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MONOAMINE OXIDASE AND ITS INHIBITORS CORRELATING TO NEURODEGENERATIVE DISORDERS (REVIEW)

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ABSTRACT

Monoamine oxidase (MAO) (*EC 1.4.3.4*), an insoluble mitochondrial enzyme is the focus of a substantial literature. The enzyme catalyzes the oxidation of a large number of xenobiotic and biogenic amine substrates, including small-molecule monoamines as well as of proteins with modified amino acids. Monoamine oxidase has an important role in peripheral tissues and central nervous system where it performs the metabolism of vasoactive and neuroactive amines. Preferentially this enzyme targets phenylethylamine, benzylamine and a large number of neurotransmitters such as NE, 5-HT, DA, EP and PEA. The basic function of this enzyme is the modulation of brain neurotransmitters that are associated with numerous disorders such as neurodegenerative diseases including schizophrenia, anxiety, depression, migraine and sexual maturation. Direct study of this enzyme is the biggest constraint due to the accessibility problem. For various practical purposes only lymphocytes despite of their harvesting problem have been used in routine studies as an enzyme source. After the discovery of enzyme structure, substrate and activity the major concern of scientists was to work for MAO inhibitors development for the treatment of depressive illness. This review focuses on MAO structure, types, activity and role in various diseases.

KEYWORDS: Monoamine Oxidase, Parkinson disease, Alzheimer disease, Neuro-degenerative diseases, Schizophrenia, cerebral ischaemia.

INTRODUCTION

Monoamine oxidase (MAO) (*EC 1.4.3.4*) is a flavin-containing enzyme and belongs to MAO family, which share overall structural similarity (Fig 1). Enzymes of this family have identical FAD binding domains, but substrate binding sites varied from each other (Fig.1).[1,2] There are two different types of MAO in humans MAO-A and MAO-B. The main role of MAO is the regulation of the activity of neurotransmitters such as DA, NE, PEA, 5-HT and EP. The enzyme also performs a wide range of pathophysiological functions (table 1) such as regulation of cardiac activities and blood pressure[3] as well as involved in the onset of various neurological and psychiatric diseases including depression, anxiety, mood, migraine, schizophrenia, neurodegenerative diseases and sexual maturation.[4]

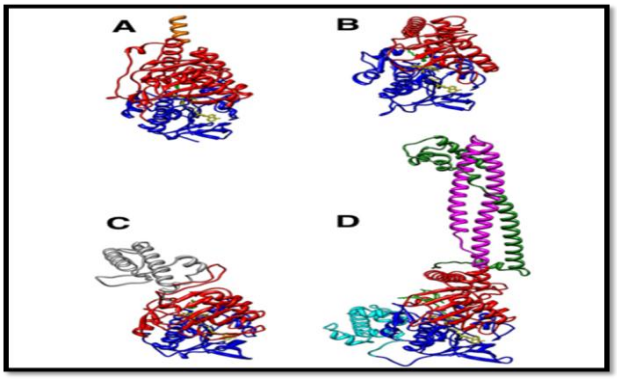

Fig. 1: Representations of MAO-B in ribbon form of (A) Human, (B) Maize PAO, (C) Bacterial LAAO, and human LSD1 (D) designed using the Chimera program (115) and the following Protein Data Bank (PDB) files: 2UXN, 1H83, 1OJA, and 2JB2,. The FAD-binding sites are in blue color while substrate-binding sites are red.

Monoamine oxidase catalyzes the reaction between R-CH_2-NH_2 and dioxygen for the removal of amines that results in R-CHO, H_2O and NH_3 formation (Fig. 2).[4] When flavoprotein oxidizes, the enzyme catalyzes the substrate oxidation by two half- reactions such as

oxidative half-reaction and reductive half-reaction. In reductive half reaction, the flavin cofactor accepts a hydride ion from substrate and is reduced than the molecular oxygen again oxidized the reduced cofactor in the oxidative step. As the flavin cofactor can accept one or two electrons there are several mechanisms that have been proposed for the electron transfer from substrate to cofactor.

In another possible mechanism, hydrogen atom is directly transferred from the α-carbon of substrate to cofactor.[5] In the nucleophilic mechanism, a covalent intermediate is formed by the attack of substrate amino group to the C4α of the cofactor.[6] The enzyme interacts with two substrates that are oxygen and amine. The oxidation of amine substrate is irreversible,[7] while the oxygen only interacts with the reduced enzyme due to which the analysis of steady-state kinetics is easy.

