Monoamine oxidase inhibitors: Promising therapeutic agents for Alzheimer's disease (Review)

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Abstract. Activated monoamine oxidase (MAO) has a critical role in the pathogenesis of Alzheimer's disease (AD), including the formation of amyloid plaques from amyloid β peptide (Aβ) production and accumulation, formation of neurofibrillary tangles, and cognitive impairment via the destruction of cholinergic neurons and disorder of the cholinergic system. Several studies have indicated that MAO inhibitors improve cognitive deficits and reverse Aβ pathology by modulating proteolytic cleavage of amyloid precursor protein and decreasing Aβ protein fragments. Thus, MAO inhibitors may be considered as promising therapeutic agents for AD.

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Abbreviations: Aβ, amyloid β peptide; AD, Alzheimer's disease; APP, amyloid precursor protein; BACE, β-site APP cleavage enzyme; ChE, cholinesterase; CNS, central nervous system; CSF, cerebrospinal fluid; DA, dopamine; EP, epinephrine; 5-HT, serotonin; MAO, monoamine oxidase; MAPK, mitogen-activated protein kinase; MMSE, Mini Mental State Examination; NE, norepinephrine; NFT, neurofibrillary tangle; PD, Parkinson's disease; PEA, β-phenylethylamine; PKC, protein kinase C

Key words: Alzheimer's disease, monoamine oxidase, neurodegeneration, β-amyloid, tau

1. Introduction

Monoamine oxidase (MAO) catalyzes the oxidative deamination of biogenic and xenobiotic amines and has an important role in the metabolism of neuroactive and vasoactive amines in the central nervous system (CNS) and peripheral tissues. The enzyme preferentially degrades benzylamine and phenylethylamine and targets a wide variety of specific neurotransmitters involved in the primary substrates of MAO in the brain, including epinephrine (EP), norepinephrine (NE), dopamine (DA), serotonin (5-HT), and β-phenylethylamine (PEA) (1,2). The unique position of MAO in modulating the function of a diverse series of specific neurotransmitters in association with various conditions, including mood disorders (3), anxiety and depression (4,5), schizophrenia (6), attention deficit hyperactivity disorder (7-9), migraine (10), sexual maturation (11) and neurodegenerative diseases (12), has attracted significant attention to the protein as a therapeutic target.

Compelling studies have shown that the involvement of MAO in AD and neurodegenerative diseases plays an important role in several key pathophysiological mechanisms (13,14). MAO-B has been proposed as a biomarker, whereas activated MAO-B leads to cognitive dysfunction, destroys cholinergic neurons, causes disorder of the cholinergic system and contributes to the formation of amyloid plaques.

The present review focused on evidence supporting the central role that MAO has in AD pathogenesis, including the formation of amyloid plaques from amyloid β peptide (Aβ) production and neurofibrillary tangles (NFTs), and cognitive impairment via the destruction of cholinergic neurons and disorder of the cholinergic system. Studies reporting that MAO inhibitors improve cognitive deficits and reverse Aβ pathology by modulating proteolytic cleavage of amyloid precursor protein (APP) and decreasing Aβ protein fragments are also

discussed. Finally, on the basis of current advances in the use of MAO inhibitors for the treatment of AD, MAO inhibitors are discussed as a promising therapeutic target for AD.

2. MAO

Monoamine oxidase (EC1.4.3.4, a flavin-containing enzyme) is widely distributed in animal tissue and catalyzes the oxidative deamination of primary amines by reaction between dioxygen and R-CH_2-NH_2 to form R-CHO, NH_3 and H_2O_2 (Fig. 1). MAO removes an amine group by catalyzing the oxidative deamination of monoamines, resulting in the corresponding aldehyde and ammonia. MAO exists as two isozymes in humans: MAO-A and MAO-B, which are distinct due to different amino acid sequences, three-dimensional structures, distributions in organs and tissue, inhibitor sensitivities and substrate specificity. The two isozymes are found in and outside the CNS.

