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Modulation of monoamine oxidase (MAO) expression in neuropsychiatric disorders: genetic and environmental factors involved in type A MAO expression

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Abstract Monoamine oxidase types A and B (MAO-A, MAO-B) regulate the levels of monoamine neurotransmitters in the brain, and their dysfunction may be involved in the pathogenesis and influence the clinical phenotypes of neuropsychiatric disorders. Reversible MAO-A inhibitors, such as moclobemide and befloxatone, are currently employed in the treatment of emotional disorders by inhibiting the enzymatic degradation of dopamine, serotonin and norepinephrine in the central nervous system (CNS). It has been suggested that the irreversible MAO-B inhibitors selegiline and rasagiline exert a neuroprotective effect in Parkinson's and Alzheimer's diseases. This effect, however, is not related to their inhibition of MAO activity; in animal and cellular models, selegiline and rasagiline protect neuronal cells through their anti-apoptotic activity and induction of pro-survival genes. There is increasing evidence that MAO-A activity, but not that of MAO-B, is implicated in the pathophysiology of neurodegenerative disorders, but also in gene induction by MAO-B inhibitors; on the other hand, selegiline and rasagiline increase MAO-A mRNA, protein, and enzyme activity levels. Taken together, these results suggest that each MAO subtype exerts effects that modulate the expression and activity of the other isoenzyme. The roles of MAO-A and -B in the CNS should therefore be re-evaluated with respect to the "type-specificity" of their inhibitors, which may not be unconditional during chronic treatment. *Mao-a* expression, in particular, may be implicated in pathogenesis and phenotypes in neuropsychiatric disorders. MAO-A expression is modified by *mao* polymorphisms affecting its transcriptional efficiency, as well as by mutations and polymorphism of parkin, Sirt1, FOXO, microRNA, presenilin-1, and other regulatory proteins. In addition, childhood maltreatment has been shown to have an impact upon adolescent social behavior in children with *mao-a* polymorphisms of low transcriptional activity. Low MAO-A activity may increase the levels of serotonin and norepinephrine, resulting in disturbed neurotransmitter system development and behavior. This review discusses genetic and environmental factors involved in the regulation of MAO-A expression, in the contexts of neuropsychiatric function and of the regulation of neuronal survival and death.

Keywords Monoamine oxidase · Types A and B MAO · Mitochondria · Expression · Genetic and environmental factor · Neurodegenerative disorders · Abnormal behavior · Cell death · Neuroprotection

Abbreviations

AD	Alzheimer's disease
BDNF	Brain-derived neurotrophic factor
CNS	Central nervous system
DA	Dopamine
DISC1	Disrupted-in-schizophrenia 1

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DSP-4	*N*-(2-Chloroethyl)-*N*-ethyl-2-bromobenzylamine
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
GDNF	Glial cell line-derived neurotrophic factor
5-HT	5-Hydroxytryptamine (serotonin)
KLF11	Krüppel-like factor
LRRK-2	Leucine repeat-rich kinase 2
MAO-A and MAO-B	Type A and B monoamine oxidase
MAPK	Mitogen-activated protein kinase
MDMA	3,4-Methylenedioxymethamphetamine
NE	Norepinephrine
NGF	Nerve growth factor
NHLH2	Nescient helix loop helix transcription factor 2
NMDA	*N*-Methyl-D-aspartate
NT-3	Neurotrophic factor-3
PD	Parkinson's disease
PEA	Phenylethylamine
ROS	Reactive oxygen species
SNP	Single-nucleotide polymorphisms
UPS	Ubiquitin−proteasome system
VPA	Valproic acid (2-propylpentanoic acid)

Introduction

Monoamine oxidase [monoamine: oxygen oxidoreductase (deaminating), EC 1.4.3.4, MAO] catalyzes the oxidative deamination of monoamine neurotransmitters, dietary amines, hormones and drugs in the brain and peripheral tissues, thereby regulating their levels and biological functions. The oxidation of monoamines by MAO produces the corresponding aldehydes and hydrogen peroxide, a potent reactive oxygen species (ROS), and oxidative stress induced by MAO is potentially a risk factor for neuronal loss in aging and age-related neurodegenerative disorders, such as Parkinson's disease (PD). The action of the selective MAO inhibitors, clorgyline [3-(2,4-dichlorophenoxy)-*N*-methyl-*N*-prop-2-ylyl-propan-1-amine] and selegiline [(−)deprenyl, (2*R*)-*N*-methyl-1-phenyl-*N*-pro-2-ynyl-propan-2-amine] allowed the differentiation of two MAO isoenzymes, types A and B (MAO-A, MAO-B) (Johnston 1968; Youdim and Bakhle 2006), that exhibit different affinities for their substrates: serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine (NE) are more efficiently oxidized by MAO-A, while phenylethylamine (PEA), benzylamine, and octopamine are primarily metabolized by MAO-B. Dopamine (DA) and tyramine are the substrates for both MAO-A and -B in the rodent brain, but in the human brain DA is preferentially oxidized by MAO-B (Fornai et al. 1999; Glover et al. 1977).

The molecular and genetic characteristics of both MAO-A and -B have been characterized. They are composed of different proteins, but share 70 % identical amino acid sequences, and the same coenzyme, FAD, is bound to the cysteine of a pentapeptide sequence, Ser-Gly-Gly-Cys-Tyr, via a covalent thioester linkage. They are encoded by distinct but adjacent genes on the X chromosome, arranged tail-to-tail and running in opposite directions, and have identical patterns of intron and intron–exon organization (Edmondson et al. 2007; Shih et al. 1999, 2011). These results suggest that these *mao* genes are derived from the duplication of a common ancestral gene (Grimbsby et al. 1991). The expression of *mao-a* and *mao-b,* however, is differentially regulated by their divergent promoter organization (Shih et al. 2011).

MAO-A and MAO-B are expressed in the brain and most peripheral tissues, and are localized on the mitochondrial outer membrane. In the brain, MAO-A occurs predominantly in catecholaminergic neurons, MAO-B in serotonergic and histaminergic neurons and astrocytes (Riederer et al. 1989: Saura et al. 1996; Tong et al. 2013); MAO-B accounts for more than 80 % of total MAO activity in the human brain (Collins et al. 1970a). In peripheral tissues, MAO-A is predominant in fibroblasts and placental tissue, whereas MAO-B activity is greater in platelets and lymphocytes. The expression of MAO subtypes in cells synthesizing the substrates of the other isoenzyme suggests that these oxidases may protect their host cells by also degrading these substrates.

