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Monoamine oxidase inactivation: from pathophysiology to therapeutics

Marco Bortolato[1], **Kevin Chen**[1], and **Jean C Shih**[1,2]

1*Department of Pharmacology and Pharmaceutical Sciences, School of Pharmacy, University of Southern California, Los Angeles, CA*

2*Department of Cell and Neurobiology, Keck school of Medicine, University of Southern California, Los Angeles, CA*

Abstract

Monoamine oxidases (MAOs) A and B are mitochondrial bound isoenzymes which catalyze the oxidative deamination of dietary amines and monoamine neurotransmitters, such as serotonin, norepinephrine, dopamine, β-phenylethylamine and other trace amines. The rapid degradation of these molecules ensures the proper functioning of synaptic neurotransmission and is critically important for the regulation of emotional behaviors and other brain functions. The byproducts of MAO-mediated reactions include several chemical species with neurotoxic potential, such as hydrogen peroxide, ammonia and aldehydes. As a consequence, it is widely speculated that prolonged excessive activity of these enzymes may be conducive to mitochondrial damages and neurodegenerative disturbances.

In keeping with these premises, the development of MAO inhibitors has led to important breakthroughs in the therapy of several neuropsychiatric disorders, ranging from mood disorders to Parkinson's disease. Furthermore, the characterization of MAO knockout (KO) mice has revealed that the inactivation of this enzyme produces a number of functional and behavioral alterations, some of which may be harnessed for therapeutic aims. In this article, we discuss the intriguing hypothesis that the attenuation of the oxidative stress induced by the inactivation of either MAO isoform may contribute to both antidepressant and antiparkinsonian actions of MAO inhibitors. This possibility further highlights MAO inactivation as a rich source of novel avenues in the treatment of mental disorders.

Keywords

Monoamine oxidase; depression; Parkinson's disease; oxidative stress

1. Introduction

Monoamine oxidase (MAO) [amine: oxygen oxidoreductase (deaminating) (flavin-containing); MAO; E.C. 1.4.3.4] is a mitochondrial bound enzyme, which catalyzes the oxidative deamination of dietary amines, monoamine neurotransmitters and hormones. This

Corresponding author: Jean C. Shih, Dept. of Pharmacology and Pharmaceutical Sciences, School of Pharmacy, University of Southern California, Rm. 518, 1985 Zonal Ave., Los Angeles, CA 90089. Tel.: 323-442-1441; Fax: 323-442-3229; E-mail: jcshih@usc.edu.

broad array of substrates includes several notable biogenic molecules: indoleamines such as serotonin (5-hydroxytryptamine, 5-HT) and tryptamine; catecholamines, such as dopamine (DA), norepinephrine (NE) and epinephrine; trace amines, such as beta-phenylethylamine (PEA), tyramine and octopamine.

The rapid degradation of brain monoamines, such as 5-HT, NE and DA is essential for the correct functioning of synaptic neurotransmission (Fig. 1–Fig. 3). Monoaminergic signaling is regarded as one of the key mechanisms for the modulation of mood and emotion, as well as the control of motor, perceptual and cognitive functions.

The chemical reaction catalyzed by MAO, exemplified in Fig. 4, consists in the degradation of monoamines into the corresponding aldehydes, which are then oxidized into acids by aldehyde dehydrogenase (ALDH) or converted into alcohols or glycols by aldehyde reductase (ALR). The byproducts of these reactions include a number of potentially neurotoxic species, such as hydrogen peroxide and ammonia. In particular, hydrogen peroxide can trigger the production of reactive oxygen species (ROS) and induce mitochondrial damage and neuronal apoptosis.

In this review article, we will summarize the therapeutic actions and pathophysiological implications of MAO inactivation, as evidenced by pharmacological (MAO inhibitors) and genetic tools (MAO knockout mice). We will then use these two complementary approaches to present the possibility that oxidative stress may contribute to the role of MAO in a vast range of neuropsychiatric disorders.

2. Molecular characteristics of MAO

Two different types of MAO, named A and B, have been characterized. The distinction between these two isoforms was first defined on the basis of substrate and inhibitor sensitivity, before their molecular characterization. In fact, although the spectrum of enzymatic actions mediated by these two isoenzymes overlap to some degree, MAO A displays a higher affinity for 5-HT and NE, while MAO B prefers PEA. The metabolism of DA and other monoamines (such as tryptamine and tyramine) is generally contributed by both isoforms. Notably, however, DA degradation is mainly degraded by MAO A in the rodent brain, while MAO B plays a substantive role in this process in humans and other primates. Irrespective of tissue- and species-based differences in substrate specificity, the two isoenzymes are best distinguished based on pharmacological criteria: MAO A is selectively inhibited by low doses of clorgyline [1], whereas MAO B is blocked by low doses of deprenyl (selegiline) [2].