With regard to the functions of MAO, a wide range of pathophysiological roles have been suggested, including the regulation of cardiac function and blood pressure (15), as well as involvement in a number of psychiatric and neurological disorders, including mood, depression, schizophrenia, migraine, sexual maturation and neurodegenerative diseases. The notable role of MAO is in the regulation of neurotransmitter activity, since the primary substrates of MAO in the brain are specific neurotransmitters, including EP, NE, DA, 5-HT and PEA.

3. Involvement of MAO in neurodegeneration

An increasing number of studies have demonstrated the involvement of MAO in neurodegenerative diseases, including Parkinson's disease (PD) (16,17), AD (18,19), Lewy body diseases with dementia (20) and depression (17,21). MAO is involved in neurodegeneration via oxidative stress, which has a central role in neurodegenerative diseases (22). Other mechanisms have been identified, including neuroinflammation (23), triggering of apoptosis (18,24), failure of aggregated-protein clearance (25-27) and glial activation (28) by MAO.

PD is the second most common age-related neurodegenerative disease after AD, and is characterized by progressive loss of dopaminergic neurons in the substantia nigra, depletion of DA in the striatum, abnormal mitochondrial and proteasomal functions and accumulation of α-synuclein (29,30). It has been suggested that the increased turnover of DA and dopaminergic neurodegeneration are associated with oxidative stress derived from an increased production of hydrogen peroxide, which is formed during the oxidative deamination of DA by MAO (29,31). A recent study showed that activated MAO induces α-synuclein aggregation, which may be associated with early Parkinsonism and dopaminergic neurodegeneration in the substantia nigra in SMAD family member 3-null mice (32). The evidence that either inhibition or iron chelation of MAO exerts neuroprotective effects strongly indicates that MAO is a major component in the process of PD neurodegeneration under oxidative stress (17). In PD, dopaminergic cell death in the substantia nigra is linked to a marked glutathione decrease and mitochondrial dysfunction (24). MAO in the mitochondrial outer membrane induces oxidative stress resulting in neuronal degeneration through the production of hydrogen peroxide by

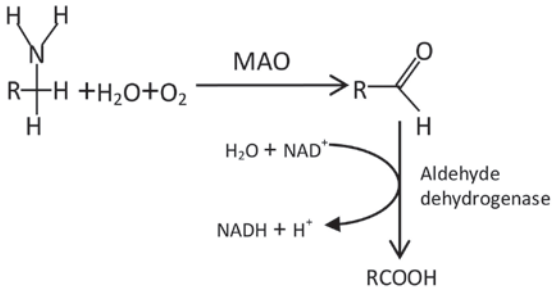

Figure 1. General reaction catalyzed by MAO. The reaction of a base (R, arbitrary group) with one ammonia and two hydrogen components plus water and oxygen, catalyzed by MAO, generates the aldehyde, ammonia and H_2O_2. MAO, monoamine oxidase.

oxidation of monoamine substrates (18,33,34). These results suggest that MAO is involved in the neurodegenerative pathogenesis of PD that manifests as increased oxidative stress and a major impairment of the glutathione pathway.

Studies have shown that activated MAO in the brains of patients with AD is a biomarker for AD (35-37). This was demonstrated by [^{11}C]-L-deprenyl using whole hemisphere autoradiography (38-40), epidemiology (41,42), morphology (43), as well as single-photon emission computed tomography (44). Such studies demonstrated that: i) MAO activity in platelets was significantly increased in patients with AD and acted as a marker of behavioral characteristics in dementia disorders (41,45-48); ii) there were early and persistent alterations in MAO-A and -B in the brains of patients with AD (49); iii) activated MAO led to cognitive dysfunction (50); iv) activated MAO destroyed cholinergic neurons and caused disorders of the cholinergic system (51); v) activated MAO contributed to the formation of amyloid plaques (13,14) and vi) activated MAO was associated with the formation of NFTs.

Pharmacological studies have demonstrated that MAO inhibitors exert neuroprotective effects in patients with AD (21,52,53) through the following mechanisms: Improvement of cognitive impairment (50,54,55); antioxidant and enhancement of iron chelating activities (56-59); regulation of APP and Aβ expression processing (56,60), involving the activation of certain signaling pathways, including the p42/44 mitogen-activated protein kinase (MAPK) and protein kinase C (PKC) signaling pathways (61); and inhibition of cholinesterase (ChE) activity (62-64).

