

REVIEW ARTICLE

D Amino acid Oxidase-Role in Physiological process: A Review

Nithya S¹, Dr. T. S. Shanmugarajan^{2*}

¹Department of Pharmacology, School of Pharmaceutical Sciences, Vels Institute of Science Technology and Advanced Studies (VISTAS), Pallavaram, Chennai 117.

²Department of Pharmaceutics, School of Pharmaceutical Sciences, Vels Institute of Science Technology and Advanced Studies (VISTAS), Pallavaram, Chennai 117.

*Corresponding Author E-mail: smrajan@velsuniv.ac.in

ABSTRACT:

D-amino acid oxidase (DAAO) metabolizes exogenous D-Serine that acquires all through growing older, and might modulate the extent of availability of D-serine levels within the brain, appearing as a detoxifying agent. D Serine is the significant D Aminoacid in brain responsible for cognitive function. D-serine, a D-amino acid that is directed by DAAO, is an intense, endogenous co-agonist of the N-methyl-D-aspartic acid (NMDA) receptor. Since NMDA receptor dysfunction is believed to be associated with the positive (psychotic), negative effects in schizophrenia, there has been much enthusiasm for creating powerful and particular DAAO inhibitors for the treatment of these diseases. DAAO regulation in maintenance of D-aminoacid levels has been identified with a few physiological processes ranging from hormone secretion to synaptic transmission, Production of Neurotransmitters like Dopamine, Epinephrine and Norepinephrine and cognitive function. Various genetic examinations have distinguished a transformation on chromosome 13 in schizophrenia patients that encodes quality items (G30 and G72) which are identified with levels of DAAO in their brains. A few research reports have been portrayed the synthesis of novel, specific, small molecule inhibitors of DAAO. Many of these compounds, when administered, increased the D-serine levels in the blood and brain. Also, numerous examinations reveals the significance of DAAO expression and enzyme action has been said to be enhanced in submit mortem brain tissue samples from patients with schizophrenia compared with healthy controls. The present review gives the significance of DAAO and their involvement in different physiological process. Involvement of this protein in new drug development. This protein might be a good focus for different physiological studies for insight think in not so distant future. This article features the examination made on DAAOI

KEYWORDS: DAAO, Physiological process, regulation, Secretion, Amino acids.

1.INTRODUCTION:

DAAO flavoenzyme catalyses the oxidative deamination of D Amino acids into corresponding α ketoacids, Ammonia and Hydrogen Peroxide and it's far observed to have capacity position in healing improvement of drugs for various illnesses [1]. DAAO are the accountable enzymes for the normal manufacturing of D Amino acids inside the frame [2].

This enzyme alters and continues the ranges of production of D Amino acids in brain that have capacity position in diverse neurological phenomena [3]. This

enzyme is of high biological activity because of its position in production of α Ketoacids, qualitative and quantitative analysis of various pills, it's far worried inside the first step of organic enzyme response in conversion of cephalosporin's into their product 7 Aminocephaloranic acid [4]. And it's also one of the key things within the manufacturing of semi artificial penicillin derivatives [5]. Those enzymes have purposeful role in the protection of D Serine ranges in mind. They have got therapeutic role in regulation of Nervous System, hormone secretion at the side of amino acids and also chargeable for the development of diverse sicknesses below modified DAAO interest [6].

2. AMINO ACID OXIDASE-ROLE IN PHYSIOLOGICAL PROCESS:

2(a). Production of α Ketoacids:

D Amino acid Oxidase to provide α Ketoacids from D, L or D Amino acids. The ketoanalogues of vital amino acids, specially the branched chain amino acids isoleucine and valine are crucial healing marketers for remedy of continual uraemia and are therefore valuable excellent chemical merchandise. Starting from the Racemic combinations of Aminoacids, Optically energetic L Aminoacids also are produced concurrently [7, 8].

2 (b). Regulation of D-serine levels:

Almost 1/2 of the research articles on DAAO posted within the final 10 years had been devoted to the role of D-serine as a neuromodulator of NMDA (N-methyl-D-aspartate)-receptors, which are at play in many pathological strategies. The allele combination of G72 and DAAO genes increases the probability of developing schizophrenia. The rise in expression stages of G72 increases DAAO activity in human brain, ensuing inside the decreasing tiers of D-serine, which is thought to bind to the glycine-binding web site of NMDA-receptors. Therefore, the reduced ranges of D-serine decrease the practical pastime of NMDA-receptors, which is meant to be one of the motives for the development of schizophrenia main to cognition deficit. Presently, that is a working speculation supported with the aid of many researchers [9,10]. It have to be referred to that NMDA-receptors are equally essential for other physiological procedures together with learning and memory formation, improvement of epilepsy, and many others. On the equal time, different researchers could not discover a correlation among daao and pGL72 protein gene polymorphism and predisposition to schizophrenia.

2(c).Synthesis of Compounds for drug improvement:

4-Methylthio-2-oxobutyric acid (MTOBA) is an essential compound in pharmaceuticals. Being a metabolic precursor of methional, a robust inducer of apoptosis,

MTOBA is used as an anticancer drug [6]. In methionine dependent cancer cells, the MTOBA content material is decrease than in normal cells. MTOBA can be without problems produced via oxidative deamination of D-methionine. Very currently, a more price-effective approach for MTOBA production changed into proposed based on the remedy of a racemic combination of D, L-methionine. D-Methionine conversion within the reaction changed into~98%. Every other crucial substance produced with the assist of DAAO is L-6-hydroxynorleucine. This chiral compound is used for the synthesis of Omapatrilat and an entire collection of metalloproteinase inhibitors.