The unequivocal demonstration of the different molecular nature of the two isoforms, however, came with the cloning of the cDNA of the two genes, performed by our group about 20 years ago [3]. This breakthrough allowed a number of critical discoveries on MAO A and MAO B genes, which proved essential for a better understanding of the biological functions of these two molecules. Both genes are located in the chromosome X (Xp11.23) [4], in opposite direction with tail-to-tail orientation, and display identical number of exons (15) and intron-exon organization, suggesting that the two genes are likely derived from the duplication of a common ancestral gene.

The deduced primary sequences of the two isoenzymes have 70% identity, and contain a pentapeptidic sequence (Ser-Gly-Gly-Cys-Tyr), that binds the cofactor FAD through a thioester covalent linkage to the cysteine [3]. The primary sequence is highly critical for the differences in catalytic activity between MAO A and MAO B. In mutagenesis studies, we and others established that the internal segment (between aminoacids 152 and 366) confers inhibitor and substrate specificities [5,6]. Both proteins are predominantly located in the outer membrane

of mitochondria, to which they are anchored by the C-terminal domain [7]. The 3D-structure of MAOs has been modeled [8] and solved only in recent years [9–11].

Over the last 20 years, our group and others have afforded significant contributions in the understanding of the genetic and transcriptional regulation of MAO A and B genes and promoters [12–17]. While the results of this research are beyond the scope of the present article and have been reviewed elsewhere [18], it is worth noting that recent evidence shows that MAO A and MAO B are activated and repressed by different transcription factors, which may account for the differences in the localization of these two isoenzymes [19]. For example, although in humans they are both expressed in most peripheral tissues and organs, MAO A is prevalent in fibroblasts and placental tissue [20], while MAO B is the only isoform in platelets and lymphocytes [21,22] (for a review, see reference [18]).

Immunohistochemical and autoradiographic studies have established that, in the brain, MAO A is predominantly localized in catecolaminergic neurons, whereas MAO B is mainly expressed in serotonergic and histaminergic neurons, as well as in astrocytes [23–25]. This finding, albeit well documented by several laboratories, is in apparent contrast with the pharmacological evidence that serotonin levels are enhanced only following MAO A, but not MAO B, inhibition. The reasons of this mismatch, however, are still mostly elusive.

3. Pharmacological inactivation of MAO: MAO inhibitors

The development of MAO inhibitors started with the serendipitous finding of antidepressant effects in patients treated with iproniazid, a hydrazine-based antitubercular agent structurally similar to isoniazid [26]. This discovery, together with the demonstration that iproniazid was a potent MAO inhibitor [27], led to the design and production of other MAO inhibitors, such as phenelzine. Following the ascertainment that hydrazine-based MAO inhibitors caused liver toxicity, however, novel chemical categories of drugs were established (Table 1).

Another undesirable side effect of MAO non-selective inhibitors, was the so-called “cheese reaction”, consisting in severe, potentially lethal hypertensive crises with cerebral hemorrhages, following the consumption of cheese, wine and other fermented foods, typically rich in tyramine and sympathomimetic amines [28]. Due to the lack of intestinal metabolism by MAO B, these compounds are absorbed and enter circulation, to induce increased NE release in the medulla, which in turn activates the sympathetic system and, in absence of MAO A-mediated metabolism, causes the sudden increment in blood pressure. While the presence of this untoward effect led to the development of novel categories of antidepressant agents with different mechanisms of action (such as tricyclic antidepressants and serotonin selective reuptake inhibitors), the quest for MAO inhibitors devoid of untoward effects prompted research to characterize selective MAO A and MAO B inhibitors. Subsequently, MAO B inhibitors, such as d-deprenyl (selegiline) revealed that these compounds were efficacious in the therapeutic management of Parkinson’s disease.

The characterization of novel chemical families of MAO inhibitors was paralleled by investigations on their putative endogenous counterparts. Several lines of research have identified some peptides that act as MAO inhibitors, such as neurocatin [29] or isatin (for a review see reference [30]). However, the physiological role of these molecules remains highly elusive.

Depression and mood disorders

MAO inhibitors are the first category of antidepressants ever developed, and show high mood-enhancing efficacy. The mechanism of antidepressant action is generally interpreted as based

on MAO A inhibition and the consequent ability to counter the reduction in 5-HT and NE (and, to a more limited extent, DA) that characterizes depression.

The current guidelines for treatment, of major depression disorder, issued by the American Psychiatric Association and the British Association for Psychopharmacology, suggest that MAO inhibitors should be considered as second- choice agents, after serotonin selective reuptake inhibitors and tricyclic agents, due to the numerous side effects of these compounds. Indeed, the introduction of selective agents, which display a better tolerability profile, has gradually supplanted the use of MAO inhibitors in the clinical practice. However, the development of reversible inhibitors of MAO A (RIMAs) has renewed interest for this category of compounds [31,32], particularly in view of their efficacy in treatment-resistant depression [33], dysthymia [34] and atypical depression, a subtype of major depressive disorder characterized by bulimia, fatigue and hypersomnia [35].

