	Asc-1 IR reduced in PFC (p=0.011) and CB (p=0.028), with Asc1 mRNA unchanged.

[a] ACC: anterior cingulate cortex; CB: cerebellum; HC: hippocampus; IR: immunoreactivity; PC: parietal cortex; PFC: prefrontal cortex; PVC: primary visual cortex; STG: superior temporal gyrus.

[b] Mood disorder subjects also studied.

[c] Stated, but data not presented.

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Table 4
Functional effects of DAO inactivity or inhibition in rodents relevant to schizophrenia

Study	Findings[a]
DAO mutant (ddY/DAO-) mice	
Hashimoto et al 2005231	Normal LMA. Reduction of stereotypy and ataxia induced by MK-801.
Maekawa et al 20059	Increased LTP in CA1, and improved spatial learning in the water maze.
Almond et al 200617	Reduced LMA. PPI unaffected. Reduced responses to PCP, and to a glycine site antagonist.
Hashimoto et al 2008232	Marked reduction of methamphetamine-induced stereotypy.
Labrie et al 200953	Elevated anxiety in females in the open-field and elevated-plus maze.
Labrie et al 2009205	Improved memory for a new target location in the water maze. Improved extinction memory.
Selective DAO inhibitors	
Adage et al 200810	Normalised PCP-induced PPI deficit after acute or chronic treatment. Chronic treatment normalised PCP-induced LMA. No effects on baseline PPI or LMA.
Hashimoto et al 2009201	Potentiated D-serine efficacy in attenuating MK801-induced PPI deficit.
Horio et al 2009203	Potentiated D-alanine efficacy in attenuating MK-801-induced PPI deficit.
Smith et al 2009202	No acute effects on MK801-induced deficits in novel object recognition, or on amphetamine-induced LMA or mesolimbic dopamine release.

[a] LMA: locomotor activity. LTP: long-term potentiation. MK-801: dizocilpine. PCP: phencyclidine. PPI: prepulse inhibition of startle.