ABSTRACT
Monoamine oxidase (MAO) isoenzymes A and B are mitochondrial-bound proteins that catalyze the oxidative deamination of dietary amines and monoamine transmitters. Others include: serotonin, epinephrine, 2-phenylethylamine, and dopamine. MAOs can potentially modulate all the processes involving bioactive amines, including regulation of mood, emotional behavior, and other brain function. MAO enzymatic activity plays a role in the pathophysiology of a wide range of mental and neurodegenerative disorders, including personality disorders, depressive syndromes, and Parkinson’s disease. Similarly, the byproducts of MAO-mediated reactions include some chemical species that can cause mitochondrial damage leading to neurotoxicity, and can affect the function of other organs such as the heart. In this article, genetic variations, anatomical distribution, and physiological functions of MAO-A and MAO-B are described. [Psychiatr Ann. 2014;44(11):495-501.]

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he history of monoamine oxidase (MAO) started in 1928, when Mary Hare published the results of her study on a new enzyme that catalyzed the oxidative deamination of tyramine.\(^1\) The enzyme, called "tyramine oxidase" by Hare, was later found to metabolize not only tyramine, but also other primary, secondary, and tertiary amines such as norepinephrine (NE) and epinephrine (E). Zeller\(^2\) used the name "monoamine oxidase" first.

In 1968, Johnson\(^3\) discovered that MAO exists in two forms—MAO-A and MAO-B. Both isoforms differ in substrates, inhibitors, morphological distribution, and physiological role. Under physiological conditions, MAO-A preferentially oxidizes serotonin (5-hydroxytryptamine [5-HT]) and NE; MAO-B oxidizes phenylethylamine. Dopamine (DA) and tyramine are substrates for both enzymes. The functional role of MAOs is species-dependent. For example, metabolism of DA in rodents is mediated mainly by MAO-A, but in primates (including humans) by MAO-B. Both enzymes also differ in inhibitor sensitivities—at least at low concentrations MAO-A is preferentially inhibited by clorgyline\(^3\) and MAO-B by deprenyl.\(^4\)

**MOLECULAR STRUCTURE OF MAO-A AND MAO-B**

MAO-A is composed of 527 amino acids and MAO-B of 520 amino acids, with molecular weights of 59,700 and 58,000 kDa, respectively.\(^5\) During post-translational modifications, the N-terminus is acetylated, and flavin adenine dinucleotide (FAD) is covalently attached to cysteinyl residues, namely Cys406 in MAO-A and Cys 397 in MAO-B.\(^6,7\) Substrate preference seems to depend on a number of internal residues.\(^8\) In most tissues, MAO-A and MAO-B are anchored to the mitochondrial outer membrane by a C-terminal transmembrane polypeptide. Both enzymes are dimeric in their membrane-bound forms, although only the crystal structure of human MAO-B is dimeric; the crystal structure of MAO-A is monomeric. Furthermore, both isoenzymes are differentially oriented in the outer mitochondrial membrane.\(^9\)

**MAO GENES AND POLYMORPHIC VARIANTS**

Genes encoding relevant isoenzymes were cloned in 1988.\(^10\) They are situated on the X chromosome at the locus Xp 11.23-11.4 and share about 70% sequence identity with 15 exons, 14 introns, and identical exon-intron organization.\(^11\) Exon 12 codes for the covalent FAD-binding site, and is the most conserved exon—showing 93.9% amino acid identity between MAO-A and MAO-B. The maximal promoter activity for MAO-A and MAO-B was found in a 0.14- and 0.15-kb fragment, respectively, of the 5’-flanking sequence.\(^12\) It is postulated that differences in promoter organization of MAO-A and MAO-B genes may correspond to their different tissue- and cell-type specific expression, especially in catecholaminergic and serotoninergic neurons in the brain.\(^13\)