Anxiety disorders

MAO inhibitors are indicated for some anxiety-spectrum disorders, namely social phobia, panic disorder, post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD). Again, moclobemide and other RIMAs are a promising category of drugs to address these disorders, and may be an optimal choice particularly for PTSD and panic disorder [36]. Accordingly, MAO inhibitors have shown the highest efficacy in OCD, especially when accompanied by phobic anxiety [37].

Attention deficit hyperactivity disorder and Tourette's syndrome

Deprenyl was initially tested in cases of ADHD associated with Tourette's syndrome based on preliminary reports of the ability of MAO B inhibitors to have stimulant effects and ameliorate hyperactive behavior. This approach proved highly successful, with a general improvement of ADHD symptoms and a marginal improvement of tics [38,39]. Subsequent trials confirmed that deprenyl reduces ADHD symptoms, with particular efficacy on the attentional impairments of this disorder [40,41]. An intriguing mechanism of action of MAO B inhibition in ADHD may lie in the increased level of PEA, which is assumed to act as an endogenous amphetamine [42]. Accordingly, amphetamine derivatives are first-line therapeutic agents for ADHD.

Parkinson's Disease

The rationale behind the usage of MAO B inhibitors in Parkinson's disease (PD) was originally based on the concept that DA is preferentially deaminated by this isoenzyme in the human nigrostriatal dopaminergic system. Thus, the increase in DA levels caused by MAO B inhibitors should compensate for the nigrostriatal deficits in this neurotransmitter [43,44]. Studies on the prototypical MAO B inhibitor, deprenyl, revealed that the actions mediated by this compound also reflect the neuroprotective actions elicited by MAO inhibition. Accordingly, recent evidence shows that moclobemide, the prototypical reversible inhibitor of MAO A (RIMA) has also antiparkinsonian effects. As stated previously, one of the byproducts of MAO mediated reaction is hydrogen peroxide, which contributes to the formation of other ROS and can trigger mitochondrial damage and neuronal death. This evidence is bolstered by the finding that MPTP is activated into the parkinsogenic toxin MPP+ by MAO B, and that increased MAO B activity in the astrocytes causes Parkinsonian manifestations [45]. Emerging evidence shows that some of the neuroprotective actions of deprenyl and its analog rasagiline, however, do not depend on MAO B inhibition, but on other mechanisms (see reference [46] for a review).

Alzheimer's Disease

Age-related increases in MAO B activity, as well as the neuroprotective effects of its inhibitors, have been considered as rational bases to use MAO B inhibitors in Alzheimer's disease (AD) management. Although the therapeutic effects of MAO B inhibitors for AD has been challenged by recent meta-analyses [47], several preclinical experiments support the concept that MAO B blockade induces cognitive improvement.

Other neurodegenerative diseases

In view of the numerous similarities between PD and other neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS) and Huntington's disease, deprenyl and rasagiline has been tested in both disorders. In spite of some promising results in animal models, however, clinical results have not been encouraging so far.

4. Genetic inactivation of MAO: MAO knockout (KO) mice

Although MAO isoforms can be distinguished based on the affinity for low doses of inhibitors, studies have shown that neither MAO A nor MAO B inhibitors are completely selective at high doses, which would be needed to ensure a total inactivation of each isoenzyme. To obviate this problem, our group and others have developed several lines of transgenic mice with nonsense mutations for each MAO isoform. The characterization of the phenotypes of these animals has afforded substantial contributions to our understanding of the role of MAO in the regulation of behavior and brain functions. A synopsis of the behavioral features displayed by different lines of MAO KO mice is presented in Table 2 (based on references [48–51] and unpublished data).

MAO A KO mice

The first line of KO animals engineered to experiment the functions of MAO A in vivo was obtained by targeted insertion of an interferon cassette in the exon 2 of MAO A gene [49]. Because of the X-linked characteristics of this mutation, hemizygous males in this strain exhibit a significant increase in brain levels of 5-HT and NE and a modest increase in DA. The most striking behavioral characteristics in these mice is a dramatic enhancement of aggressive traits, as measured both in the resident-intruder paradigm [49,52], and in encounters with cage mates. The neurochemical underpinnings of aggressiveness in MAO A KO mice are only partially understood, but may reflect developmental components. Indeed, administration of clorgyline in adults does not induce aggressiveness, while chronic injection with clorgyline in perinatal stages produces a decrease in latency to attack in adult rats [53]. Interestingly, this effect may be correlated to the observation that MAO A KO pups display 5-HT concentrations nine times higher than WT mice at the same stage [49], while the difference in adult animals is only twofold.

MAO A KO mice also exhibit higher retention of aversive or fear-related memories than WT animals, including freezing response after footshock [54] and retention of condition passive avoidance [55].

