TYPE A MONOAMINE OXIDASE REGULATES LIFE AND DEATH OF NEURONS IN NEURODEGENERATION AND NEUROPROTECTION

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Abstract

In Parkinson's disease, type B monoamine oxidase (MAO-B) is proposed to play an important role in the pathogenesis through production of reactive oxygen species and neurotoxins from protoxicants, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. In addition, inhibitors of MAO-B protect neurons in the cellular and animal models of Parkinson's and Alzheimer's diseases. However, the role of type A MAO (MAO-A) in neuronal death and neuroprotection by MAO-B inhibitors has been scarcely elucidated. This chapter presents our recent results on the involvement of MAO-A in the activation of mitochondrial death signal pathway and in the induction of prosurvival genes to prevent cell death with MAO-B inhibitors. The roles of MAO-A in the regulation of neuronal survival and death are discussed in concern to find a novel strategy to protect neurons in age-associated neurodegenerative disorders and depression.

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I. Introduction

Monoamine oxidase [MAO; monoamine: oxygen oxidoreductase (deaminating) EC 1.3.3.4] is a key enzyme in the catabolism of monoamine neurotransmitters and xenobiotic amines. Type A MAO (MAO-A) and type B MAO (MAO-B) are designated according to the substrate specificity and sensitivity to distinct inhibitors. MAO-A preferentially oxidizes serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine (NE) and is selectively inhibited by clorgyline. MAO-B oxidizes β-phenylethylamine and benzylamine, and selegiline [(−)deprenyl] is a typical MAO-B inhibitor. Dopamine (DA) is oxidized by both the isoenzymes. MAO-A and MAO-B are coded by different genes localized closely in the chromosome X (Xp11.23; Shih *et al.*, 1999). They are distributed differentially in distinct cells of the brain regions, indicating their specified role in neuronal functions. MAO is now proposed to play an important role in age-dependent neurodegenerative disorders, including Parkinson's and Alzheimer's diseases, and also in depression (Bortolato *et al.*, 2008; Riederer *et al.*, 2004; Youdim and Bakhle, 2006).

In Parkinson's disease (PD), MAO is considered to be associated with selective loss of DA neurons in the substantia nigra (Cohen *et al.*, 1997). MAO oxidizes DA and other monoamine transmitters and generates reactive oxygen species (ROS). MAO-B expression in the brain increases with aging (Fowler *et al.*, 1997). In PD, the results on MAO-B levels in the brain are conflicting, whereas in Alzheimer's disease (AD), MAO-B activity was reported to increase as a function of activated astrocytes, whereas MAO-A activity decreased (Kennedy *et al.*, 2003). Even subtle elevation of MAO-B activity impaired mitochondrial function (Kumar *et al.*, 2003); therefore, MAO-B may induce a malignant cycle among oxidative stress, mitochondrial dysfunction, impaired ubiquitin–proteasome system, excitotoxicity, and apoptotic signaling to cause neuronal death. On the other hand, selegiline is applied in patients with PD as a monotherapy or an adjunct of L-DOPA therapy to increase available DA, reduce ROS production, and alleviate oxidative stress (Birkmayer *et al.*, 1977). MAO-B oxidized MPTP, a protoxicant, into 1-methyl-4-phenylpyridinium (MPP^+), a parkinsonism-inducing neurotoxin (Heikkila *et al.*, 1984). Selegiline prevented MPTP oxidation and also neurotoxicity of MPP^+. These findings suggest that MAO-B may be a pathogenic factor in PD and MAO-B inhibitors (MAO-B-Is) may function as agents to halt or delay neuronal loss. The "MAO-B" hypothesis was extended to a clinical trial called "Deprenyl and tocopherol antioxidative therapy for parkinsonism" (DATATOP) study (Parkinson Study Group, 1993). However, this trial failed to prove the neuroprotection by selegiline, even though selegiline serves a symptomatic treatment in early PD and shows neuroprotective effects in animal and cellular models.

Recently, more direct role of MAO was found in neuronal death besides the production of ROS and neurotoxins. An endogenous dopaminergic neurotoxin,

N-methyl(*R*)salsolinol (*NMR*Sal; Maruyama *et al.*, 2001; Naoi *et al.*, 2004), bound to MAO-A and activated mitochondrial apoptosis signaling (Naoi *et al.*, 2006; Yi *et al.*, 2006a). MAO-A was upregulated in apoptosis induced by serum-withdrawal in SK-N-BE(2)-C cells, and the cell death was decreased in MAO-A-deficient mice, suggesting that MAO-A might be associated with apoptotic signal pathway (Ou *et al.*, 2006).