4. Increased MAO activity in the platelets of patients with AD?

MAO activity has previously been found to be high in the brain and in platelets in patients with AD, while the activity of MAO-B in the brain increases with age due to an increased concentration of MAO-B (35). Compared with age- and gender-matched controls, MAO activity in platelets was significantly higher in patients with dementia of the Alzheimer type, and the MAO-B but not the MAO-A activity was significantly higher in the hippocampus and cortex of the gyrus cinguli in the AD group (65). In the aging controls, MAO-B activity in the brain was positively correlated with age (35,65).

Studies on the association between platelet MAO-B activity, clinical features and cerebrospinal fluid (CSF) monoamine

metabolites have demonstrated the importance of MAO-B activity in platelets as a biological marker of AD (47,66). An increased activity of this enzyme may constitute a marker for vulnerability towards behavioral disturbance (47). According to a Mini Mental State Examination (MMSE) of three groups with 23 patients in the early (MMSE score of 19-24), 23 patients in the middle (MMSE score of 10-18) and 28 patients in the late (MMSE score of 0-9) phases of AD, as well as 49 age-matched healthy females, significant correlations between MMSE scores and MAO-B activity and age were identified, suggesting that these markers may indicate the severity and/or clinical progress of AD (42,45).

However, several studies have indicated that MAO activity in platelets is not associated with the pathogenesis of AD (67-69). The MMSE indicated that no correlation was present between platelet MAO-B activity and the cognitive score in patients with AD (54). No significant differences were found in the levels of the amine metabolites homovanillic acid and methoxyhydroxyphenylglycol in the CSF of drug-free patients with AD as compared with those in a group of controls, showing that AD was not associated with changes in central catecholamine metabolism and increased platelet MAO activity (70). In view of MAO being involved in the metabolic inactivation of several monoaminergic neurotransmitters, including 5-HT, melatonin, NE and EP (21,70,71), a complex dysfunction in the MAO system is likely to be present in AD (48,69). Furthermore, MAO activity may be used to distinguish patients with AD due to the existence of a biologically-based behavioral subtype of AD (72). Different results may be obtained for MAO in AD for different species and in different experimental settings.

5. Alterations in MAO levels in the brains of patients with AD

Early and persistent alterations in MAO levels in the brains of patients with AD have been demonstrated by several studies that show the role of the hyperoxidation phenomena by MAO in the mechanism of neuronal cell death in AD. The oxidative degradation catalyzed by MAO produces free radicals and may thus be involved in the neurodegenerative process (73,74). In the CNS, the MAO-A isoform appears to be present mainly in catecholaminergic neurons, whereas the MAO-B form is primarily located in the glia and in serotonergic neurons (49). Radioenzymatic assay at brain autopsy revealed that the changes in MAO-A and -B in the prefrontal cortex occur in the early stages of AD and remain relatively constant as the disease progresses (49). It has also been revealed that MAO-A and -B protein and/or mRNA levels are increased in several brain areas, including the frontal lobe of the neocortex, as well as the parietal, occipital, temporal and frontal cortex (37,75-77). This indicates that the mechanism in MAO enzymes may be transcriptional or post-transcriptional and may be responsible for the increase in protein activity as well as important for the progression of AD.

Although the occurrence of activated MAO-B in the brains of patients with AD has been evidenced, it appears that MAO-A has a different appearance in different parts of the brains of patients with AD. Immunostaining showed that the activity of MAO-B was significantly increased in the cortical areas and in the hippocampus in AD, reflecting the underlying cell loss and substantial gliosis in these areas of the brain (76), while MAO-A was increased in the hypothalamus and frontal pole (37). Furthermore, MAO-A activity appears to be lower in the locus ceruleus in patients with AD, and is accompanied by an ~80% decrease in the number of neurons (78), revealing that activated MAO-A in neurons is involved in the pathology of this disease as a predisposing factor. In comparison, increased MAO-A activity appeared more significant in the glia of patients with AD (79). Thus, the changes in MAO-A levels in patients with AD appear to have multiple mechanisms.