In general, the impact of MAO A deficiency in the brain seems to induce a general increase in the resistance to the effects of environmental stressors,: for example, MAO A KO display a typical reduction in immobility in the forced swim test [49], which is a validated animal model of depression [56]. This particular model can capture, among other factors, the inclination of the animal to resign to a stressor perceived as highly threatening. Upon a closer ethological analysis of the reactive behaviors enacted by MAO A KO mice in the forced swimming test, we found that, in this model, the reduction in immobility is mainly due to an increase of swimming behaviors, which is considered homologous with goal-directed activity. We

observed similar phenomena in another highly validated model of depression-like behaviors, the tail-suspension test, in which mice are suspended by the tail to a hook for six minutes [57]. Although the overall immobility time remained comparable between MAO A KO and WT mice [58], there was a clear difference in the modalities of motor activation between the two genotypes, with MAO A KO mice displaying a significantly higher number of body torsions and attempts to reach the hook than WT mice. Of note, the number of fecal boli produced during exposure to the tail suspension was also significantly reduced in MAO A KO mice in comparison to WT counterparts. MAO A KO mice also typically exhibit a reduction in acoustic startle reaction [49]. Interestingly, these data are in keeping with recent evidence showing that MAO A KO display attenuated endocrine responses to major stressors, such as restraint, cold temperature, prolonged water deprivation and chronic variable stress [59].

Overall, these results strongly suggest that MAO A KO mice may display impairments in the perception of external stress and in the mediation of adaptive responses to stress, which could also underpin the dramatic increase in aggressive behaviors against both intruders and cage mates. The psychological evaluation of aggressive traits in Brunner syndrome, a genetic disorder caused by a nonsense mutation of MAO A gene, reveals that the affected subjects respond to relatively trivial stimuli or as a manifestation of bereavement with impulsive aggression and violent acts [60]. These alterations may be underpinned by sensory dysregulation, as suggested by the disruption of the barrel fields in the somatosensory cortex [49]. Interestingly, this alteration may actually parallel the enhanced aggression of MAO A-deficient mice. In fact, administration of the 5-HT synthesis inhibitor *p*-chlorophenylalanine to MAO A KO mice reverses both the structural changes and the aggressive behavior of adults [61]. Further clues to the possible links between alterations in somatosensory cortex and aggression come from the work of Chen et al [62], who observed that both aggressive phenotype and the alterations of the barrel fields were rescued by a forebrain-specific knock-in approach of MAOA into MAO A KO mice.

MAO B KO mice

MAO B KO mice show increased brain levels of PEA, but not 5-HT, NE and DA. This alteration was not associated with significant changes in locomotor patterns in the open field and in the elevated plus maze, but it did reduce immobility time in the forced swim test, upon single or repeated presentation [50].

While low MAO B levels have been repeatedly associated with increased responsiveness to novelty, extraversion and behavioral disinhibition the experimental observations in our lab do not seem to confirm this trait in MAO B KO mice. For example, MAO B KO mice fail to exhibit differences in nicotine consumption and preference in comparison with WT animals [63] and engage in social encounters less than WT counterparts (unpublished data). One of the reasons underlying this discrepancy may reflect the observation that, while in humans MAO B exerts a remarkable contribution to DA metabolism, this role is mainly served by MAO A in rodents [64]. Indeed, MAO B KO mice do not display apparent alterations in DA release or reuptake [65].

It is not surprising that the phenotypical alterations observed so far in MAO B KO mice are more subtle than those in MAO A KO mice, since PEA is present in very small concentrations in the brain [66,67] and is thought to serve amphetamine-like functions in the modulation of the neurotransmission and signaling of DA and NE [68,69]. PEA is co-synthesized with dopamine by L-DOPA decarboxylase [70].

In particular, recent lines of evidence indicate that PEA is the main activator of the trace-amine-associated-receptor 1 (TAAR1) [71,72], which, in turn, modulates cathecolaminergic signaling [72]. Interestingly, MAO B KO mice display several abnormalities that may be linked to the

alterations induced by high levels of PEA: for example, they display attenuation of the hyperlocomotive effects of amphetamine [73], as well as alterations in the distribution of cerebral blood flow [74]. PEA is also likely responsible for a reduction in D2-like receptors and a supersensitivity of D1 receptors in the striatum of these mutant animals [65].

Recently, PEA and TAAR1 have attracted attention as potentially important targets for schizophrenia, mania, ADHD, and methamphetamine dependence [72]. MAO B KO mice represent a unique model to study the long-term consequences of high levels of PEA in behavior and brain function.

MAO AB KO mice

We have recently characterized and developed a novel line of MAO AB KO line, harboring a spontaneous point mutation of MAO A and ablation of MAO B [51]. These mice display an array of unique phenotypes, which cannot be recapitulated by the mere summation of MAO A KO and MAO B KO. Levels of PEA, 5-HT, NE and DA are highly increased in comparison to MAO A and MAO B KO. Furthermore, the behavioral phenotype in these mutant animals is characterized by low novelty-induced locomotion, high levels of anxiety-like behaviors in the elevated-plus maze, low latency to attack in the resident-intruder paradigm [51].

