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Review Article

D-AMINO ACID OXIDASE: A REVIEW

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ABSTRACT

Over many years, D-serine and glycine were found to be the endogenous ligands for glycine-binding site for N-methyl-D-aspartate receptors. D-serine before being used up by the cells undergoes oxidative deamination by the enzyme D-amino acid oxidase (DAAO) and makes D-serine levels reduced in the brain, thereby affecting brain functions. In this review, we will discuss about the synthesis, location, therapeutic potential of DAAO function, role in cognition, and neuropathic pain.

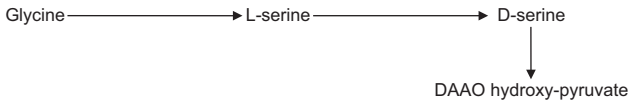
Keywords: D-serine, Glycine, N-methyl-D-aspartate receptors, D-amino acid oxidase, Cognition, Neuropathy.

INTRODUCTION

D-serine and glycine are the classes of proteogenic amino acids that are synthesized in our body for their utility and consumption [1]. Glycine need for the N-methyl-D-aspartate receptor (NMDAR) is released by glycine neurons by one way and also synthesized by amino acid L-serine by another [2]. D-serine has a high affinity for the glycine site on NMDARs, and that glial cells are equipped with an enzyme that can convert regular L-serine into the neurotransmitting amino acid D-serine by an enzyme that can go back and forth between D- and L-serine (D-serine racemase) [2-4]. Thus, D-serine can be derived from glycine or from L-serine, both of which can be transported into glial cells by their own transporters, and then glycine can be converted into L-serine by serine hydroxymethyltransferase, and finally L-serine can be converted into D-serine by the enzyme D-serine racemase [5-7]. D-serine's actions are not only terminated by synaptic reuptake via the inwardly acting glial serine transporter, but also by an enzyme D-amino acid oxidase (DAAO) that converts D-serine into hydroxy-pyruvate [8-11].

IN GLIAL CELLS

Serine hydroxyl methyl D-serine racemase transferase



DAAOs are the flavin-dependent oxidases that are involved in the oxygen-dependent oxidative deamination of D-amino acids that results in the formation of ketoacids, ammonia, and hydrogen peroxide [12-16]. It catalyzes stereospecifically the oxidative deamination of D-amino acids. DAAO is being reported in many organisms including animals, humans, and microorganisms. Until now, no DAAO has been obtained from plant source [17]. The significant levels of DAAO protein and enzyme are found in kidney, liver, and brain of mammals [18,19]. They destroy the D-amino acids originating from the bacterial source. The occurrence of DAAO in human brain was left unexplored until 1990 [20,21]. Until 1990 the presence of DAAO in brain was being left unexplored but after 1990 research was made for extending their study and they were found for their potential role. NMDARs are ionotropic glutamate receptors controlling synaptic plasticity and memory function. Binding of an agonist to the NMDAR exhibits fast magnesium-unbinding kinetics causing increasing ion channel opening and leading to depolarization, thereby facilitating short-term memory [29].

ROLES OF DAAO

DAAO provides microorganisms with exogenous D-amino acids as a source of carbon nitrogen and energy to a regulatory role in the human brain, where it controls the levels of the neuromodulator D-serine [30-34]. It supports the levels of D-amino acids that play an important role in the regulation of vital processes such as aging, neural signaling, and hormonal secretion. Changes in the levels of D-amino acids have a major impact on the organisms. Elevation of few amino acid levels in the brain promotes long-term potentiation [35-40].

REGULATION OF D-SERINE LEVELS

D-serine is considered to be the important player in the brain development and function. D-serine is localized in the areas of the brain that have high NMDAR expression and is considered to be an important endogenous co-agonist of NMDARs in many brain regions, including the forebrain and hippocampus [41-44]. D-serine regulates NMDAR-mediated synaptic transmission and plasticity. It has also been shown to be a key mediator in neuronal migration in the cerebellum. It has been proposed that neurons, which contain high serine racemase, may play an important role in synthesizing D-serine while glial cells appear to play a more important role in its release [45-47]. In light of its critical role in the normal development of neuronal circuits, it is hardly surprising that D-serine also participates in adult psychiatric health. D-serine regulation has been investigated extensively as a causative factor and in some cases as a potential therapeutic in schizophrenia, as well as a broad spectrum of other neurological disorders [48-50]. Curiously, it appears to be beneficial for both NMDAR hypofunction (schizophrenia) [51-54] and hyperfunction (depression) disease models. The explanation for this might lie in its differential effects on neuronal and glial subpopulations or in the particular brain regions impacted. It is tempting to speculate based on the important roles played by D-serine in the developing brain [55-57] that its ability to remediate disease may in part depend on enhancing functional connectivity by supporting NMDAR-dependent synaptic plasticity, dendritic arborization, and synaptic transmission in the mature brain.