On the other hand, MAO-B-Is, selegiline and rasagiline, were proved to protect neuronal cells in animal and cellular models at a dose with little inhibition of MAO-B activity. MAO-B-Is suppress the activation of mitochondrial death signal pathway and prevent "intrinsic" apoptosis, and they increase prosurvival and antiapoptotic molecules, including *Bcl-2*, neurotrophic factors (NTFs), and antioxidant enzymes (Naoi and Maruyama, 2010). MAO-B-Is increased prosurvival genes in MAO-B-expressing astrocytes (Semkova *et al.*, 1996), and also in MAO-A-expressing human SH-SY5Y and rat pheochromocytoma PC12 cells (Akao *et al.*, 2002a,b; Naoi and Maruyama, 2009, 2010).

On the other hand, rasagiline and related propargylamine derivatives of MAO-B-Is require strict enantiomeric structure for the protective function (Maruyama *et al.*, 2002, 2003, 2004a,b), suggesting the occurrence of the binding site for MAO-B-Is. MAO-A was confirmed as one of the targets of MAO-B-Is (Naoi *et al.*, 2007; Naoi and Maruyama, 2009). In addition to irreversible MAO-B-Is, reversible MAO-A-Is, *N*-propargylamine (Yi *et al.*, 2006b), moclobemide (Chiou *et al.*, 2006), and befloxatone (Inaba-Hasegawa *et al.*, in preparation) protected neuronal cells. Therefore, it should be reexamined whether MAO-B-Is require MAO-A or MAO-B for their neuroprotective function.

In this chapter, we review our recent results on the role of MAO-A in regulation of death cascade, using cellular models expressing selectively MAO-A and MAO-B and those, where MAO expression was reduced by RNA interference with small interfering RNA (siRNA). MAO-A was confirmed to be the target protein of the endogenous neurotoxin and associated with mitochondria-dependent apoptosis. On the other hand, MAO-A was involved also in the suppression of apoptotic signal pathway of reversible and irreversible MAO-A- and MAO-B-Is. The "Janus"-faced roles of MAO-A are discussed in relation to the pathogenesis and treatment of age-dependent neurodegenerative disorders and depression. The future development of novel neuroprotective agents might be expected among compounds with affinity to MAO-A and potency to induce prosurvival genes.

II. Type A and B MAO in Cell Death of Neurons

Cell death of selective neurons in distinct brain regions is one of the pathological characteristics in neurodegenerative disorders. The postmortem studies suggest that programmed cell death (PCD) may occur in the brains of patients with

PD, AD, and other neurodegenerative disorders (Jellinger, 2001). Apoptosis, a form of PCD, is initiated by activation of mitochondrial apoptosis pathway or death receptor-mediated signal pathway (Kroemer *et al.*, 2007). The apoptosis cascade is well regulated and activated in a step-wise way, and proposed as a main target of neuroprotection therapy (Mattson *et al.*, 2008). Therefore, this review will be focused on the role of MAO in intrinsic apoptosis initiated by mitochondrial signal pathway.

MaoA and *MaoB* gene are proposed as pathogenic factors for neuronal loss in AD and PD. *MaoB*-gene polymorphisms were reported to be associated with PD (Bialecka *et al.*, 2007; Parsian *et al.*, 2004). In *MaoB*, specific G to A transition polymorphism in intron 13 (Singh *et al.*, 2008), a polymorphic GT repeat in intron 2, and longer repeat units than normal range (186 or 188 bp vs. 168–190 bp) were reported in a subgroup of older PD patients (Gao *et al.*, 2008). On the other hand, *MaoA* gene may be associated with the development, plasticity, and physiological function of the brain, and also with neuropsychiatric disorders and behaviors (Shih and Thompson, 1999). Association of various polymorphisms in *MaoA* was reported with AD (Wu *et al.*, 2007), major depressive disorder (Yu *et al.*, 2005), autism (Cohen *et al.*, 2003) attention-deficient hyperactivity disorder (ADHD; Roohi *et al.*, 2009), and frontotemporal dementia (Reif *et al.*, 2008).

MAO-B is considered to account for neuronal loss through ROS production by the enzymatic oxidation of monoamine substrates. Activated astrocytes expressing MAO-B were found to increase in the brain of patients with PD, AD, and postischemia or posttrauma brain. MAO-B knockout (KO) mice showed to resist MPTP toxicity through reduced enzymatic oxidation of this protoxicant (Grimsby *et al.*, 1997). However, few results are available to support the direct association of MAO-B with neuronal PCD in PD and AD.