6. MAO activation contributes to cognitive impairment in patients with AD

Numerous studies have shown that monoamine neurotransmitter systems have a determining role in cognition at the biomolecular level, including memory (80), orientation (81,82), attention (83), paranoid thinking (84), as well as behavior and emotion (81,85). MAO can disturb the balance of certain other brain chemical neurotransmitters, including glutamatergic action, ChE, acetylcholinesterase, 5-HT and NE (86-91), and, therefore, causes symptoms of cognitive impairment. MAO-A and -B exhibit different substrate specificity and inhibitor selectivity. Extensive studies have revealed that MAO-A preferentially acts on 5-HT and NE (92-94) and MAO-B acts positively on 2-phenylethylamine and benzylamine (95,96). NE has a determinant role in executive function, regulating cognition, motivation and intellect, which are fundamental in social relationships (97). Activated MAO is a contributing factor in neuronal NE pathways and highlights the specific role of NE in the symptoms of disordered executive function (97). Activated MAO is also a detrimental element for the function of the cholinergic system, which is mostly associated with memory and emotion (51,86,88). A recent population-based study showed a significant interaction between MAO-A and catechol-O-methyltransferase genotypes, such that increased prefrontal catecholamine availability was associated with an enhanced working memory (80). Although there are no reports on the direct association between MAO and the aforementioned neurotransmitter systems in AD, numerous studies suggest that activated MAO is indirectly involved in the close association between cognitive impairment and several neurotransmitter systems in AD (98-100). It is well accepted that oxidative stress (associated with MAO) contributes to the disturbance of aforementioned neurotransmitters, including NE and the cholinergic system, which have a critical role in the cognitive impairment in AD (100-103). Considering that neuroinflammation is a key element in cognitive impairment and an intermediate for oxidative stress (104-107), MAO may act as a proinflammatory mediator, which causes cognitive impairment in AD. Elevated monoamine levels in the brain resulting from MAO induce changes in other neurotransmitter systems and lead to cognitive impairment.

7. Activated MAO contributes to the formation of amyloid plaques

The amyloid hypothesis was proposed >100 years before it was demonstrated that the amyloid plaque, a pathological

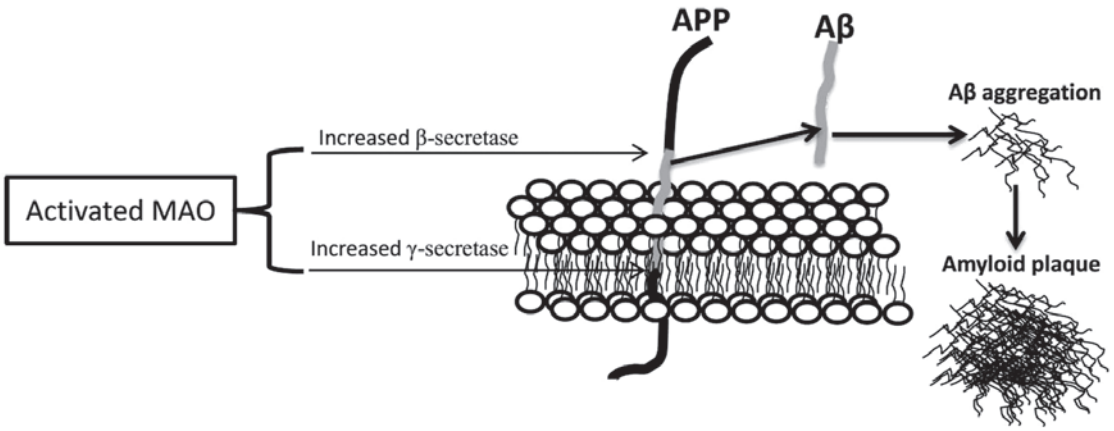

Figure 2. Aβ generation through modulation of APP processing by activated MAO. Activated MAO increases the expression of β-secretase and γ-secretase, improves Aβ generation and contributes to the formation of amyloid plaques. Aβ, amyloid β peptide; MAO, monoamine oxidase; APP, amyloid precursor protein.

characteristic of AD, is induced by the generation and deposition of Aβ (108). Aβ is the root cause of the pathogenesis of AD, and various mechanisms of neuronal degeneration have been proposed, including the formation of free radicals triggered by Aβ, the interaction between oxidative stress and the production of Aβ, the association between inflammatory processes and Aβ (109,110), as well as genetic factors and apoptosis associated with the generation of Aβ.