5. A role for oxidative stress in the outcomes of MAO inactivation?

As discussed above, the wealth of evidence suggests that the therapeutic potentials of MAO A and MAO B inhibition overlap significantly. In fact, MAO A inactivation elicits antidepressant effects and is also an effective strategy in the therapy of PD, as indicated by the clinical effects of RIMAs. In parallel, MAO B inhibitors have neuroprotective properties; moreover, deprenyl has also been shown to significantly ameliorate depressive symptoms [75–77], and MAO B KO mice display lower levels depression-like behaviors [50], suggesting that MAO B also plays a role in responsiveness to stress and, maybe, in the pathophysiology of depression.

In line with this scenario, it is tempting to suggest that additional mechanisms, not strictly related to the monoamine substrates of depression, may underpin some of the therapeutic effects of MAO inhibitors. An intriguing mechanism may be the reduction of the oxidative stress and redox unbalance induced by MAO activation. As mentioned before, peroxide is one of the byproducts of MAO reactions, and the therapeutic action of deprenyl and rasagiline in Parkinson's disease and other neurodegenerative disorders has been extensively linked to the reduction of the oxidative stress mediated by ROS. Conversely, the role of oxidative stress and mitochondrial damage in depression and anxiety has emerged only recently [78]. Growing evidence highlights that patients affected by depression exhibit a significant increase in immune-inflammatory markers [79–81], which in turn lead to production of ROS and oxidative stress [82,83]. Accordingly, preliminary studies have shown that plasma of patients affected by major depression displays significantly lower total antioxidant potential and higher peroxide levels than controls [84]. Furthermore, severity of depression is generally inversely correlated to several indices of oxidative stress [85–87]. Although very little is currently known on the role of oxidative stress in anxiety, it is remarkable that the anxiety-spectrum disorders where an implication of oxidative stress has been shown are the same addressed by MAO inhibitors: obsessive-compulsive disorder [88,89], panic disorder [90], social phobia [91] and post-traumatic stress disorder [92].

These concepts suggest that stress-induced activation of MAO may cause oxidative damage to the mitochondrion. Accordingly, we have shown that the non-specific MAO inhibitor, used in therapy for its antidepressant properties, abolishes the oxidative damage induced by the oxygen peroxyde generated during the MAO-catalyzed oxidation of tyramine [93]. The dysregyulation of redox balances and mitochondrial damage induced by MAO activation may

result in neuronal apoptosis and brain damage. Indeed, in previous work we have shown that serum-starvation-induced apoptosis increases MAO A levels and is typically reduced in MAO A deficient cortical neuronal cell cultures [16]. Furthermore, we found that neurodegenerative toxicity and striatal lesions induced by malonate are greatly attenuated by both MAO A and MAO B inhibition [94].

In conclusion, oxidative stress may account for some of the therapeutic functions of MAO A and B in behavioral regulation. This possibility implies that the differential anatomical expression and distribution of the two MAO isoforms in the brain may be a critical factor to define their role in the pathogenic processes underpinned by oxidative stress, as well as in the therapeutic actions mediated by MAO A and MAO B inhibitors. MAO A, B and AB KO represent unique models to explore this fascinating hypothesis and to gain insight into new therapeutic horizons for psychiatric disorders.