The major substrates of MAO-A, 5HT, NE and DA, are neurotransmitters essential to central nervous system (CNS) function, and their levels are partially regulated by MAO-dependent degradation. The signal pathways activated by these monoamines modulate mood, emotion, motor, perceptual and cognitive functions. Abnormal MAO-A activity is therefore associated with psychiatric dysfunction (Shih et al. 1999), as up- or down-regulation of its expression affects emotional and behavioral phenotypes via the enhanced or diminished oxidation of 5-HT and NE (Meyer et al. 2006; Bortolato et al. 2008; Johnson et al. 2011). Reversible MAO-A inhibitors, moclobemide [4-chloro-*N*-(2-morpholin-4-ylethyl)benzamide], and befloxatone ((5*R*)-5-(methoxymethyl)-3-[4-[(3*R*)-4,4,4-trifluoro-3-hydroxyl-butoxy]-phenyl]-1,3-oxazolidin-2-one), are accordingly employed as therapeutic agents for depression and anxiety disorders.

On the other hand, MAO-B produces ROS, as well as toxins from pro-toxicants, such as the 1-methyl-4-phenylpyridinium ion (MPP^+) from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Heikkila et al. 1984);

conversely, increased hydrogen peroxide levels enhanced MAO-B activity, but not that of MAO-A (Konradi et al. 1966). This identification of "MAO-B" as a potential pathogenic factor in PD stimulated the development of MAO-B inhibitors as disease-modifying agents; selegiline and rasagiline [(1*R*)-*N*-prop-2-ynyl-2,3-dihydro-1*H*-amine], for example, protect neuronal cells in cellular and animal models (Ebadi et al. 2006; Youdim et al. 2006; Magyar 2011; Naoi et al. 2013a).

The role of MAO itself in neuronal death, moreover, should be re-evaluated in light of recent results achieved in animal and cellular models, in which MAO expression is knocked out or knocked in. The current paper reviews the role of MAO isomers in the regulation of neuronal death and survival, as well as in other CNS functions. The involvement of MAO in neuroprotection by MAO-B inhibitors will be re-evaluated with respect to the induction of anti-apoptotic, pro-survival genes, as is the MAO-type specificity of inhibitors in these effects. The MAO-B inhibitors rasagiline and selegiline, as well as the preferential MAO-B substrate PEA, induce *mao-a* expression (Inaba-Hasegawa et al. 2013; also further paper in preparation), so that the MAO-B activity may modify the expression and function of MAO-A. Finally, deficient MAO expression during development has been reported to increase the risk for antisocial behaviors in adolescence and adulthood, and the interaction of genetic and environmental factors will be discussed in the context of a potential link between MAO activity and the pathogenesis and phenotypes of neuropsychiatric disorders.

The role of MAO-A and MAO-B in neuronal loss

Monoamine oxidase types A has been associated with apoptosis induced by neurotrophic factor deprivation in PC12 cells: the mRNA levels and activity of MAO-A were increased during apoptosis, and both MAO-A activation and apoptosis were prevented by clorgyline and PD169316, an inhibitor of p38 mitogen-activated protein kinase (MAPK) (De Zutter and Davis 2001). In serum starvation-induced apoptosis in human neuroblastoma SK-N-BE(2)-C cells, the transcription factor R1 (RAM2/CDCA7L/JPO2) was down-regulated, and MAO-A expression increased; apoptosis was attenuated in MAO-A deficient mice, suggesting a direct role for MAO-A in cell death (Ou et al. 2006a). Yi et al. (2006) reported that the pro-apoptotic DA neurotoxin, *N*-methyl(*R*)salsolinol, competitively binds MAO-A and activates mitochondrial apoptosis signaling in SH-SY5Y cells; down-regulation of MAO-A expression by short interfering RNA (siRNA) reduced both toxin binding and cell death, whereas MAO-B overexpression affected neither binding nor toxicity. In another study, MAO-A activity was increased via post-transcriptional modification during staurosporine-induced apoptosis, and enhanced apoptotic signaling via increased oxidative stress (Fitzgerald et al. 2007). Rotenone, a complex I inhibitor, induced apoptosis in SH-SY5Y cells via oxidative stress, and this was accompanied by increased MAO-A mRNA, protein and activity levels; MAO-A knockdown by targeted microRNA (miRNA) reduced ROS generation, but increased complex I activity and ATP levels, as well as those of glutathione and Bcl-2, suggesting that MAO-A may down-regulate basal mitochondrial function (Fitzgerald et al. 2014).

CNS MAO-B activity increases with age, and this may play a major role in neurodegeneration secondary to ROS production and neurotoxins. MAO-B-deficient mice were resistant to MPTP toxicity (Grimsby et al. 1997), and MAO-B expression increased the sensitivity to MPTP in PC12 cells that originally express only MAO-A (Wei et al. 1996). The role of MAO-B was examined in the cytotoxicity of a NE toxin, *N*-(2-chloroethyl)-*N*-ethyl-2–bromobenzylamine (DSP-4), and of a 5-HT toxin, 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") in MAO-B deficient mice: while DSP-4 markedly depleted NE in both wild and MAO-B knockout mice, indicating that MAO-B was not involved in its toxicity, MDMA caused massive loss of both 5-HT and DA in wild-type animals, but in MAO-B deficient mice DA depletion was much more profound than in wild-type mice (Fornai et al. 2001). MAO-B may also be involved in MDMA-induced loss of 5-HT, which can be prevented by selegiline (Sprague and Nichols 1995) or MAO-B knockdown with an antisense oligonucleotide (Falk et al. 2002). The mechanism underlying the role of MAO-B in 5-HT depletion has, however, not been clarified, whereas MDMA is a potent MAO-A inhibitor. Specific binding of [^{3}H-methyl]-L-deprenyl to brain tissue was abolished by MAO-B knockout mice (Ekblom et al. 1998), as was the protection afforded by selegiline in ischemic infarction, cerebral edema and neurological impairment (Holschneider et al. 1999). To elucidate the role of MAO isoenzymes in neuronal death, however, these results must be further explored in MAO-A knockout animals exposed to other neurological and neurotoxic insults.

A new aspect of the "MAO-B dogma" in PD: MAO meets parkin

The *mao-b* gene is a candidate pathogenic factor for PD, and a G/A polymorphism in intron 13 was associated with an approximately twofold increased risk for PD (Tan et al. 2000; Singh et al. 2008). In one study, G/A dimorphism influenced *mao-b* processing by enhancing intron 13

removal efficiency, and was associated with increased MAO-B protein and activity levels in PD patient platelets (Jakubauskiene et al. 2012); another, however, could not confirm these findings (Hernan et al. 2002). Further, immunochemical studies in parkinsonian brains could not establish the direct involvement of MAO-B in neuronal loss: cell loss in MAO-B-containing DA cells of the substantia nigra pars compacta was no greater than in MAO-B-negative DA neurons. Astrocytes express increased levels of MAO-B in PD as a consequence of neuroinflammation, but they may offer neuroprotection by their removal of toxic molecules from the extraneuronal space and the release of trophic factors and antioxidant molecules (Damier et al. 1996). MAO-B elevation in PD does not, therefore, necessarily entail the involvement of MAO-B in neuronal loss.