On the other hand, MAO-A was confirmed to be directly associated with apoptosis induced by *N*M*R*Sal (Yi *et al.*, 2006a). This neurotoxin induces mitochondrial membrane permeability transition (MMPT), the release of molecules with less than 1.5 kDa, such as cytochrome *c* (Cyt *c*) and proapoptotic factors, the swelling of mitochondria, and the decline in mitochondrial membrane potential ($\Delta\Psi_m$; Akao *et al.*, 2002a; Maruyama *et al.*, 1997, 2001). Released Cyt *c* binds to AIF1 (apoptotic protease-activating factor-1), recruits caspase 9, and activates caspases 3, 6, and 7. Apoptosis is advanced through the cleavage of poly(ADP-ribose) polymerase (PARP) and other death substrates, such as caspase-activated DNase (CAD), the transfer of activated factors into nuclei, and finally the condensation and aggregation of nuclear DNA, accompanied with the translocation of glyceraldehydes-3-phosphate dehydrogenase (GAPDH), as shown in Fig. 1.

Inhibition of MAO-A expression with siRNA decreased *N*M*R*Sal-induced apoptosis in SH-SY5Y cells in accord to the reduction of the RNA, protein, and activity of MAO-A, whereas MAO-B overexpression did not induce MPPT and apoptosis. (Yi *et al.*, 2006a). Some ligands of imidazoline-binding site and the

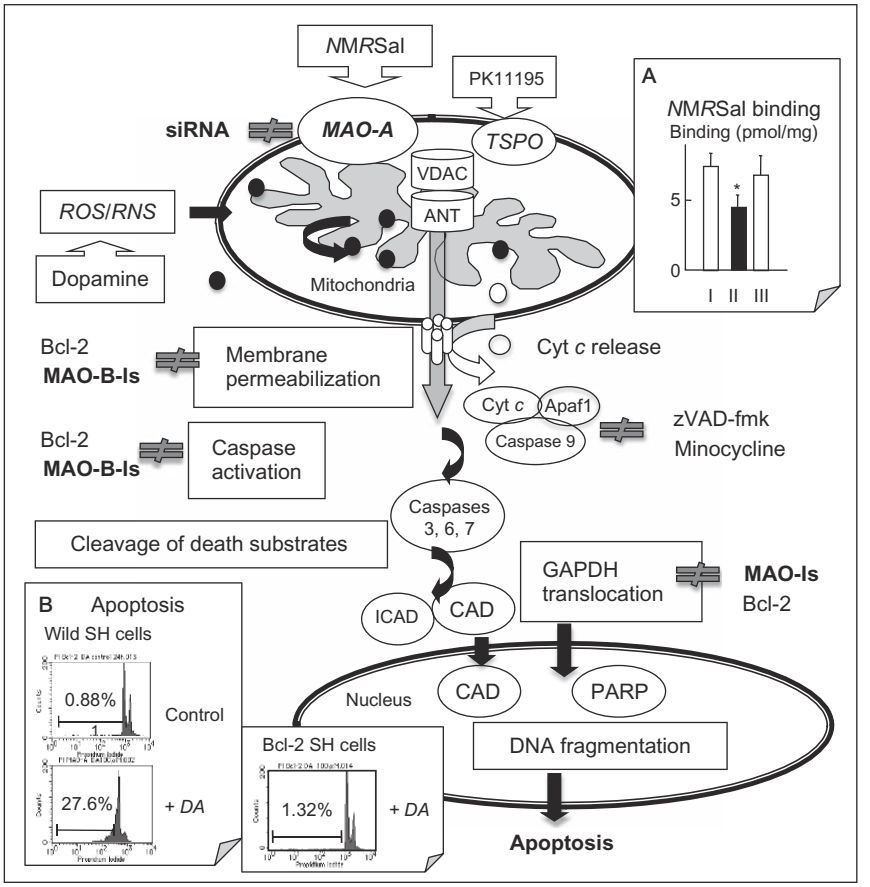

FIG. 1. The role of MAO-A in apoptosis pathway and the regulation of death signaling by Bcl-2 and rasagiline. An endogenous neurotoxin, *N*M*R*Sal, binds to MAO-A and opens MPP, followed by release of Cyt *c* and proapoptotic proteins in the cytoplasm, activation of caspases, and then activates death substrates (CAD) through cleavage of the inhibitory subunit (ICAD), which a caspase inhibitor, benzyloxycarbonylvalyl-alanyl-aspartyl fluoromethyl ketone (zVAD-fmk) and minocycline inhibit. These death substrates enter into nuclei, cleave DNA, and induce apoptosis. Bcl-2 and rasagiline prevent MMPT and apoptosis. (A) The treatment with siRNA reduces *N*M*R*Sal binding to mitochondria. The binding of *N*M*R*Sal was quantified in mitochondria from control (I), MAO-A-siRNA (II), or nonspecific siRNA-treated SH-SY5Y cells (III). (B) Bcl-2 overexpression in SH cells (Bcl-2 SH) reduces DA-treated apoptosis, as shown by FACS. GAPDH is incorporated in nuclei during apoptotic process, and irreversible MAO-B-Is and reversible MAO-A-Is prevent the translocation.