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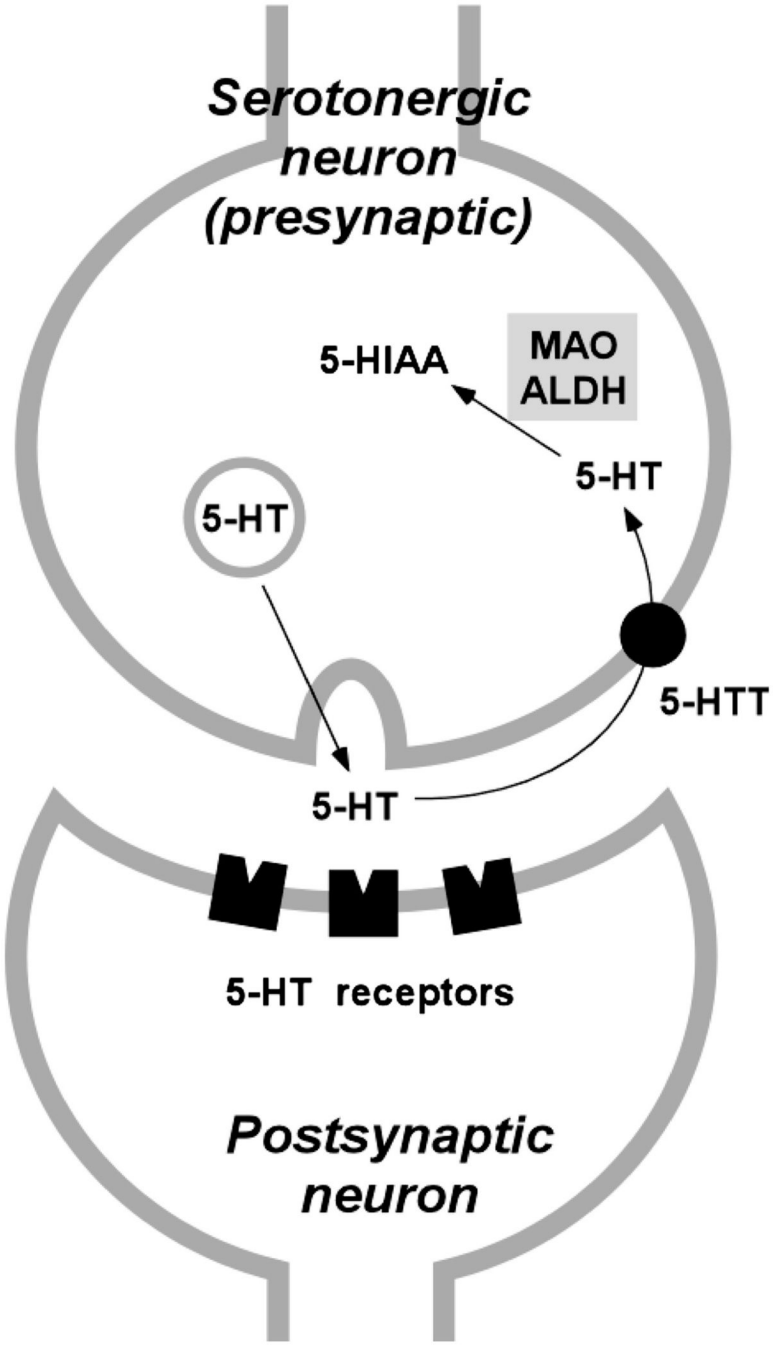

Figure 1. Synaptic processing of serotonin (5-HT)

Following release, 5-HT receptor activation and reuptake by 5-HT transporter (5-HTT), serotonin is degraded by MAO (monoamine oxidase) and ALDH (aldehyde dehydrogenase) into 5-hydroxyindole-3-acetic acid (5-HIAA).