Mutations of several genes, including those encoding α-synuclein (PARK1), parkin (PARK2), ubiquitin-C-hydrolase-L1 (Uch-L1, PARK5), PINK-1 (PARK6), DJ-1 (PARK7) and LRRK2, have been reported in the familial form of PD, some of which are also associated with nigrostriatal DA neuronal degeneration in idiopathic PD (Cookson and Bandmann 2010; International Parkinson Disease Genomic Consortium 2011). Parkin, a protein-ubiquitin-E3 ligase, targets the substrates for the ubiquitin–proteasome system (UPS), and its dysfunction causes selective degeneration of DA neurons and the accumulation of α-synuclein, a major component of Lewy bodies. MAO transcription is down-regulated by parkin (Jiang et al. 2006), and MAO-B activity in *parkin*-knockout mice is increased, with elevated DOPAC levels (Itier et al. 2003). In SH-SY5Y cells and mouse fibroblast cell line NIH3T3 cells, *parkin* transfection decreased the MAO-B mRNA, protein and activity levels (Casarejos et al. 2005), whereas it did not increase the ubiquitination and degradation of MAO-A (Jiang et al. 2006). MAO expression was increased significantly in B lymphocyte cell lines derived from PD patients with homozygous deletion of exon 4 in *parkin* (Jiang et al. 2006). These results indicate that parkin suppresses MAO expression, whereas *parkin* mutation not only impairs the UPS, but also up-regulates MAO levels, increasing DA oxidation, thereby inducing cell death (Fig. 1). Conversely, elevated MAO-B levels decreased the ability of parkin to clear damaged mitochondria (Siddiqui et al. 2012).

Parkin mediates the degradation of estrogen-related receptors (ERRs), which may account for its suppression of MAO expression (Ren et al. 2011). A nuclear orphan receptor and its co-activator, peroxisome proliferator-activated receptor (PPAR) cofactor 1 [(PGC-1), induce *mao-a* and *mao-b* in HeLa and SH-SY5Y cells and in rat midbrain neuronal cultures by binding to the ERR binding site in the human *mao* promoter (Willy et al. 2004; Zhang et al. 2006; Jiang et al. 2006)]. ERR is a transcription factor of the nuclear receptor superfamily, and induces genes involved in mitochondrial oxidative metabolism and biogenesis. Parkin was found to bind ERRs (α, β and γ) and increase their ubiquitination and degradation, while *parkin* transfection suppressed ERR-mediated induction of endogenous *mao-a* and *mao-b* (Schreiber et al. 2003).

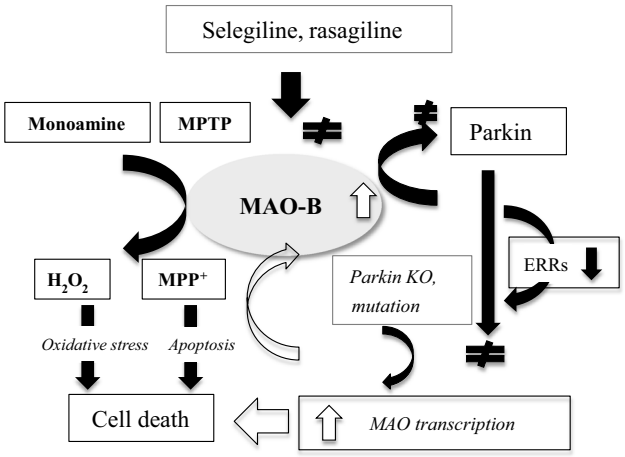

Fig. 1 The role of MAO-B in the neuronal death in neurodegenerative disorders. MAO oxidizes monoamine substrates to produce ROS, and MPTP to MPP^+, activating death signal pathway (apoptosis). According to the previous "MAO-B hypothesis", MAO-B inhibitors inhibit enzymatic oxidation and subsequent death processing. Parkin suppresses MAO-B expression directly, or indirectly by degradation of estrogen-related receptors (ERRs), but a parkin mutation activates transcription of MAO and accelerates cellular dysfunction

In summary, parkin suppresses MAO-B expression, and mutations that reduce its activity increase MAO-B-catalyzed oxidation of monoamines, and the consequently elevated ROS production poses a threat to DA neurons.

"MAO-B-selective" inhibitors also bind to MAO-A

An important issue concerning the role of MAO-B in neuronal function and death is the question of whether MAO-B inhibitors are truly type-specific in vivo after long-term administration (Riederer and Lachenmayer 2003). Type-specificity of MAO inhibitors is limited to specific concentration ranges; rasagiline, for instance, also binds to MAO-A and inhibits its enzymatic activity in vitro, despite its affinity for MAO-A (inhibitor constant (K_i) = 9.7 μM) being much lower than for MAO-B (K_i = 0.7 μM) (Hubalek et al. 2004). At higher concentrations, rasagiline irreversibly inactivates both MAO-A and MAO-B by forming a covalent adduct with the flavin cofactor, as in the case with MAO-B, whereas aminoindan, a rasagiline metabolite, inhibits both isoenzymes, but does not covalently bind the cofactor (Binda et al. 2005).

Specific MAO-B inhibitors also suppress MAO-A activity at the higher doses in vivo. The inhibition of MAO-A and -B in the brain is usually estimated by measuring the metabolites of the type-specific substrate employed, either 5-HT (MAO-A) or PEA (MAO-B). MAO-B activity in the rat striatum was reduced by more than 90 % after a single administration of selegiline (2.5 mg/kg body weight), or rasagiline (1 mg/kg), but MAO-A activity was also 40 % lower (Youdim and Tipton 2002). The half-life for recovery of MAO-B following a single injection of selegiline was 4–9 days in rats (Green et al. 1977; Felner and Waldmeier 1979; Youdim and Tipton 2002), but 2–3 days in humans (Clarke et al. 2003). Five days' treatment at a higher dose of selegiline (5 mg/kg) administered subcutaneously inhibited MAO-A activity in the rat brain by 85 and MAO-B by 99.9 %, but only by 18 and 92 %, respectively, if administered orally (Magyar 2011). Following long-term treatment (21 days) with selegiline (0.25 mg/kg) or rasagiline (0.05 mg/kg), rat striatal MAO-A activity was reduced by 40 and 15 %, respectively, whereas MAO-B activity was almost totally abolished; clorgyline (0.2 mg/kg) inhibited MAO-A activity by 95 %, and that of MAO-B by 30 % (Lamensdorf et al. 1996). Long-term treatment of the common marmoset with rasagiline (0.1 mg/kg, 7 days) selectively inhibited brain MAO-B activity by 80 %, but at 0.5 mg/kg also inhibited MAO-A (Götz et al. 1997). These results suggest that the administration form and route each influence the plasma and CNS drug concentrations achieved, as well as the MAO type-specificity, as confirmed for 'Zydis Selegiline' (buccal absorption) in humans (Clarke et al. 2003).