POTENTIAL THERAPEUTIC FUNCTIONS OF DAAO INHIBITORS (DAAOIS)

Involvement of D-amino acid and D-amino acid oxidase has been implemented in much physiological process. At present, research is focused on the role of DAAO and D-amino acids in the involvement of psychiatric disorders such as schizophrenia [58-60]. In particular, D-serine and glycine play an important role in neuronal signaling by

functioning as co-agonists of the NMDAR. The NMDAR functions as a molecular coincidence detector and requires the presence of both agonist (glutamate) and co-agonist (D-serine, glycine, and/or D-alanine) for the ligand-gated ion channel to open. Importantly, D-serine has been reported to be the predominant NMDA co-agonist in the forebrain, and there is accumulating evidence that D-serine regulates cortical and hippocampal NMDAR activity [61-64].

Regulation of NMDAR co-agonists through the pharmacological manipulation of DAAO and glycine transporters has been investigated as putative novel therapeutics to treat schizophrenia. Currently, typical and second-generation atypical antipsychotics are the frontline of treatment for schizophrenia. These therapeutics are moderately effective in treating the positive symptoms of schizophrenia; however, they fall short of addressing the cognitive deficits and negative symptoms associated with this disease [65-68]. Therapeutics that modulate D-serine and other NMDAR co-agonists may better address the multiple symptomatic domains of schizophrenia. The NMDAR is thought to play a central role in the pathophysiology of schizophrenia and NMDAR dysfunction may underlie the behavioral and neurobiological deficits observed in this disease [2,3,22,23,25,27,53,59,65]. Accordingly, decreasing NMDAR function by administering NMDAR antagonists such as ketamine and phencyclidine produced psychotomimetic symptoms, negative symptoms, and cognitive deficits in animals and normal human subjects [69-71].

NMDAR antagonists also reinstated schizophrenia-like symptoms in remitted patients and exacerbated psychosis in patients free of antipsychotic medication [72-75]. Furthermore, increasing NMDAR function by co-administration of glycine, D-serine, or D-alanine with atypical antipsychotics improved positive, negative, and cognitive symptoms in schizophrenia patients when compared to antipsychotic treatment alone [76-83].

DAAOI INVOLVEMENT IN PSYCHOSIS AND COGNITION

DAAOIs could be useful clinically for reducing the dose of D-serine necessary to improve psychosis or cognitive deficits associated with schizophrenia. As a result, the co-administration of DAAOIs with D-serine could ameliorate some of the side effects associated with the administration of high doses of D-serine, such as nephrotoxicity [84-92].

DAAOI INVOLVEMENT IN NEUROPATHIC PAIN [4,11,35,36,42,46,]

Beyond its hypothesized involvement in schizophrenia, there is also evidence suggesting a role of D-serine and potentially DAAO in the response to painful stimuli. Intracerebral administered D-serine is effective in several pain models although the effects of D-serine on pain responsiveness might greatly differ depending on the brain region where it is administered for an example of potentiation of the pain response by D-serine. However, there is a significant amount of research showing that NMDAR antagonists might be also useful for treating pain.

CONCLUSION

The DAAOI needs to be explored further for their involvement in therapeutic potential for positive and negative symptoms for schizophrenia. The few published studies characterizing novel DAAOIs have yielded conflicting results. This may be for several reasons including the use of DAAOIs with different properties including potency and pharmacokinetics. Relatively, few of the published studies have related efficacy (or lack thereof) to the extent of peripheral/brain DAAOI or have demonstrated an increase of brain extracellular D-serine following a behaviorally effective dose of an inhibitor. Furthermore, the relative contributions of peripheral D-serine which can be actively transported into the brain are poorly understood. Interestingly, preclinical studies have provided data that combining a DAAOI with D-serine may be more effective in terms of antipsychotic-like activity; however, a clinically acceptable strategy for this combination remains to be determined.

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