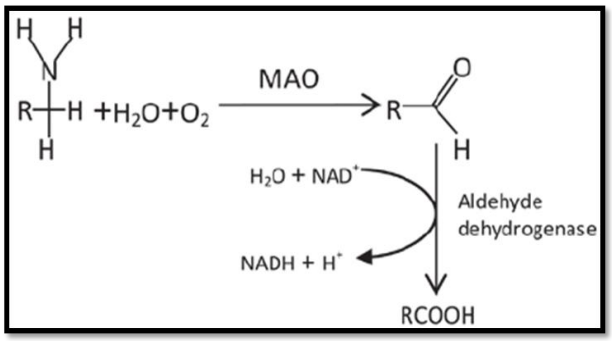

Fig. 2: MAO catalyzed reaction producing Ammonia, Aldehyde, and H_2O_2

Subtypes of enzyme: monoamine oxidase A and B

MAO is found in two forms in human which are MAO A and MAO B,[4] these two forms are different in three – dimensional structures, amino acid sequences, substrate specificity, inhibitor sensitivities and division in tissue and organs.[4] The oxidation of primary, secondary and tertiary amines, which also includes numerous neurotransmitters to corresponding imines is carried out by these isoenzymes which are proteins found in outer mitochondrial membranes. Then the hydrolysis of oxidized products occurs to ketone or aldehyde without enzyme.[8]

Structure of isozymes

About 70% amino acids are same in both isoenzymes and both of these enzymes have a covalently bound cofactor FAD, which is attached to the amino acid cysteine through 8α-methylene of ring.[9] FAD-binding domain is the part of both isoenzymes, which is also present in numerous other flavoprotein oxidases, the domain that binds to membrane as well as to the substrate.[10,11] MAO A and MAO B attach to the mitochondrial outer membrane via the C-terminal α-helical region.[12,10,11] The iso-alloxazine ring of FAD is present in a wrinkled and stressed state.[10] MAO and MAO B have substrate binding sites that are hydrophobic in nature and mainly enclosed by aliphatic and aromatic amino acids.[10,11] The conserved lysine interacts with a molecule of water, which is a significant exception.[13] MAO and MAO B prefer to bind with substrate that have neutral amino group.[14]

Substrate specificity

The metabolism of dopamine and serotonin (5-hydroxytryptamine) is carried out by MAO A. MAO B have a preference to oxidize phenylalanine, dopamine and benzylamine, while serotonin and norepinephrine are metabolized at slow rate by this isoenzyme.[15,16,17,18] 1-methyl-4-phenylpyridinium, which causes parkinson's disease is formed by MAO B.[19] To cure Parkinson disease, stress, Alzheimer and various other neurodegenerative disorders inhibitors of monoamine oxidases have been used at clinical level.[20,21]

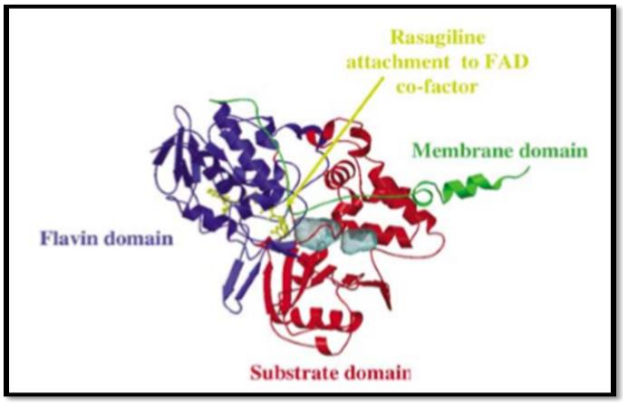

Fig. 3: Crystal structure of human MAO B.

Table 1: Specific substrates of MAO A and MAO B.

Sr. No.	Isoenzyme	Specific substrate
1.	MAO A	Serotonin (5-hydroxytryptamine) Dopamine
2.	MAO B	Phenylalanine, Dopamine, Benzylamine Serotonin, Norepinephrine 1methyl-4-phenylpyridinium

Source of enzyme

Although, MAO is present abundantly all over the body but the ease of use is one significant problem in its undeviating study in human beings.[22] Even though, some rare approaches have been used to measure the activity of enzyme in samples from numerous sources such as jejuna mucosa,[23] skin fibroblasts[24] buccal scrapings[25] and muscle,[26] for more realistic studies, the most easily available enzyme source for regular studies is from various formed elements of blood. Lymphocytes have been used as enzyme source though their harvesting is difficult,[27] however, it is comparatively simple to acquire pure preparation of blood platelet.[28]