The type-specific binding of MAO inhibitors can also be assessed by radioactively or photo-labeled irreversible inhibitors that bind to the isoalloxazine ring of the FAD cofactor via an 8α-(*S*-cysteinyl) linkage. For activity-based protein profiling, derivatives of pargyline (*N*-methyl-*N*-propargylbenzylamine) and selegiline have been employed to detect MAO-A and MAO-B, respectively. Type-specificity was confirmed, but the in situ labeling was not correlated with enzymatic activity and protein levels. In addition, both isolated and membrane-bound MAO, as well as enzyme localized in mitochondria or cytoplasm, exhibited varying affinities for ligands, underlining the difficulty involved in quantitative determination of in vivo MAO inhibitor binding (Krysiak et al. 2012).

A 70 % reduction of plasma MAO-A activity was recently reported in parkinsonian patients treated with rasagiline or selegiline on a long-term basis, in comparison with both patients not receiving MAO-B inhibitors and with healthy controls (Bartl et al. 2014).

In summary, these results clearly demonstrate that the type-specificity of MAO-B inhibitors is not absolute with regard to their entire spectrum of effects: the MAO-B inhibitors selegiline and rasagiline can bind MAO-A as well as MAO-B, and this is potentially relevant to their effects upon brain function.

Role of MAO in neuroprotection by MAO-B inhibitors

Selegiline was reported to prolong life expectancy in PD when used as an adjunct to L-DOPA therapy, suggesting its neuroprotective potency (Birkmayer et al. 1985). Selegiline also protected neuronal cells in mice against the neurotoxicity of a noradrenergic toxin, DSP-4 (Yu et al. 1994), of the excitotoxin, *N*-methyl-D-aspartate (NMDA) (Shimazu et al. 1999), of the recreational drug 'ecstasy' (MDMA, Alves et al. 2007), as well as that of the DA neurotoxin, MPTP. We have previously reviewed in vivo neuroprotection by rasagiline (Naoi and Maruyama 2010).

The mechanism underlying neuroprotection has been most intensively studied in cellular models. Selegiline and rasagiline suppress mitochondrial death signal pathways and induce pro-survival genes, including those for the anti-apoptotic Bcl-2 protein family, and of neurotrophic factors (Wadia et al. 1998; Akao et al. 2002; Maruyama et al. 2001, 2004; Tatton et al. 2002; Naoi et al. 2006, 2011, 2013b). MAO-A mediated Bcl-2 induction by rasagiline in SH-SY5Y cells, an effect suppressed by knockdown of MAO-A expression with siRNA. Rasagiline neither induce Bcl-2 in MAO-B overexpressed SH-SY5Y cells nor in MAO-B-expressing human colon carcinoma Caco-2 cells (Inaba-Hasegawa et al. 2012) and glial U118MG cells (Inaba-Hasegawa et al. 2015), suggesting that MAO-B itself is not involved in Bcl-2 induction by this inhibitor. Further, the concentration of rasagiline that induces Bcl-2 is much lower than that inhibits MAO-A (picomolar rather than micromolar, Inaba-Hasegawa et al. 2012).

Induction of pro-survival genes by rasagiline and selegiline has been confirmed in vivo in the , mouse and non-human primate (Weinreb et al. 2005, 2009; Gyárfás et al. 2010; Maruyama and Naoi 2013). Daily administration of rasagiline to Japanese monkeys increased the cerebrospinal fluid (CSF) levels of the neurotrophins glial cell-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), neurotrophic factor-3 (NT-3), and nerve-growth factor (NGF) (Maruyama and Naoi 2013).

Clinical trials of selegiline and rasagiline in PD patients have achieved beneficial symptomatic results, but further evidence is required to determine whether they can arrest or even reverse disease progression (Riederer et al. 2004; Finberg 2010). The contribution of MAO inhibition to improvement is generally assessed by comparing the enzyme activity with the degree of clinical benefit. Recent findings, however, indicate that any

protective effect is not dependent upon MAO inhibition, so that the role of MAO in neuroprotection effected by these inhibitors should be assessed using different criteria (Gerlach et al. 2012), improved study designs for evaluation of its disease-modifying activity (Ahlskog and Uitti 2010), and clinical markers, such as BDNF levels, an increase in which was confirmed in the CSF following selegiline treatment in parkinsonian patients (Maruyama and Naoi 2013).

Rasagiline and selegiline may bind to MAO at the sites other than the substrate-binding site. An I_2-type binding site for imidazoline has been identified on MAO-B: the amino acid sequence 149–222 for this site was established by photoaffinity labeling (Raddatz et al. 1995). I_2 ligands bind and inhibit MAO-A and -B both in vivo and in vitro (Saura et al. 1992; Ozaita et al. 1997). The I_1 receptor was identified as a target for the *S*-enantiomer of rasagiline, TV1022, via which the inhibitor increased the levels of phosphorylated p42 and p44 MAPK in PC12 cells and neonatal rat ventricular myocytes, and protected the cells from serum deprivation-induced apoptosis. 5-HT inhibited the specific binding of TV1022, suggesting the localization of I_1 receptor on MAO-A (Barac et al. 2012). It remains to be confirmed, however, whether binding to the I_1 receptor increases pro-survival Bcl-2 and neurotrophic factor levels.

MAO inhibitors may also bind proteins other than MAO (Holt et al. 2004). A PET study found that [^{11}C]clorgyline and its deuterium substitute irreversibly bound a non-MAO-A site in the white matter of human brains, but the binding site was not further characterized (Fowler et al. 2001). Several binding site candidates have been proposed, including glyceraldehyde 3-phosphate dehydrogenase (GAPDH; Tatton et al. 2000), D_2 receptors (Pizzinat et al. 2003), DA transporter (Fang and Yu 1994), a sigma site (Itzhak et al. 1991), and the quinpirole (LY 171555) binding site (Levant et al. 2001). There are no reports, however, that these receptors directly mediate neuroprotection afforded by MAO inhibitors.

In summary, the role of MAO itself in neuroprotective effects of MAO-B inhibitors has not been fully clarified, and the in vivo investigation of MAO in knockout animals may yield more concrete information.