Four main MAO-A polymorphisms have been studied as potential risk factors for psychiatric disorders. These are: MAO-A (CA)n, a dinucleotide polymorphism in intron 2; a 23 bp variable-number tandem repeat (VNTR) near exon 1; two restriction fragment length polymorphisms (Fnu4HI and EcoRV); and one of the most extensively studied, MAO-A-uVNTR. The promoter region of MAO-A contains a 30 base pair variable number of tandem repeats sequence (VNTR), consisting of 2, 3, 3, 3, 4, or 5 repeated copies.\(^14\) The MAO-A gene containing 3.5 or 4 repeats can be transcribed even 10 times more efficiently than polymorphism with 2, 3, or 5 repeats.\(^15\)

It has been suggested that the MAO-A-uVNTR polymorphism may be associated with human psychiatric and neurological disorders. Transcription of the 3-repeat allele reduces MAO-A activity, resulting in increased synaptic serotonin. Increased concentration of serotonin can escalate the risk for aggression and antisocial behavior (ASB). An association of polymorphism MAO-A-uVNTR and ASB was shown recently.\(^16\) Several studies suggest that the MAO-A gene may be involved in the pathogenesis of depression and major depressive disorder.\(^17,18\) High activity of 4R allele of the MAO-A promoter uVNTR polymorphism was found to be associated with depression in male patients and linked to increased levels of aggressiveness and impulsivity.\(^19\) However, no association of MAO-A genes with depression and Alzheimer’s disease was found in the recent VITA (Vienna-Transdanube-Aging) study.\(^20\) A linkage has been shown between the MAO-A-uVNTR polymorphism and autism spectrum disorders,\(^21\) alcoholism,\(^22\) and suicide attempt.\(^23-25\) The MAO-A-uVNTR polymorphism was recently found to contribute to impulsive violent crimes after exposure to heavy drinking.\(^26\) However, no such relation has been shown in schizophrenia\(^27,29\) and heroin dependence.\(^30\) Significant heterogeneity was observed for the association between MAO-A VNTR polymorphism and attention-deficit/hyperactivity disorder (ADHD).\(^31\)

Although many studies on polymorphism of MAO in Parkinson’s disease (PD) have been published, the association is still not clear.\(^32\) It was shown that the MAO-A EcoRV and Msp1 polymorphisms were three times more frequent in PD patients than in controls;\(^33\) however, other studies did not confirm that outcome.\(^34\) In Caucasians, polymorphism in intron 13 and in exon 14 of MAO-B gene were shown to be associated with increased risk for PD.\(^35\)

It should be remembered that a large number of individual factors including diet, tobacco smoking, physical activity, stress, and aging has been shown to modify MAO expression and activity.
ANATOMICAL LOCALIZATION OF MAO-A AND MAO-B

As mentioned above, MAO-A and MAO-B differ in their anatomical localization, but both are present in most of the brain regions. MAO-A is found predominantly in catecholaminergic (dopaminergic and noradrenergic) neurons, while MAO-B is most abundant in serotonergic and histaminergic neurons as well as in glial cells. The role of MAO-B in serotonergic neurons remains unclear because serotonin is mainly metabolized by MAO-A. It seems that this localization may serve a protective role for serotonin. Recently, it has been shown that regional distribution of MAO-A and MAO-B in the brain is highly heterogeneous. Highest levels of both enzymes were observed in hypothalamus, nucleus basalis, and hippocampal uncus. The highest concentration of MAO-A was shown in locus coeruleus and of MAO-B in raphe nuclei. The striatum and globus pallidus were shown to contain low levels of MAO-A but high levels of MAO-B, in contrast to cerebral cortices, which had high levels of MAO-A. Skin fibroblasts and placenta express solely MAO-A, while in platelets and lymphocytes only MAO-B is present. The greatest activity of MAO-A is found in the placenta, liver, kidney, adrenal gland, heart, lung, and intestine. MAO-B can also be found in these tissues, although with lower activity. The exception is skeletal muscle, where activities of both enzymes are similar. MAO-A mRNA is also detectable in the lung, kidney, brain, spinal cord, liver, spleen, and adrenal gland. Highest concentrations of MAO-B mRNA have been shown in the small intestine, kidney, liver, adrenal gland, heart, spinal cord, and lung.