Assay of MAO activity

The shortage of clear reproducibility is one of the persistent problems being faced in platelet literary

studies.[22] Variety of anticoagulants has been used for collection of blood samples, as well as strategies used for the platelet harvesting for enzyme assay. In this approach the anticoagulants being used are EDTA and citrate.[22] EDTA is advantageous as it reduces the amount of ionised calcium adequately to check aggregation of platelet, whereas citrate may be the substance of choice for 'platelet function test'.[28] It has been found that specific MAO activity can vary if changes are made in procedure employed for platelet harvest by White *et al.* (1976).[29] Things like contamination of leukocyte, variations in subpopulations of improved platelets and contamination of platelet plug with proteins of plasma may hold significant importance.[22]

Majority of the groups do the preparation of plasma, concentrated in platelet by centrifugation of entire blood at slow rate; then a platelet button is obtained by spurning the supernatant at a faster rate, after that washed and stored platelet button at frozen temperature.[22] There is excellent proof, on the other hand, that the populations of platelet involve heterogeneity and massive, thick platelets settle more easily and exhibits more activity per unit of protein than the light and smaller ones.[22]

Major contribution of MAO in neurodegeneration and ageing

Effect of ageing on MAO activity in brain

The alterations in human brain MAO activity was studied by Robinson *et al.* (1975).[30] To assay the enzyme activity, benzylamine (Bz) was used as a substrate. Positive correlation between MAO-B of hindbrain and age was observed, especially the increased enzyme activity was observed during the middle age.[31] For this purpose 13 brain samples were assayed, 6 from persons younger than 45 years of age and seven from over 45 years of age. In the results high activity was observed in older persons then younger ones. Oreland and Fowler (1979)[32] checked enzyme activity from 12 persons with ages between 2 and 95 years, they concluded that the activity of MAO-B is age dependent.

Role of MAO in the onset of neurodegenerative diseases

MOA is involved in various neurodegenerative diseases, through oxidative stress.[33] These diseases include Parkinson's disease (PD), Alzheimer's disease , dementia, depression as well as various other mechanisms including the triggering of apoptosis,[34,35] neuroinflammation,[36] glial activation[37] by MAO and failure of aggregated-protein clearance.[38,39,40]

Alzheimer's disease

Alzheimer disease is a chronic type of neurological diseases that slowly starts and worsens over time. According to studies, the activated MAO in brain is a biomarker for AD.[41,42,43] The studies demonstrated that in case of AD following changes occur.

MAO activity as a biomarker for dementia

Previously, increased activity of MAO has been found in the AD patients's platelets. MAO-B activity is a biological marker of AD that has been proved by studies on the relationship among platelet clinical features, cerebrospinal fluid (CSF) and MAO-B activity.[44,45]

Changes in the brain's MAO activity of AD patients

Alterations of MAO level in brain lead to the hyperoxidation by this enzyme which causes the neuronal cell death in AD patients. The oxidative degradation catalyzed by MAO produces "free radicals" that promotes the neurodegenerative process (Fig. 4).[46,47]

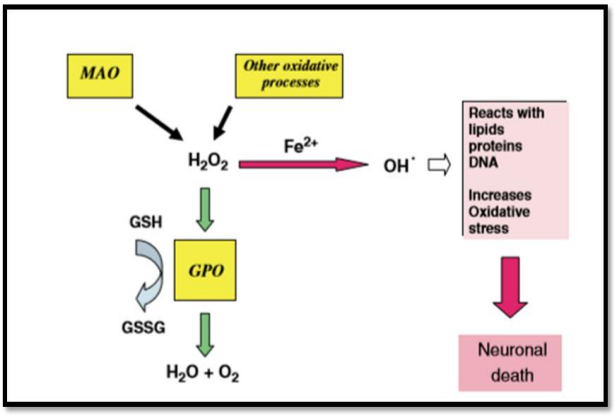

Fig. 4: Neurodegeneration by free radicals.