Induction of MAO-A expression by MAO-B inhibitors plus substrate

MAO-A expression is activated by the transcription factor Sp1 (simian virus 40 promoter factor 1), and suppressed by binding of the Sp1 site by the transcription repressor R1 (RAM2/CDCA7L/JPO2) (Chen et al. 2005) (Fig. 2). The

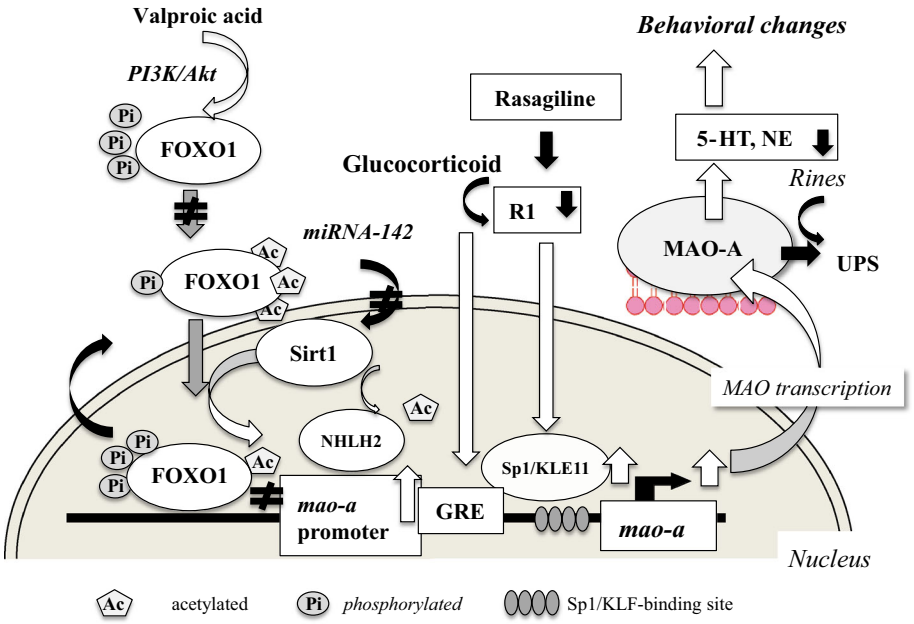

Fig. 2 Regulation of MAO-A expression by rasagiline and other factors. Rasagiline reduces MAO-A specific repressor R1 levels, and activates Sp1 and KLE11, leading to induction of MAO-A transcription, which occurs also in apoptosis caused by serum withdrawal. Sirt1 deacetylates NHLH2 and stimulates MAO-A expression; in HIV encephalitis, *mi*RNA-142 down-regulates Sir1 and increases MAO-A levels. FOXO1 binds to the *mao-a* promoter region and suppresses transcription, Sirt1 and VPA down-regulate FOXO1 by deacetylation or phosphorylation, thereby preventing FOXO1 from entering the nucleus. Glucocorticoids amplify KLE1l expression and KLE1l-induced *mao-a* transcriptional activation, in addition to directly binding to its own specific receptors, suppressing R1 synthesis. Rines ubiquitinates MAO-A and promotes its degradation in the USP. The up- or down-regulation of MAO-A activity decreases or increases 5-HT and NE levels in the brain, and is associated with emotional and behavioral abnormalities

R1-Sp1 pathway is activated by p38 MAPK signaling (De Zutter and Davis 2001; Ou et al. 2006a, 2006b). Glucocorticoids and androgens induce MAO-A expression through regulation of R1 translocation, direct or indirect interaction with the Sp1 or R1 on the Sp1-binding site of the *mao-a* gene promoter, or direct interaction with glucocorticoid receptor (Ou et al. 2006b). MAO-A induction by chronic stress is mediated by a glucocorticoid-KLF11 (Krüppel-like factor 11 = a transforming growth factor-β early inducible gene 2, TIEG2) pathway (Grunewald et al. 2012).

We recently found that rasagiline and selegiline up-regulated MAO-A mRNA, protein levels, as well as in the case of rasagiline, its enzymatic activity, whereas clorgyline, a MAO-A inhibitor, did not (Fig. 2). Rasagiline reduced R1 levels, while mithramycin-A, a specific inhibitor of Sp1 binding to GC-rich region promoters (Sp1 response elements), significantly inhibited rasagiline induction of *mao-a*. Rasagiline did not increase MAO-A expression in MAO-B overexpressed SH-SY5Y cells, so that its induction of *mao-a* probably does not involve MAO-B. Selegiline, on the other hand, increased R1 levels, and MAO-B overexpression enhanced MAO-A induction, indicating that selegiline and rasagiline induced MAO-A expression by different signal pathways (Inaba-Hasegawa et al. 2013).

PEA, a selective MAO-B substrate, also increased MAO-A mRNA and protein levels, as well as those of Bcl-2 in MAO-A expressing SH-SY5Y cells, but not in U118MG cells expressing only MAO-B (Inaba-Hasegawa et al. 2015). Substrates for MAO-A include an ethylamine side chain attached to an aromatic ring, and PEA analogs can bind to the substrate-binding site of MAO-A as reversible inhibitors (Miller and Edmondson 1999). MAO-A oxidizes PEA derivatives to a reduced MAO-imine complex that is oxidized, whereas for MAO-B it is the free reduced enzyme that reacts with oxygen in the rate-limiting step (Nandigama and Edmondson 2000). These results suggest that PEA binds to MAO-A and induces *mao-a* in a similar manner to rasagiline, but the detailed molecular mechanism requires further investigations. DA and bromocriptine, a D_2 receptor agonist, up-regulated the mRNA, protein and catalytic activity of MAO-A in rat mesangial cells, an effect mediated by a D_2-like receptor and inhibited via the cAMP-PKA pathway (Pizzinat et al. 2003); human *mao-a* and *mao-b* promoters contain a putative cAMP responsive element (Zhu et al. 1994), consistent with regulation of *mao* transcription by this pathway. Earlier papers had reported that L-DOPA increased MAO activity in rat tissues (Collins et al. 1970b; Lyles 1978).

The *mao-b* promoter, like that of *mao-a*, is activated by Sp1 and Sp4 binding to Sp1 site, and down-regulated by competitive binding by the transcription repressor Sp3 and by R1; the organization of the binding elements in the two genes, however, is different (Shih et al. 2011). Further, KLF11 activates *mao-b* gene expression, also by binding Sp1 binding sites (Ou et al. 2004; Chen et al. 2011). MAO-B protein and KLF11 levels were increased in the prefrontal cortex of alcohol-dependent subjects, and blood alcohol content was positively correlated with KLF11 levels and MAO-B activity (Udemgba et al. 2014), suggesting that MAO-B might be involved in neuronal dysfunction and death in alcoholism (Ou et al. 2011). Ethanol also induced the nuclear translocation of GAPDH and increased MAO-B activity in U118MG and SH-SY5Y cells, enhancing KLF11-induced expression, leading to cell death that could be prevented by rasagiline and selegiline (Ou et al. 2009). The *mao-b* promoter also includes response elements for glucocorticoid, retinoic acid, and estrogen-related receptors (Shih et al. 2011).

In summary, *mao-a* expression and MAO-A activity can be induced by various factors, including MAO-B inhibitors and the MAO substrates PEA and DA, and *mao* induction in the brain should be discussed with respect to the role played by MAO in the pathogenesis and phenotypes of neuropsychiatric disorders.