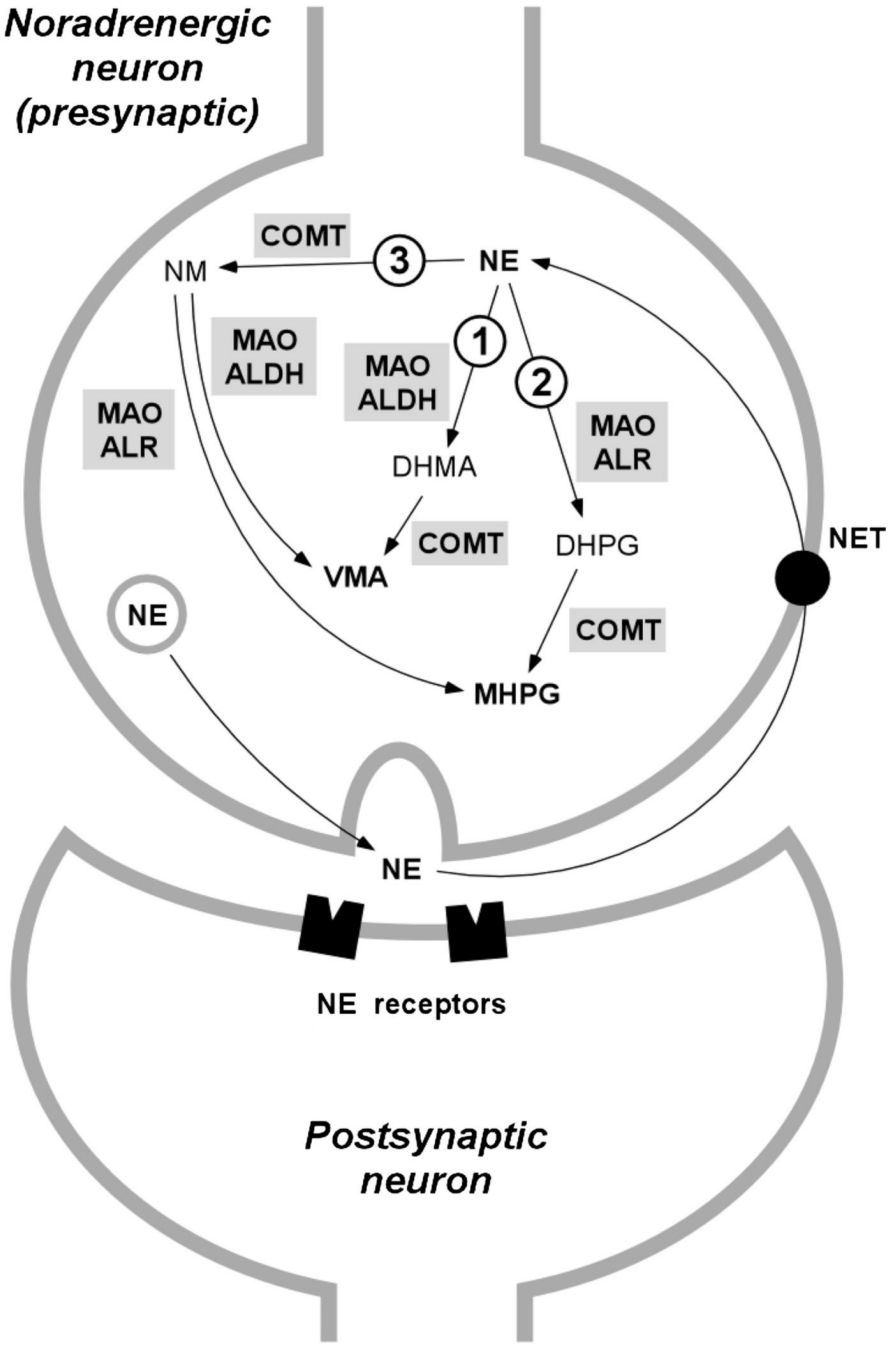

Figure 2. Synaptic processing of norepinephrine (NE)

Following release, NE receptor activation and reuptake by NE transporter (NET), NE is degraded by three main enzymatic pathways. (1) In the first pathway, MAO (monoamine oxidase) and ALDH (aldehyde dehydrogenase) convert NE into 3,4-dihydroxymandelic acid (DHMA); this compound is then processed by catechol-*O*-methyltransferase (COMT) into vanillylmandelic acid (VMA). (2) In the second pathway, MAO and ALR (aldehyde reductase) convert NE into 3,4-dihyroxyphenylglycol (DHPG), which is further degraded by COMT into 3-methoxy-4-hydroxyphenylglycol (MHPG). (3) In the third pathway, COMT metabolizes NE into normetanephrine (NM), which is then converted into either MHPG (via MAO/ALR) or VMA (via MAO/ALDH).