It has been postulated that anatomical distribution of both enzymes, whether in peripheral tissues or the central nervous system, is related to their functional roles. Interestingly, levels of both enzymes are age dependent; aging is associated with increase of MAO-B but not MAO-A. In the fetus, the liver is the organ with the highest activities of both MAO-A and MAO-B, but in the brain, lung, aorta, and digestive system MAO-A activity is more pronounced than MAO-B. At 19 weeks gestation, the amounts of MAO-B transcripts are lower than MAO-A. The highest concentrations of both enzymes were detected in the frontal cortex and locus coeruleus. A study examining MAO activity in the frontal cortex of the brain throughout life (from the childhood to senescence) showed that MAO-A activity decreased during the first 2 years of life and then remained constant until death. MAO-B remained constant during childhood and rose throughout adult life. As MAO-B is mostly located in glial cells, the observed increase with aging may be associated with the proliferation of these cells. Increasing MAO-B activity with aging may represent an important factor in the pathogenesis of neurodegenerative diseases, such as Parkinson’s and Alzheimer’s disease.

PHYSIOLOGICAL ROLES OF MAO

The physiological role of MAOs is the metabolic degradation of both endogenous and exogenous amines. In the periphery, MAOs prevent entry of dietary amines into the circulatory and nervous systems (both central and peripheral)—both MAO isoforms regulate the intracellular influence of amine neurotransmitters on neurons by terminating its action and regulating the contents of intracellular amine stores. MAO catalyzes the following reaction: RCH2NH2 + H2O + O2 → RCHO + NH3 + H2O2, which consists of three main steps:

1. Conversion of amine into the corresponding imine with simultaneous reduction of FAD to its hydroquinone form (FADH2).
2. Spontaneous hydrolyzation of imine and production of aldehyde and ammonium.
3. Oxidation of FADH2 to FAD and formation of hydrogen peroxide.

Aldehydes produced during the reaction are toxic; they are oxidized by NAD (P)+-dependent aldehyde dehydrogenase (functionally coupled with MAO) to corresponding carboxylic acid or are reduced to alcohols or glycols by either aldehyde reductase or alcohol dehydrogenase.

MAO (coupled with either aldehyde dehydrogenase or reductase) and catecholamine-0-methyl-transferase (COMT) metabolizes three major catecholamines, DA, NE, and E, that function as neurotransmitters. DA is metabolized to either homovanillic acid (HVA) or 3-methoxy-4-hydroxyphenylethanol, which can be converted to HVA by alcohol dehydrogenase. MAO converts NE and E into 3,4-dihydroxyphenylglycerol aldehyde, and further into 3,4-dihydroxyphenylethylene glycol or 3,4-dihydroxyphenylalanine acid.

Endogenous substrates of MAO include 5-HT, DA, NE, E, tyramine, 2-phenylethylamine, and octopamine, but it also catalyzes the oxidative deamination of dietary amines and lateral medulla and DA in substantia nigra, ventral tegmental area, and hypothalamus. NE is also released by peripheral sympathetic nerves onto blood vessels and secreted with E by the adrenal medulla. Catecholamines play important roles in the regulation of mood, memory, behavior, and autonomic function. Foods that are especially rich in tyramine and other sympathomimetic amines include certain kinds of cheeses and fermented

The highest concentration of MAO-A was shown in locus coeruleus and of MAO-B in raphe nuclei.
drink (beer, wine). Tyramine was first isolated from cheese and later named after the Greek (tyros) for cheese. Normally functioning MAO metabolizes exogenous amines and prevents their entry into the systemic circulation. People prescribed MAO inhibitors, who consume dietary amines, can experience an extensive release of NE from peripheral adrenergic neurons, causing a severe hypertensive response called the “cheese reaction.”52