Role of MAO activity in cognitive dysfunctionality

Cognitive dysfunction is a disorder in which a person looses intellectual abilities like remembering, thinking and reasoning that results in trouble with concentration, verbal recall and basic arithmetic.[49]According to studies, MAO disturbs the balance of certain chemical neurotransmitters, which causes cognitive impairment. Oxidative stress imbalances the NE and the cholinergic system that are responsible for cognitive impairement in AD.[49,50,51,52]

Importance of MAO activity in amyloid plaques formation

Amyloid plaques are pathological marker of AD, formed in the result of production and accumulation of AB.[53] AB is involved in various neuronal degeneration mechanisms including: triggering of free radicals formation, relationship among Aβ production and oxidative stress, interaction between Aβ and inflammatory process,[54,55] association of apoptosis and Genetic factors with the Aβ generation.

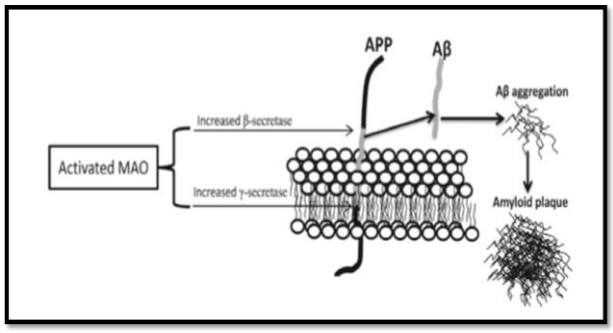

Fig. 5: Generation of Aβ through APP processing in the presence of activated MAO.

Oxidative damage in AD patients is responsible for the formation of amyloid plaques. MAO promotes oxidative stress by producing free radicals of oxygen and other reactive species that leads to neurodegeneration in AD.[56,57,58] Molecular studies have shown that AB generation is involved in APP processing by MAO (APP proteolysis generate AB that form plaques in Alzheimer patients) (Fig. 5).[59,60,61,62]

Schizophrenia

Murphy and wyatt (1972)[63] identified low MAO activity in schizophrenic patients by experimental studies, it was concluded that test patients of chronic schizophrenia have lower MAO activity than control. Schildkraut *et al.* (1976)[64] and meltzar *et al.* (1976)[26] associate verbal auditory hallucinations with low MAO activity. The main reason of low activity was the mutation of MAO molecule itself that leads to schizophrenia.

Alcoholism

Sullivan (1978),[65] use tryptamine as a substrate to check the role of MAO in alcoholism concluded that MAO activity was lowered in alcoholism patients than control. However, Brown (1977),[66] and Takashashi (1976),[67] studied that the activity again becomes normal as the acute stage vanished. Moreover, it was concluded that alcohol itself have no effect on the MAO activity in haumans.

Migrane

It was proposed by Hanington (1978)[68] that migrane may be result of mutation in MAO molecule, and the attacks might initiate by consuming tyramine containing foods. Patients, who consume MAO inhibitors, suffer a hypertensive response after eating amine-containing foods.[69] Several studies reported that migrannous patients have lower level of MAO activity than normal due to which the rate of oxidative deamination reduced and release amine substrates in the circulation.

MAO inhibitors as neuroprotactives

The MAO inhibitors have been continuous source of surprises and their potential as therapeutics agents is one of a kind, particularly in the treatment of neuro-degenerative diseases especially in Alzheimer and Parkinson disease including treatment of numerous other disorders like stroke and ageing as well. Reversible and non-reversible MAOA, MAOB or both have this potential.

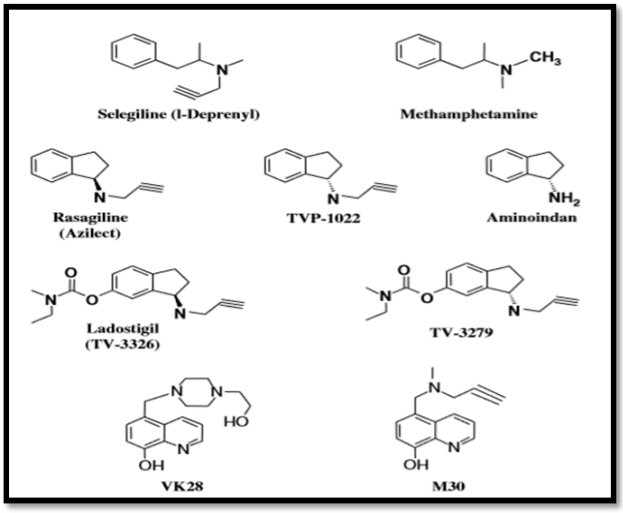

Fig. 6: Structures of MAO inhibitors.