Studies on the pathogenesis of AD have revealed that oxidative damage is present in AD, which is the progressive neurodegenerative disease of ageing. Increased oxidative stress in patients with AD contributes to Aβ generation and the formation of amyloid plaques. It has been established that MAO, a marker of oxidative stress, is linked to the production of reactive oxygen species and other molecules that cause oxidative stress, which results in neuronal damage and neurodegeneration, including AD, indicating that excessive MAO activity contributes to neurodegeneration in AD (62,111-113). Molecular biology studies have shown the critical role of Aβ generation through the modulation of APP processing by MAO (60,61,114,115) (Fig. 2).

Aβ generation is the result of two sequential cleavages of APP by β-secretase (β-site APP cleavage enzyme, BACE) and γ-secretase. Extracellular cleavage by β-secretase is the first step of Aβ production, between the Met671 and Asp672 residues of APP, which results in a soluble extracellular fragment and a cell membrane-bound fragment (C99). C99 is then further cleaved by γ-secretase within the hydrophobic transmembrane domain at either Val711 or Ile713, finally releasing Aβ and the intracellular domain of APP. The non-amyloidogenic pathway, in which APP is sequentially cleaved by α- and γ-secretase, may prevent the production of Aβ (116,117). Several studies have reported that propargylamine-containing compounds, including ladostigil and M30, irreversible and selective MAO-B inhibitors, act as modulators of the proteolytic cleavage of APP via activation of the p42/44MAPK and PKC signaling pathways (61,118-120). It was also demonstrated that M30 effectively inhibited Aβ accumulation and tau phosphorylation in APP/presenilin 1 mice, where it markedly downregulated the levels of phosphorylated cyclin-dependent kinase 5 and increased PKC and glycogen synthase kinase-3β phosphorylation (121). Furthermore, deprenyl, an irreversible MAO-B inhibitor, was able to increase processing of APP through the non-amyloidogenic pathway via MAPK and PKC-dependent signaling pathways, and increase α-secretase activity in a dose-dependent manner *in vitro* through the involvement of protein trafficking (122). In Aβ-injected mice it was found that co-administration of donepezil with selegiline significantly alleviated cognitive impairment, indicating a synergistic cognition-improving effect by MAO inhibitors (123).

Substantial basic biomolecular and clinical studies suggest that neuroinflammation, with overexpression of cytokines and inflammatory mediators, is centrally involved in the pathogenesis of AD (124-126). One notable feature of the pathophysiology of the brains of patients with AD is that oxidative stress can induce an active, self-perpetuating cycle of chronic neuroinflammation, which further promotes oxidative stress and contributes to irreversible neuronal dysfunction and cell death (127). The interaction between oxidative stress and neuroinflammation is an important contributing factor to Aβ generation. Furthermore, oxidative stress and neuroinflammation are critical in the pathogenic cascade of neurodegeneration in AD, suggesting that therapeutic efforts aimed at these two mechanisms may be beneficial. It has been evidenced that several MAO inhibitors restrain the production of Aβ by inhibiting neuroinflammation, such as the inhibition of nuclear factor κB activity, the downregulation of the expression of interleukin 1β and tumor necrosis factor α, and the limitation of glial activation (38,128,129).

8. Is activated MAO associated with the formation of NFTs?

NFTs are well known as a primary pathological marker of AD. It has been indicated that oxidative stress not only is a major factor in the early stages of AD, but also contributes to the formation of NFTs via the aggregation of hyperphosphorylated tau protein. Activated MAO, a trigger for oxidative stress, produces reactive oxygen species in mitochondria and benefits the pathogenesis of neurodegeneration (130). Theoretically, it is possible that activated MAO is associated with the forma-