Modulation of MAO-A expression in neuropsychiatric disorders

Following the discovery of the absence of the *mao-a* gene in Norrie disease (Brunner et al. 1993a), the association of MAO-A dysfunction with neuropsychiatric disorders has attracted increasing attention (Murphy et al. 1990; Shih and Thompson 1999). Abnormal MAO-A activity has been reported in several neuropsychiatric disorders, including schizophrenia (Sun et al. 2012), depression (Rivera et al. 2009), antisocial aggressive behaviors (Nelson and Trainor 2007), anxiety, attention deficient hyperactivity disorders (ADHD) (Jiang et al. 2001), autism spectrum disorders (Cohen et al. 2011), and AD (Takahashi et al. 2002). PET imaging studies have identified changes in MAO-A expression in various psychiatric disorders; reduced expression of MAO-A has been linked with violent and aggressive behaviors in males (Sims et al. 1989), while elevated MAO-A activity, measured using [^{11}C]harmine-PET, was detected in major depression (Meyer et al. 2006).

The phenotypes of atypical Norrie disease patients suggested that MAO-A deficiency might be associated with abnormal social behaviors and aggression (that is, a persistent predisposition to violence) (Brunner et al. 1993b; Caspi et al. 2002). Cortical and subcortical MAO-A

activity measured using [^{11}C]clorgyline-PET was negatively correlated with aggression as assessed by a multidimensional personality questionnaire (Alia-Klein et al. 2008). Functional polymorphisms in the *mao-a* promoter provide a possible link between MAO-A deficiency and abnormal behaviors, and such variants are now considered to be more significant than deficient MAO-A activity per se. Four such polymorphisms have been the focus of investigations to date (Bortolato and Shih 2011):

- *mao-a*-$(CA)_n$, a dinucleotide repeat polymorphism in intron 2 (Black et al. 1991);
- a 23 base pair (bp) variable number of tandem repeats (VNTR) region near exon 1 (Hinds et al. 1992);
- two restriction fragment length polymorphisms (VFLP), *Rnu*4HI and *Eco*RV (Lim et al. 1994);
- *mao-a-uVNTR*, a 30 bp VNTR polymorphism located 1.2 kb upstream of the *mao-a* transcription initiation site. PCR products consist of five fragment sizes, including 2, 3, 3.5, 4 or 5 copies of the repeated sequence; the 3.5R and 4R copies are transcribed more efficiently than the 2R, 3R or 5R, while 2R exhibits the lowest promoter activity (Sabol et al. 1998); an association of the 2R variant with delinquent behavior in adolescence has been suggested (Guo et al. 2008).

The interaction of genetic and environmental factors has also emerged as a central issue in the regulation of *mao-a* expression. Childhood maltreatment increases the risk of the later criminality, although most mistreated children do not become delinquents or criminals in young adulthood and adolescence. Maltreated male children with *mao-a* gene versions that result in lower MAO-A expression engaged in violent behavior to a greater extent than those with higher expression levels (Caspi et al. 2002). Similarly, the lower expression allele of *mao-a-uVNTR* was associated with higher impulsivity in male subjects with a history of abuse before 15 years of age (Huang et al. 2004). An association between low affinity allele *mao-a* polymorphisms in women with a history of childhood sexual abuse and the later development of alcoholism and antisocial personal disorders has been reported (Ducci et al. 2008). A novel 10 bp VNTR ~1,500 bp upstream of the transcriptional site has been associated with antisocial personality disorder in female children with a history of child abuse (Philibert et al. 2011). In female patients with panic disorder, longer, higher activity *mao-a* promoter alleles were significantly more frequently found than in control females (Deckert et al. 1999). A recent study of Finnish prisoners reported a highly significant association of lower activity *mao-a* polymorphisms with violent behaviors (homicides, attempted homicides or batteries; Tiihoren et al. 2014).

The interaction of adverse in utero environments with the *mao-a-uVNTR* polymorphism has also been described: the impact of maternal life events on negative emotionality in infants at 5 weeks postpartum was greater in infants with *mao-a-uVNTR* of low transcription efficiency. (Hill et al. 2013). On the other hand, *mao-a* genes associated with higher MAO-A levels were reported to protect against the consequences of childhood maltreatment, abuse and neglect for the development of antisocial behavior (Widom and Brzustowicz 2006).

The effects of various genetic and epigenetic events on allelic *mao-a* expression with respect to this polymorphism were explored by Pinsonneault et al. (2006) using brain tissue from healthy female persons, as well as female schizophrenia and bipolar disorder patients; no clear disease associations were detected, but the investigation had been focused on dissecting genetic from epigenetic influences upon MAO-A expression.

Interaction between the environmental and genetic factors seems to continue during the postpartum period and can modulate the adolescent behavioral abnormalities. It should be emphasized, therefore, that parental care can moderate the influence of childhood stressors on behavioral abnormalities associated with *mao-a-uVNTR* polymorphisms (Kinnally et al. 2009); for instance, physical discipline before the age of 6 years reduced the levels of delinquent behavior of subjects with *mao-a uVNTR* of low transcriptional activity (Edwards et al. 2010).

Lower transcription efficiency *mao-a* polymorphisms, resulting in elevated CNS 5-HT and NE levels, may modify neurotransmitter system development, leading to reduced tolerance for stress caused by maltreatments (Caspi et al. 2002). Results obtained in MAO-A knockout mice support this hypothesis: in MAO-A null mice, 5-HT and NE levels were elevated, and aggressiveness and maladaptive defensive activity were increased (Scott et al. 2008). MAO-A may moderate the impact of childhood trauma upon adult psychopathology, explaining why the linkage between the two is usually observed only when childhood environmental stress was severe. Further, MAO-A knockout was associated with neurodevelopmental alterations and sensorimotor cortical deficits, with excessive 5-HT levels and enhanced activity of the 5-HT1B receptor (Salichon et al. 2001). MAO-A silencing with siRNA during in vitro embryogenesis induced a reduction of the crown rump length, and impaired cerebral development, the consequence of reduced apoptosis in the neuroepithelium and impaired activation of caspases 3 and 9 (Wang et al. 2011). MAO-B knockout, in contrast, did not alter development or affect apoptosis. An animal model involving peripubertal exposure to stress found increased aggression in adulthood, and hyperactivity in the amygdala and hypoactivation of the medial orbitofrontal cortex after social challenge. MAO-A expression levels were increased in the frontal cortex, but not in the amygdala of the treated rats. Increased histone H3

acetylation at the promoter region of the *mao-a* gene was detected, suggesting the epigenetic control of MAO-A expression (Márquez et al. 2012).