The therapeutic use of MAO inhibitors are as follows:

Affective diseases

For many years depression has been treated with MAO inhibitors.[70] The antidepressant properties of the MAO are the result of the selective MAO-A inhibition in the central nervous system leading to the uptake in the level of the noradrenaline, 5-HT and dopamine in the brain. "Tranylcypromine" and "phenelzine" are irreversible inhibitors and are still used as therapeutic agents in association with reversible inhibitors like "moclobemide", "befloxatone" and "toloxatone".

The depression of Elderly peoples has been treated with reversible MAOA.[71] Monoamine oxidase A and non-selective MAO inhibitors proves more proficient to treat depressions including ("hypersomnia", "hysterical traits", "tiredness", "impression of rejection and bulimia") and phobic anxiety.[72] Monoamine oxidase B inhibitors are particularly free of the antidepressant activity and they don't show their activity unless treated with high concentration of the MAOA.

Parkinson's disease (PD)

The utilization of MAO inhibitors in the form of dopamine-saving operators or as subordinates to l-DOPA was for Parkinson's malady treatment, but due to the "cheese response" (Fig 7) this method with non-particular inhibitors is avoided to put in use.

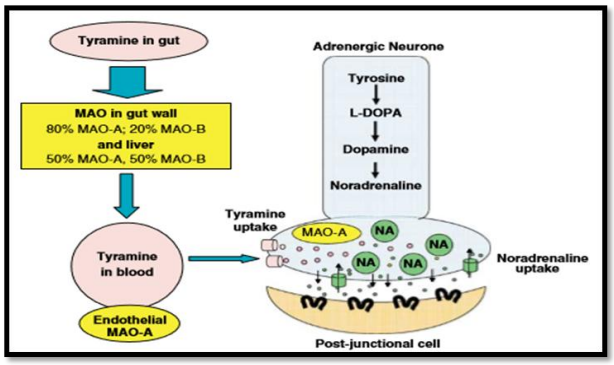

Fig. 7: Cheese reaction.

Table 2: Some MAO inhibitors used for the treatment of depression and PD.

Sr. No.	Antidepressant	Mode of Action
1.	Isocarboxazid	Irreversible
2.	Nilamide	Irreversible
3.	Iproniazid	Irreversible
4.	Phenelzine	Irreversible
5.	Tranylcypromine	Irreversible
6.	Clorgyline	Irreversible
7.	Brofaromine	Reversible
8.	Moclobemide	Reversible
Under Development		
9.	Befloxatone	Reversible
10.	Ladostigil	Irreversible
11.	M30	Irreversible
Anti-Parkinsons'		
12.	Lazabemide	Reversible
13.	Rasagiline	Irreversible
14.	Selegine	Irreversible
Under development		
15.	Ladostigil	Irreversible
16.	M30	Irreversible

Due to the gliosis during the PD the MAO-B level increases in the brain. And since MAOB is having more activity in the human basal ganglia than the MAOA hence MAOB was studied more along with its MAOB inhibitor "l-deprenyl" that is the "adjuvant" to "l-DOPA83" for the Parkinson's disease. "l-Deprenyl" is an efficient adjuvant to l-DOPA as well as a monotherapeutic agent.[73]

No significant effect was seen on the disease with the use of 1-Deprenyl except the first year of administration when it somehow slowed the disease. Current research has shown that two MAO inhibitors namely "lazabemide" and "rasagiline" can hinder the development and disabilities related to the Parkinson's disease.[74] It should be noticed that the data on this is still insufficient and even the MAO-B inhibitors have the ability to reduce the level of the disease, this factor is yet to highlighted and researched upon to take the clinical trials in notice.[75] In contrast, a reversible monoamine oxidase A inhibitor "moclobemide" had seen to posses activity against Parkinson disease.[76] It should be noted that the clinical trials might have differences due to many factors including the age of the animals for the trials since younger ones might have shown different results towards the MAO inhibitors. The other factor might be the concentrations of the drugs used. Now it has been revealed that at higher concentrations the "l-deprenyl" lost its therapeutic effects, which could be pro-apoptotic.[77,78]

Alzheimer

Medical testing procedures, by using selegiline (l-deprenyl) as test inhibitor to control Alzheimer's disease have not shown any persuasive results.[79] Since we know that MAOB activity is increased during the disease in the brain which may lead to the further disorder of stress. Hence with trails the view has been put forward that the combine use of MAOB inhibitor and standard cholinesterase inhibitors (physostigmine), may be helpful against this disease.[80] Ladostigil combines the rasagiline pharmacophore with inhibitory moiety of carbamate cholinesterase as well as with its pharmacological activities includes butyrylcholinesterase, brain-selective MAOA/B inhibition and neuroprotection.[81,82] This drug seems to be effective as an anti-depressant and anxiolytic activity and is currently in trails for the Alzheimer.[83]

Table 3: Evidence for the neuroprotective effect of MAO inhibitors in Alzheimer's disease.