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

Inhibitor	Neuroprotective mechanism	Preclinical or clinical stage	References
Rasagiline	Novel multitarget iron chelators with AChE. Regulates APP and Aβ expression processing, activates pro-survival signaling pathways and regulates cell cycle	A phase II clinical study; *in vivo* and *in vitro*	(56,57,62,131-133)
Ladostigil	Dual acetylcholine-butyrylcholineesterase; a novel MAO and AChE inhibitor. Regulates APP translation and processing	A phase IIb clinical study; *in vivo* and *in vitro*	(28,114,134,135)
Selegiline (L-deprenyl)	Antioxidant, selective inhibitor of MAO-B. Modulates proteolytic cleavage of APP, involves mitogen-activated protein kinase and activates PKC, inhibits Aβ production	The Cochrane Dementia and Cognitive Impairment Group Register of Clinical Trials; Unconfounded, double-blind, randomised trials	(61,136-141)
M-30	Iron chelator-MAO inhibitor drug; modulates proteolytic cleavage of APP	*In vivo* and *in vitro*; in clinical trials	(15,61,112,142)

Aβ, amyloid β peptide; MAO, monoamine oxidase; PKC, protein kinase C; APP, amyloid precursor protein; AChE, acetylcholinesterase.

tion of NFTs (131). However, it remains to be elucidated whether activated MAO directly leads to the aggregation of hyperphosphorylated tau protein and the formation of NFTs since, to the best of our knowledge, it has not been reported.

9. Evidence for the neuroprotective effect of MAO inhibitors in AD

An increasing number of molecular biology and pharmacology studies have shown the neuroprotective effects of MAO inhibitors on the prevention and treatment of AD (21,52,53) (Table I) (15,56,57,61,62,112,114,131-144). The main neuroprotective mechanisms of MAO inhibitors in AD include the following: i) Improvement of cognitive impairment (50,54,55), where MAO inhibitors correct chemical imbalances in the brain; ii) antioxidant activities and enhancement of iron-chelating activities (56-59), where chelators can modulate Aβ accumulation, protect against tau hyperphosphorylation and block metal-associated oxidative stress, thereby holding considerable promise as effective anti-AD drugs (145,146); iii) regulation of APP and Aβ expression processing (56,60), for example ladostigil (TV3326), a selective MAO-B inhibitor, which regulates APP translation and processing (114); iv) the selective MAO inhibitors selegiline and rasagiline have been proven to possess neuroprotective activities in cell cultures and animal models of neurodegenerative diseases through the activation of certain signaling pathways, including p42/44 MAPK and PKC (61); v) inhibition of ChE activity by the MAO inhibitor rasagiline (62-64), with MAO inhibitors also affecting other chemicals throughout the body and acting by correcting chemical imbalances in the brain.

Laboratory and clinical studies have evidenced that the MAO inhibitors are a potential therapeutic approach for the treatment of AD. Certain novel pyrazole derivatives as dual MAO inhibitors and anti-inflammatory analgesics (148) are also a novel therapeutic approach in AD. Thus, selective MAO inhibitors may be a promising alternative for AD therapy. An enhanced understanding of MAO inhibitors may result in improved treatment of AD in the future (149,150).

10. Conclusions and outlook

Activated MAO-B in the brains of patients with AD is a biomarker for AD. Studies have shown that activated MAO contributes to cognitive dysfunction, destroys cholinergic neurons, causes disorder of the cholinergic system and leads to the formation of amyloid plaques and NFTs.

Numerous studies support the involvement of activated MAO in AD. Thus, drugs used to inhibit activated MAO, including rasagiline, ladostigil and selegiline, may provide neuroprotection against AD by improving cognitive impairment, modulating the proteolytic cleavage of APP and decreasing levels of Aβ protein fragments that accumulate in the brain. Although clinical trials involving the MAO-deactivating drugs have been largely conducted, numerous questions remain to be answered regarding the clinical trials of the drugs. As MAO is well known for its effects on neurotransmitter substance and MAO inhibitors are infamous for their numerous drug interactions, these drugs may produce a number of unwanted side effects. It remains to be elucidated whether MAO inhibitors have severe long-term effects via the inhibition of chemicals that break down 5-HT, NE and DA, which may lead to intolerably high levels of any of these neurochemicals. MAO inhibitors may be particularly harmful when taken with certain foods, beverages and medicines. Future clinical studies on MAO inhibitors for the treatment of AD are required, and these may provide further insights into the mechanism of action of antioxidants as therapeutic agents for AD.

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