In summary, maternal maltreatment determines *mao-a* expression levels in children with *mao-a* polymorphisms of low transcriptional activity, resulting in high 5-HT and NE levels, altered development of monoamine system, and behavioral abnormality in adolescent. The interaction between genetic and environmental factors persists beyond birth, and the effects are still reversible in early childhood.

Modification of MAO expression by environmental and genetic factors

As previously mentioned, MAO expression and activity are modified by environmental factors, including stress (Grunewald et al. 2012), alcohol dependence (Udemgba et al. 2014), physical activity (Morishima et al. 2006), food deprivation (Jahng et al. 1998), and high-fat feeding (Lee et al. 2010). Recent studies have elucidated some of the molecular mechanisms behind the regulation of MAO expression by these factors.

Sirt1 (silencing information regulator 1) is a member of sirtuin family, which regulates metabolism and health span, and is essential for responding to the effects of caloric restriction (Houtkooper et al. 2012). Sirt1 is primarily localized in the cell nucleus, and is a NAD^+-dependent protein deacetylase that acts upon histones, transcription factors and apoptosis modulators. In the brain, Sirt1 regulates a number of transcriptional factors, such as the tumor suppressor p53, the Forkhead box O (FOXO) family, and nuclear factor-κB (NF-κB), as well as retinoic acid receptor β (RARβ) and *tau*, and is thereby involved in regulation of cell survival, proliferation, and response to stress (Gan and Mucke 2008; Donmez and Outeiro 2013). In mice, overexpressed Sirt1 activated MAO-A transcription, reduced 5-HT and NE levels, and enhanced anxiety and exploratory drive, whereas Sirt1-knockout mice exhibited lower brain MAO-A levels (Libert et al. 2011). Sirt1 binds the *mao-a* promoter in close proximity to the ATG start codon, and deacetylates the brain-specific nescient helix loop helix transcription factor 2 (NHLH2), activating the *mao-a* promoter; physical interaction of Sirt1 with NHLH2 has been shown by co-precipitation from mouse brain lysate. Expression of human NHLH2 activated the 1.1 kb *mao-a* promoter, but Sirt1 overexpression did not enhance this activation. HLH transcription factors are involved in cell proliferation, determination and differentiation in the brain (Schmid et al. 2007), suggesting that an HLH-regulated increase in MAO-A expression might be associated with development of neuronal system. One association study of *Sirt1* single-nucleotide polymorphisms (SNPs) in emotional disorders suggested a predisposing association between SNP rs10997870 and the risk of panic disorder (Libert et al. 2011). The association of this SNP with major depressive disorder was described in a Japanese population, but MAO activity was not reported (Kishi et al. 2010).

The FOXO family is deacetylated by Sirt1, and regulates genes associated with stress response, cell-cycle arrest, and cell survival (Lam et al. 2006). FOXO1 acts as a transcriptional repressor of *mao-a* by directly binding a functional FOXO1-binding site in the promoter. Sirt1 converts hyperacetylated FOXO to the hyperphosphorylated form, which is thereby excluded from moving from the nucleus into the cytosol, leading to enhanced expression of FOXO target genes involved in anti-oxidative and pro-survival functions (Lam et al. 2006). The FOXO1-Sirt1 pathway is also associated with the induction of *mao-a* expression by valproic acid (VPA, 2-propylpentanoic acid); VPA increases *mao-a* transcription, as well as its promoter and catalytic activity. VPA activates phosphoinositide-3-kinase (PI3K)/Akt signaling at the transcriptional level, phosphorylates FOXO1 in the cytoplasm and nucleus, and abolishes its repressor activity for MAO-A transcription by the translocation into the cytoplasm, where it is ubiquitinated and degraded by proteasomes (Wu and Shih 2011).

miRNAs regulate gene expression at the posttranscriptional levels and down-regulate expression by binding to the 3′ untranslated region of target mRNAs. miRNAs are cleaved from longer precursor miRNAs by two enzymes, Drosha and Dicer, into functional RNAs of ∼22 nucleotides, which are incorporated into an RNA-inducing silencing complex that suppresses translation of target mRNAs. miRNAs are abundant in the brain, and brain-specific miRNAs, miR-9, -124 and -134, are involved in the regulation of neuronal development, transmission and plasticity (Meza-Sosa et al. 2014). One species of miRNA, miR-133b, is specifically expressed in midbrain DA neurons; Dicer knockdown reduced miR-133b levels in mice, and induced the progressive loss of DA neurons and the development of a PD-like phenotype (Kim et al. 2007). miR-133b expression was down-regulated in PD brains, and miRNA loss might be associated with the onset and progression of PD and other neurodegenerative disorders (Hebert and De Strooper 2007). In a study investigating the role of miRNA with respect to panic disorder in anxiety patients, miR-22, -138-2, -148a and -488 were found to regulate several candidate anxiety genes, while miR-22 regulated *mao-a* gene expression (Muninos-Gemeno et al. 2010). In human HIV encephalitis, levels of neuronal species miR-142 were increased in frontal cortex white matter and caudate nuclei (Noorbakhsh et al. 2010). Its overexpression in a human neuron cell line down-regulated

Sirt1, and also decreased MAO-A mRNA, protein and enzyme activity levels (Chaudhuri et al. 2013), so that regulation of MAO-A expression by the miR-142-Sirt1-MAO-A pathway may contribute to changes in DA transmission in HIV-associated neurocognitive disorders (Yelamanchili et al. 2010).

Abnormal MAO activity is associated with depression in patients with AD, and is a risk factor for the development of dementia (Nishimura et al. 2005; Wu et al. 2007). Carriers of AD-related presenilin-1 (PS-1) variants A431E and L235 V were found to have a higher rate of depression, as well as reduced 5-HT and NE levels (Liu et al. 2008). These two variant PS-1 forms increased MAO-A activity in mouse hippocampal HT-22 cells; PS-1 physically interacted with MAO-A to suppress its activity, whereas PS-1/γ-secretase inhibitor DAPT (*t*-butyl 2-{2-[2-(3,5-difluorophenyl)acetamido]-propanamido}-2-phenylacetate), increased its activity significantly (Pennington et al. 2011). In PS-1(M146V) knock-in mouse, the interaction of MAO-A with PS-1 was reduced, and MAO-A activity was up-regulated by direct activation (Wei et al. 2012). Increased MAO-A activity might thus be associated with a higher risk for developing depression in carriers of AD-related PS-1 alleles (Ringman et al. 2004).

PS mutations in familial AD are linked with calcium signaling abnormalities, such as endoplasmic reticulum (ER) calcium leak (Zhang et al. 2010). Calcium selectively activated monkey brain MAO-A in vivo (Egashira et al. 2003), and MAO-A activation and increased ROS production were each correlated with intracellular calcium levels in HT-22 cells (Cao et al. 2007). Calcium increased the mRNA levels and activity of MAO-A in human cerebellar extracts by activation of p38(MAPK) signal pathways, whereas MAO-B activity was not affected (Cao et al. 2009a). Overexpression of constitutively active p38(MAPK) induced MAO-A phosphorylation and inhibited MAO-A activity in HT-22 cells (Cao et al. 2009b). These PS-1-calcium-p38(MAPK) pathway findings suggest that MAO-A expression might be modulated in AD as an adaptive response to oxidative stress, calcium overload, and cytotoxic insults, as well as in depression and brain reperfusion and ischemia.