In the central and peripheral nervous system, intraneuronal MAO-A and MAO-B protect neurons from exogenous amines, terminate the actions of amine neurotransmitters, which are pumped back into the cell after neuronal discharge, and regulate the content of intracellular amine stores. The role of MAO in these processes has been extensively studied. In contrast, much less attention has been dedicated to the products of MAOs’ activity, which include aldehydes, ammonia, H2O2, and reactive oxygen species (ROS).53

The dysregulation of redox balances and mitochondrial damage induced by MAO activation may result in neuronal apoptosis and brain damage. Hydrogen peroxide, one of the byproducts of MAO reactions, is postulated to play an important role in the pathogenesis of PD and other neurodegenerative disorders; MAOIs have been prescribed to slow the progression of neurodegenerative disorders. Some drugs are extensively linked to the reduction of oxidative stress mediated by ROS.

ROS are postulated to play a role in many pathological conditions, not just the central nervous system. For example, ROS modifies myofibrillar proteins, such as tropomyosin, actin, and desmin, involved in the contractile dysfunction of the dystrophic muscle. Moreover, it was shown that MAO is a major source of ROS in murine models of muscular dystrophies and that inhibition of MAO reduces myofiber defects and myofibrillar protein oxidation, thus protecting dystrophic skeletal muscle.54

Considerable evidence has accumulated that ROS contributes to cardiac diseases. MAO-A has been detected in human myocardium, where it mainly catalyzes 5-HT, NE, and E.55 It was shown that inhibition of MAO-A reverses oxidative stress, neutrophil accumulation, and mitochondria-dependent cell death, which indicates its role in myocardial ischemia/reperfusion.56

Inhibition of MAO-A ameliorates the up-regulation of NE and ROS production in pressure overloaded hearts. This supports the thesis that MAO-A is an important source of ROS in myocardial tissue. MAO-A has a role in maladaptive remodeling and myocardial dysfunction during hemodynamic stress.57 In the heart, 5-HT plays a role not only in cardiac development,58 but also in some pathologies such as ventricular hypertrophy59 and cardiac valvular insufficiency associated with carcinoid tumors.60 Also it was shown that during ischemia/reperfusion, serotonin accumulates in the heart, perhaps leading to the progression of myocardial injury and dysfunction.61

5-HT promotes cardiomyocyte apoptosis and MAO-A participates in the induction of cardiomyocyte damage. Moreover, pretreatment with MAO inhibitor significantly reduced infarct size in rats and prevented cardiac accumulation of ROS-generating phagocytes.62 MAO is a major source of ROS in human atrial myocardium.63 ROS generated by MAO are believed to be one of the causal factors of postoperative atrial fibrillation; ROS impairs atrial contraction, disrupts myofibrillar function, and reduces the atrial effective refractory period.64

The presence of MAOs in diverse tissues points to MAOs’ importance in controlling local concentrations of monoamines. This applies not only to the presence of E and DA in cardiomyocytes,65 as described above, but also to DA and 5-HT in the kidney66 or E and NE stimulating glucagon secretion and inhibiting insulin secretion from beta cells in the endocrine pancreas.67 Interestingly, in the adrenal medulla, a major producer of catecholamines, MAO is present only in central vein and ganglion cells but not in the secretory cells; this suggests inactivation by MAO is restricted to target organs. As both forms are found in endothelial cells of blood vessels, they possibly have a role in the sympathetic regulation of blood pressure.68