L-Amino acids containing the naphthalene organization are of superb interest for brand spanking new drug development. For example, L-2-naphthylalanine is part of the peptide drug Nafarelin [11]. To supply this amino acid from a racemate of 2-naphthylalanine, a method based totally on a three enzyme machine, e.g. RgDAAO, catalase, and L-aspartate aminotransferase, changed into advanced. To increase the RgDAAO particular activity towards D-2-naphthylalanine, both web site-directed mutagenesis and random mutagenesis ("directed evolution") techniques have been used, but inside the latter case the nice multi-point mutants had been much less active than unmarried-point mutant RgDAAO Met 213 Gly generated the usage of the former approach.

2(d).Diagnostics and prophylaxis of neurological diseases and most cancers:

Neurological illnesses along with schizophrenia and Alzheimer's and Parkinson's sicknesses bring about enormous changes within the levels of some D-amino acids (D-Ser, D-Ala, D-Asp) in serum, white and gray matters, and spinal fluid. The willpower of D-amino acids beneath normal and pathological situations created a foundation for the improvement of diagnostic standards and tracking of those diseases. Studies on DAAO knock-out mice proven the absence of compensatory results for the null DAAO activity [12]. This observation opens new horizons for the treatment of schizophrenia with enzyme inhibitors whose utility will normalize ranges of D-Ser to stimulate NMDA-receptor (for comparison, a commonplace method is direct injections of D-Ser further to anti-psychiatric prophylaxis). To recognize the new approach, the authors advanced a high throughput screening protocol for mobile-primarily based DAAO assay: the number one screen resulted in the choice of 1966 hits for similarly studies.

The others, based on a similar technique, got here up with 5-methylpyrazol-3-carbonic acid as a drug candidate. Its injection into rats results in large increase of D Ser in cerebral cortex and midbrain; moreover, its

continuous injection for 4 weeks gave no aspect effects.

DAAO is its relevance to cancer diagnostics and probably remedy. It's been tested that parenteral injection of D-amino acid-containing solutions into cancer sufferers consequences in stepped forward nutritional popularity and inhibits most cancers mobile growth. Later, research performed on rats showed no DAAO activity in most cancers cells [13].

2(e).Evidences with Schizophrenia:

Gene affiliation studies have provided some other link among DAAO and schizophrenia. DNA from 213 schizophrenic sufferers and 241 normal individuals from Canada have been genotyped and two overlapping gene products, G72 and G30, were identified in a section from chromosome 13q34 that has been genetically connected to schizophrenia [14]. The G72 gene product was discovered to increase activity of DAAO and became in the end termed D amino acid oxidase activator (DAOA). This locating shows that increased D-serine metabolism as a result of expanded DAAO pastime may additionally produce a discount in NMDA receptor pastime. This speculation was tested, inside the outcomes the DAAO expression have been upregulated in tissue from schizophrenic patients, but, the will increase in expression and activity had been no longer related to diagnosed SNPs or the gene products G72 and G30. Similarly to human genetic research, DAAO mutations were studied inside the mouse. DdY/DAO-mice is an evidently happening mouse pressure that lacks DAAO activity and has extended tiers of D-serine within the blood and cerebellum. Those mice also have practical modifications in synaptic transmission along with improved NMDA-mediated excitatory submit synaptic currents and superior hippocampal long time potentiation, a molecular correlate of learning and memory. DdY/DAO-mice also show progressed cognitive overall performance within the Morris water maze task³⁶ and accelerated occupancy of the NMDA receptor compared to wild kind animals³⁸. Taken together, these locating advices that DAAO inhibitors might be useful as novel therapeutics to deal with psychiatric and cognitive problems.

2(f).Production of D Neurotransmitters/as key factor in producing Neurotransmitter:

Dopamine is a prophylaxis and remedy medication for Parkinson's disease. Very recently, it's been shown that D-3, 4-dihydroxyphenylalanine (D-DOPA) is a better substrate for human DAAO than D-Ser [15]. The catalytic performance (kcat/Km) for D-DOPA is 14-fold higher than that for D-Ser. thus, human DAAO affords an altered metabolic route for D-DOPA conversion into dopamine. Increasing levels of Dopamine.

2(g). Biocatalyst-Cephalosporin C conversion:

Development of antibiotic resistance is assets of microorganisms. Resistance closer to penicillin-based antibiotics made cephalosporin-primarily based antibiotics of different generations the most famous ones utilized in exercise: extra than 1/2 of antibiotics used worldwide are cephalosporins [16]. 7-Aminocephalosporanic acid (7-ACA) is a starting compound for the production of diverse semi-synthetic cephalosporin of different generations, and until recently it has been produced with the aid of chemical hydrolysis of the herbal antibiotic cephalosporin C. The disadvantage of this method is a couple of steps, low yield, and use of numerous natural solvents. As a substitute, 7-ACA may be produced the use of a biocatalytic method primarily based on DAAO and glutaryl hydrolase [17]. Currently, there are numerous diverse techniques for biocatalytic oxidation of cephalosporin C. evaluation proves being especially high priced; the enzyme does now not showcase the operational stability required for commercial production. The answer of this trouble might be based totally on the development of enzyme mutant bureaucracy with improved catalytic interest and thermal and operational stability.

3. CONCLUSION:

Evaluation of the literature on D-amino acid oxidase indicates that the interest on this enzyme is constantly developing: the quantity of courses on its physiological roles and realistic programs rises via 15-20% a year considerable fulfillment in essential research on DAAO has been carried out within the final five years and considering those the researchers are toward finding the alteration inside the gene expression for the changed DAAO levels. This may be one of the healing method for new drug development for remedy of various illnesses.

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