Disrupt-in-schizophrenia 1 (DISC1) plays an important role in neurodevelopmental processes, such as neurite outgrowth, neuronal migration, and neurogenesis, and is also a candidate susceptibility gene for schizophrenia and related psychiatric disorders (Roberts 2007; Brandon et al. 2009). DISC1 localized inside mitochondria plays an essential role through its interaction with the mitofilin protein; knockdown of DISC1-mitofilin in mice decreased MAO-A activity and impaired mitochondrial function (Park et al. 2010). Such a MAO-A deficiency might increase monoamine levels and contribute the neurochemical and clinical phenotypes in schizophrenia.

SNPs within the *mao-a* gene have been reported to be associated with paranoid schizophrenia, but this result has not been confirmed by later studies. At present, the contribution of MAO-A to the susceptibility to schizophrenia has been reported only for a Chinese Han population (Xu et al. 2004).

In contrast to its expression, the cellular mechanisms for MAO degradation have been scarcely investigated. Ubiquitination increased proteolytic degradation of MAO-A in isolated rat brain mitochondria (Buneeva et al. 1999), and ubiquitination of MAO was confirmed in HEK293 cells co-transfected with parkin, hemagglutinin epitope (HA)-tagged ubiquitin, and Myc-tagged MAO-A or MAO-B (Jiang et al. 2006). The RING finger-type E3 ubiquitin ligase Rines/RNF180 was reported to regulate MAO-A expression, monoamine levels, and emotional behaviors in mice. MAO-A activity was enhanced in the locus ceruleus of Rines-knockout mice, with down-regulation of NE and 5-HT levels. Rines promotes ubiquitination of MAO-A and its degradation in the UPS, indicating that MAO levels are regulated not only via its synthesis and post-transcriptional modification, but also via the catabolism in the UPS (Kabayama et al. 2013).

In summary, MAO-A expression and degradation are modulated by various factors, with consequences for CNS monoamine levels that may be involved in the pathogenesis and phenotypes of neuropsychiatric disorders.

Discussion

Monoamine oxidase plays a major role in the metabolism of monoamine transmitters, but more recent findings suggest that it plays a more immediate role in the function and fate of neurons. In addition to the generation of ROS and neurotoxins, MAO-A expression and activity are increased in apoptosis, and MAO-A activates mitochondrial cell death signaling via oxidative stress and mitochondrial dysfunction; it is, on the other hand, also involved in the induction of pro-survival genes. Further, MAO-A binds neurotoxins, such as MPP^+ (May 1993) and *N*-methyl(*R*)salsolinol (Yi et al. 2006), and increases mitochondrial permeability. The induction of the anti-apoptotic Bcl-2 protein family by rasagiline is mediated by MAO-A, as indicated by the consequences of MAO-A knockdown in SH-SY5Y cells and the absence of increased levels in MAO-B-expressing Caco-2 and U118MG cells. These results strongly suggest a novel role for MAO-A in the fate of CNS neurons.

In particular, numerous genetic and environmental factors regulate MAO-A expression and activity, and may be

involved in the pathogenesis of neuropsychiatric disorders. Mutations and polymorphisms of genes implicated in the pathogenesis of PD, AD, depression and schizophrenia increase MAO-A activity and thus reduce NE and 5-HT levels in the brain, which may lead to emotional and behavioral abnormalities, as discussed above. The MAO-A genotype interacts with environmental factors, such as childhood maltreatment, and may be involved in the development of antisocial behavioral patterns (Fergusson et al. 2011). MAO-A activity can be measured in blood; it has been found, for instance, that in peripheral monocytes *mao-a* (but not *mao-b*) mRNA synthesis was induced by interleukin-4 via increased intracellular peroxide levels (Chaitidis et al. 2005). For the analysis of a possible association between *mao-a* genotype and psychiatric disorders or antisocial behavior, the VNTR polymorphism might be investigated in monocytes as a surrogate marker of MAO-A activity in the brain; DNA has been extracted from peripheral blood cells, and the polymerase chain reaction (PCR) used to prepare a dinucleotide tandem repeat sequence of the MAO-A gene (Caspi et al. 2002). Conversely, MAO activity is regulated by genetic and environmental factors, and the accurate assay of in vivo brain MAO activity should be established to increase our understanding of the role of MAO in human behaviors, potentially allowing therapeutic intervention.

Low platelet MAO-B activity has been reported to be correlated with certain personal traits, type II alcoholism (Oreland 2004), and ADHD (Shekim et al. 1986; Nedic et al. 2010). In girls with ADHD, low platelet MAO-B activity was associated with symptoms of oppositional defiant disorder, and short *mao-a VNTR* variants were associated with disruptive behavior in boys (Malmberg et al. 2008). Correlation of enzyme expression in the brain with that in peripheral tissues, however, has not been completely confirmed (Winblad et al. 1979), suggesting the limits to interpreting platelet MAO-B activity as a marker of 5-HT and NE turnover in the brain.

MAO-B inhibitors, rasagiline and selegiline, enhance the expression of MAO-A, and affect the brain levels of MAO-A substrates. PEA, a MAO-B substrate, increased the expression of MAO-A itself and also Bcl-2, whereas 5-HT had no influence on MAO-A expressing SH-SY5Y cells (Inaba-Hasegawa et al. 2015). As discussed above, the pharmacological effects of MAO-B inhibitors are also partially mediated by MAO-A expressed in catecholaminergic neurons, suggesting that MAO-A and MAO-B interact with each other through the actions of their inhibitors and substrates. Following their development from a common ancestral form, the two MAO forms acquired divergent functions and patterns of expression and regulation in distinct brain cell types with specified function, but they still share common structures that are recognized by the inhibitors and substrates of the other isoenzyme. This crosstalk may be involved in the physiological functions of each oxidase and the pharmacological effects of inhibitors of the other isomer, an issue that suggests the possibility of a novel and interesting aspect of the role of brain MAOs.

Further studies on the molecular mechanism underlying the induction of MAO-A expression will clarify the role of MAO-A in determining neuronal survival, as well as in the induction of pro-survival genes by MAO-B inhibitors. Determination of the binding site(s) of selegiline and rasagiline on MAO-A will provide information regarding the most effective MAO-B inhibitor structure with respect toe gene induction. This will facilitate the identification of novel therapeutic strategies that modulate neuronal death signal pathways, protecting and sustaining CNS function.

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