The majority of data regarding the action of MAO derive from research on knock-out mice. In these studies, mutant mice demonstrated an absence of MAO-A activity in all of the examined organs (including the brain, liver, lung, kidney, testes, spleen, heart, hardierian gland), resulting in increased amounts of 5-HT, NE, and DA in the brain. Moreover, MAO-A–deficient mice also show downregulation of either brain postsynaptic 5-HT 1A, 5-HT 2A, 5-HT2C receptors, or vesicular monoamine transporters. Importantly, no significant compensatory increase in MAO-B activity was detected. Behavioral changes differ in neonatal and adult knock-out mice. In neonatal mice, prolonged righting, trembling upon locomotion, hunched posture, and sleep accompanied by violent shaking and jumps have been observed.69 The most important changes observed in adult knock-out mice include increased territorial aggression, enhancement of classical fear conditioning, and impairment of emotional memory.70

In MAO-B knock-out mice, no increase in aggressive behavior or anxiety,
and no hyperactivity or changes in working memory have been described. However, both MAO-A and MAO-B knockout mice showed increased reactivity to stress in the forced-swim test.

It is postulated that because physiological changes resulted from excessive amounts of monoamines, MAO-A knock-out mice had lower body weights and impaired thermoregulation. Both MAO-A and MAO-B knock-out mice demonstrated low to normal basal blood pressure and heart rate. 71

ROLE OF MAO IN THE PATHOGENESIS OF DISEASE

MAOs have been implicated in the pathophysiology of various neurological and psychiatric diseases, such as PD, depression, ADHD, social anxiety, personality disorders, cigarette dependency, and potentially alcoholism. 72-75 Deletion of MAO-A and MAO-B genes, a cause of an X-linked recessive neurologic disorder called Norrie disease, is characterized by blindness, hearing loss, and mental retardation. 76

In patients with PD, elevated activity of MAO-B was shown in the substantia nigra. It is postulated that oxygen radicals formed due to increased oxidation of DA by MAO-B cause oxidative damage to nigrostriatal neurons in PD. 77 Moreover, MAO-B is suggested to promote aging of the brain either by increasing the levels of toxic H₂O₂ or by bioactivation of neurotoxins. 78 MAO-B inhibitors impede the breakdown of amine neurotransmitters and are used in the treatment of PD.

In humans, MAO-A deficiency has been shown to result in borderline mental retardation and impaired impulse control. 79 In males, deletion of both genes causes profound mental retardation, severe developmental delay, stertotypical hand movements, and intermittent hypotonia. This indicates that MAO is important during neuronal development. 79

MAO may connect stress, an important precipitator, with depression. Stress has been shown to be associated with increase salivary activity of MAO-A and MAO-B, thus decreasing monoamine concentration. As both low NE and low 5-HT have been linked to depression, stress-induced increases in MAO-A and MAO-B may decrease these monoamines, leading to depression. 80 Moreover, one of the glucocorticosteroids—dexamethasone—has been shown to increase MAO-A activity. 81 In preclinical studies, dexamethasone was observed to increase MAO-A levels in the brain, skeletal muscle, and dorsal raphe nucleus. It can also induce MAO-B activity in neurons and astrocytes. 74

In humans, positron emission tomography studies showed that MAO-A density in brains of patients with major depression is elevated by 34%, compared to controls, with the highest densities in the thalamus and cingulate cortex. Both structures have been implicated in mood processes. 82

SUMMARY

MAO-A and MAO-B regulate the levels of monoamine neurotransmitters and hormones, such as dopamine, noradrenaline, adrenaline, and serotonin. Knowledge about anatomical distribution, genetic variations, and physiological functions of both isoenzymes have led to a better understanding about its involvement in pathological conditions. Studies performed in knock-out mice and in humans confirmed the role of both enzymes in the pathogenesis of neurological and psychiatric disorders. MAOs are well known; however, they are still investigated targets for drugs to be used for central nervous system diseases such as depression, anxiety, and neurodegenerative disorders. The significance of the inhibition of MAO to treat anxiety and depression is provided in the clinical papers of this issue of Psychiatric Annals.