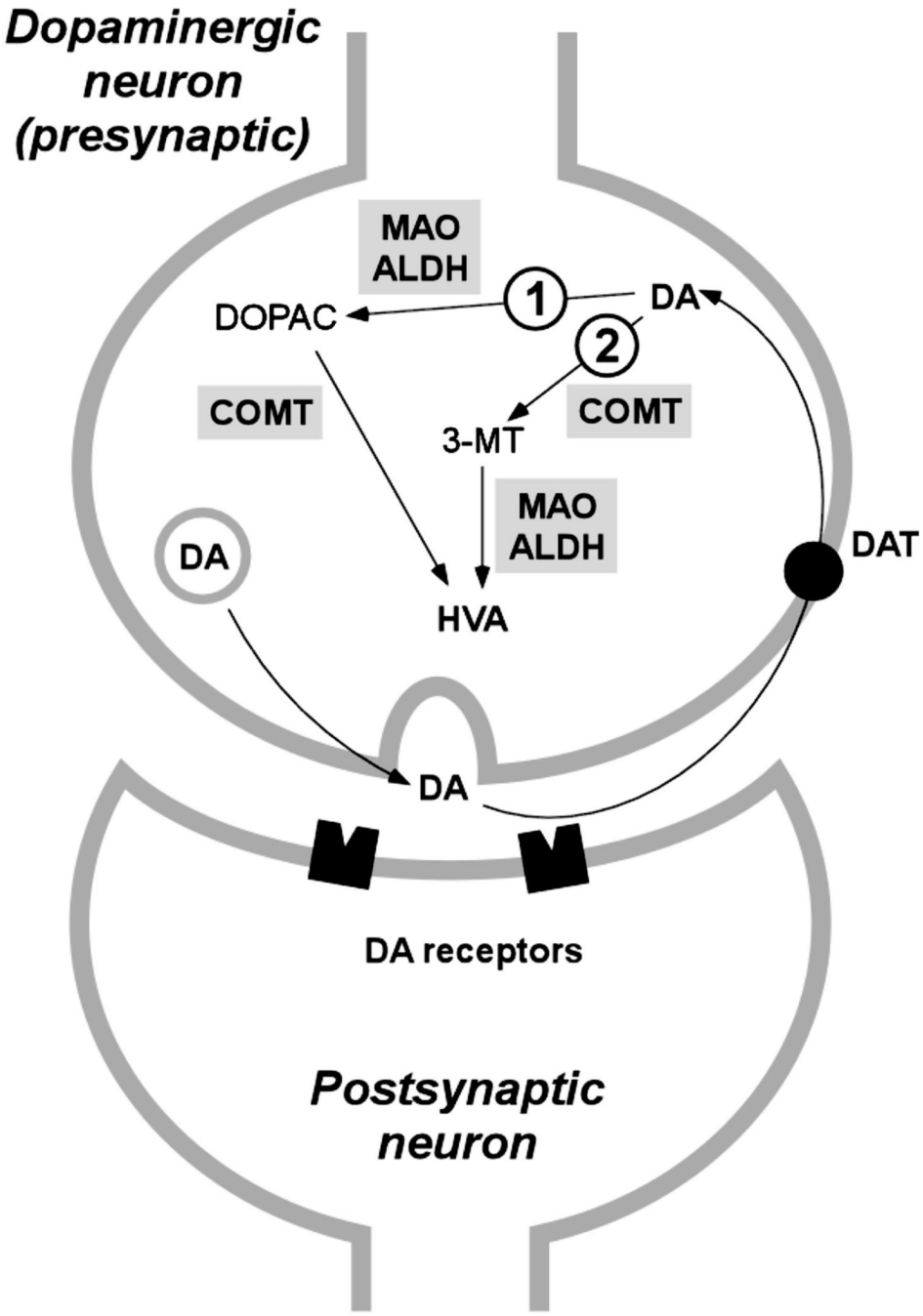

Figure 3. Synaptic processing of dopamine (DA)

Following release, DA receptor activation and reuptake by DA transporter (DAT), DA is degraded by two main enzymatic pathways. (1) In the first pathway, MAO (monoamine oxidase) and ALDH (aldehyde dehydrogenase) convert DA into 3,4-dihydroxyphenylacetic acid (DOPAC); this compound is then processed by catechol-*O*-methyltransferase (COMT) into homovanillic acid (HVA). (2) In the second pathway, COMT metabolizes DA into 3-methoxytyramine (3-MT), which is then converted into HVA by MAO and ALDH.

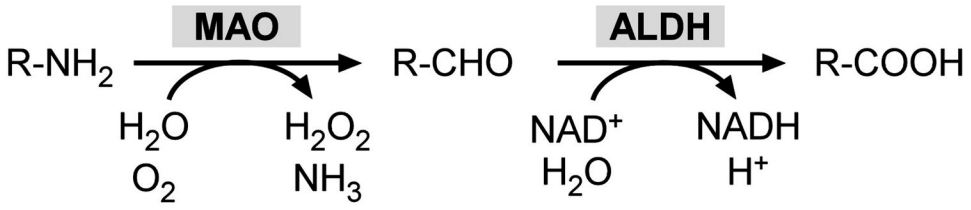

Figure 4. MAO catalyzes the oxidative deamination of monoamines

Monoamines are degraded by MAO to their correspondent aldehydes (R-CHO). This reaction produces also ammonia (NH_3) and hydrogen peroxide (H_2O_2). Aldehydes are further oxidized by aldehyde dehydrogenase (ALDH) into carboxylic acids (R-COOH). NADH is a critical cofactor for this latter reaction.

Table 1

MAO inhibitors

Group	Class	Compound	MAO selectivity
Non-selective	Hydrazines	Isocarboxazid	A and B
		Phenelzine	A and B
		Nialamide	
		Iproniazid	A and B
		Iproclozide	
	Amphetamine derivates	Tranylcypromine	A and B
Selective – irreversible	Propargylamines	Clorgyline	A
		Selegiline	B
		Rasagiline	B
Selective – reversible (RIMAS)	Piperidylbenzofurans	Brofaromine	A
	Morpholinobenzamides	Moclobemide	A
	Oxazolidinones	Toloxatone	A
		Linezolid	A
		Befloxatone	A
		Cimoxatone	A
Mixed MAO-cholhesterase inhibitors	Propylamines	Ladostigil	A and B

Table 2

Behavioral and neurochemical characteristics features of MAO A, MAO B and MAO AB KO mice (compare to WT)

Phenotypical features		**MAO A KO**	**MAO B KO**	**MAO AB KO**
Neurotransmitter levels	5-HT (serotonin)	200% ↑	-	700% ↑
	NE (norepinephrine)	130% ↑	-	200% ↑
	DA (dopamine)	110% ↑	-	200% ↑
	PEA (phenylethylamine)	-	700% ↑	1400% ↑
Locomotor activity	Open field	↓	-	↓↓
Startle reactivity		↓	?	?
Aggression	Resident-intruder aggression	↑↑	-	↑
	Aggression in familiar environment	↑	-	↑
Anxiety and fear	Plus-maze anxiety	-	-	↑
	Open-field anxiety (periphery/center ratio)	-	-	↑↑
	Fear conditioning	↑	?	?
Depression	Immobility time in forced swim test	↓	↓	?
	Immobility time in tail suspension test	↓	?	?

Keys: ↑: increase; ↓: decrease; -: no change; ?: unknown.