Sr. No.	Inhibitor	Neuro-protective Mechanism	Pre-clinical or Clinical stage
1.	**Rasagiline**	It has unique multi-target iron chelators with the AChE. It regulates the expression processing of the APP and AB. It regulates the cell cycle also and activates the pathway of signaling.	It is in the phase II clinical study both in the in-vivo and in-vitro.
2.	**Ladostigil**	It is a very rare and unique MAO and AChE inhibitor. And it regulates the processing and the translation of APP.	It is also a phase IIb clinical study both in-vivo and in-vitro.
3.	**Selegiline**	It is an anti-oxidant. It is an inhibitor of MAO-B and it regulates the proteolytic cleavage of APP, which actually include mitogen- activated protein kinase, which further activates the PKC and inhibit the production of the AB.	It is still under clinical and randomized trials

Other Neuro-degenerative disorders

The MAO inhibitors have also been studied against many other neuro-degenerative diseases which include Huntington's disease and amyotrophic lateral sclerosis (ALS), since these two contribute to somewhat same features and disorders as of Alzheimer and Parkinson such as "excitotoxicity", "iron accumulation", "inflammatory processes" and "oxidative stress" etc.

Cerebral ischaemia

l-Deprenyl alleviate chances of peripheral tissue harm which are results of cardiac failure.[84] The decline in H_2O_2 level that is produced by MAO during ischaemia-reperfusion, collectively with an amplified ratio of "B-cell leukaemia/lymphoma 2" (BCL2) to "BCL2" associated "protein X (BAX)",[85] initiation and transportation of protein kinases that has anti-apoptotic property, PKCε119 and PKCα[86,87] is the protective effect of this inhibitor. Phase II trial results have confirmed that the efficiency of l-deprenyl can improve after cerebral infarction.[88]

Ageing

MAO activity is also related to the process of ageing. To check the specific activity of MAO-A, fibroblasts of human skin were cultivated from 1 to 60 years males, five- to tenfold increase with age, while the increase in activity of MAO-B was actually less than threefold.[89] Brain MAOB activity has been reported to enhance with the age due to glial cell increased level[90] while same is not the case with the MAOA about which no change has been reported.

Neuroprotection and neurorescue

According to current ongoing research on the 1-deprenyl[91] it has been noticed that it increases the life span of Parkinson's disease patients. MAO-B inhibitors discovery has proposed a theory that the MAO-catalysed reactions' products are involved in neurotoxicity while the Inhibition of monoamine oxidase B activity would reduce the amount of H_2O_2 produced by oxidation of amine. MAO-catalysed oxidation of dopamine yields aldehyde and alcohol which enhances neurotoxicity cause midbrain lesions that are been treated with MAO inhibitors.[92] But, still all MAOB inhibitors are not effective in the neuro-protection[93,94] so MAO inhibition could not be considered as the protective method of primary importance. The results obtained from the study of structure activity with metabolites and derivatives of rasagiline and l-deprenyl have been interpreted in regard to their neurorescue and neuroprotective activities depending on their propargyl moiety.[95] But there are also propargylamine derivatives which are effective against these problems and more research on it has been still going on.

CONCLUSION

According to studies it is concluded that MAO plays very important role in catalyzation of oxidative reactions throughout body especially in brain. Due to physiological importance, its structure and mechanism has been the focus of many literary works for many years. MAO's main function is to catalyze the deamination of many amine containing substrates and the members of MAO family share many structural characters. Research shows that activity of MAOB enhances in both animals and humans with ageing. In neurodenegerative diseases especially in Alzheimer' disease the fluctuation of MAO activity has significant role in various stages of disease, however in Parkinson' disease still there is no sufficient data with confident information. Modern research in molecular biology and pharmaceutical industries has enlightened the neuroprotective role of MAO inhibitors. The drugs including "ladostigil", "rasagiline" and "selegiline", used to inactivate MAO, and involve in treatment of various neurodegenerative disorders. As many neurotransmitters are MAO substrates therefore many side effects of MAO inhibitors have been reported especially when taken along with various beverages and foods, however exact effect is still unclear.

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