18-kDa-translocator protein [TSPO, formerly called "peripheral benzodiazepine receptor"] target MAO-A to initiate apoptosis (Naoi *et al.*, in preparation). In addition, *MaoA* gene was upregulated in apoptosis of serum-withdrawn PC12

cells, through activation of the p38 mitogen-activated protein kinase (MAPK) signal pathway (De Zutter and Davis, 2001). Also in SK-N-BE(2)-C cells, serum-withdrawal induced apoptosis with increased MAO-A expression through decrease of MAO-A-targeted transcription repressor R1 (Ou *et al.*, 2006). In apoptosis induced by staurosporine, MAO-A activity was increased by a posttranscriptional mechanism in SH-SY5Y cells (Fitzgerald *et al.*, 2007). The elevated MAO-A activity was proposed to increase oxidative stress leading to activate death signal pathway.

The role of MAO-A in neurodegeneration was indirectly suggested also by previous results: the bioactivation of a MPTP analogue, 1-methyl-(2′-methylphenyl)-1,2,3,4-tetrahydropyridine by MAO-A (Heikkila *et al.*, 1988) and the binding of MPP^+ to MAO-A (May, 1993). In nonneuronal cells, MAO-A mediated oxidative stress and apoptosis after ischemia-perfusion in renal cells (Kunduzova *et al.*, 2002) and isolated rat cardiomyocytes (Bianchi *et al.*, 2005).

III. MAO-A in Neuroprotection by MAO-Is

Rasagiline and related MAO-B-Is protect neuronal cells against cell death induced by neurotoxins, oxidative stress, and withdrawal of NTFs, and also in animal models of neurodegenerative disorders (Gelowitz and Paterson, 1999; Huang *et al.*, 1999; Stefanova *et al.*, 2008; Yu *et al.*, 1994). These MAO-B-Is protected DA (Finberg *et al.*, 1998), NE (Finnegan *et al.*, 1990), and cholinergic neurons (Ricci *et al.*, 1992; Speiser *et al.*, 1998) from cytotoxicity of cell type-specified neurotoxins. These results indicate that neuroprotective MAO-Is intervene common death pathway and protect cells, regardless of the cell type and kind of insults.

A. MAO-A in the Suppression of Mitochondrial Death Signal by MAO-B-Is

Rasagiline and selegiline prevent MMPT and protect neuronal cells from PCD. *N*M*R*Sal and a TSPO ligand, PK11195, cause MMPT and release apoptogenic protein in the cytoplasm. Bcl-2 overexpression and rasagiline suppress apoptosis through regulation of MPPT (Fig. 1). Rasagiline prevented cell death caused by peroxynitrite, a reactive nitrogen species (RNS) in SH-SY5Y cells, but could not in MAO-B-expressing U118MG cells, demonstrating the involvement of MAO-A. However, ethanol induced apoptosis in the same U118MG cells through upregulation of GAPDH and MAO-B, which was prevented by rasagiline, its metabolite 1(*R*)-aminoindan, and selegiline (Ou *et al.*, 2009). The conflicting results may be due to the different insults and apoptosis pathways mediated by MPPT or GAPDH translocation.

Rasagiline and selegiline protect neurons by inhibition of PCD at the other points of death pathway. MAO-B-Is scavenge ROS–RNS (Thomas *et al.*, 1997), prevent the nuclear translocation of GAPDH (Tatton *et al.*, 2003), and down-regulate PARP-1 protein (Brabeck *et al.*, 2003). In mitochondria, rasagiline prevents the oxidative stress-caused changes in redox state, regulated by levels of reduced glutathione (GSH) and *S*-glutathionylated protein. *S*-Glutathionylation preserves the higher structure of the mitochondrial electron transport chain (Naoi *et al.*, 2008) and regulates the opening of mitochondrial permeability pore (MPP) through adenine nucleotide translocator (ANT; Costantini *et al.*, 2000).

Not only MAO-B-Is but also MAO-A-specific inhibitors, *N*-propargylamine and clorgyline, can protect neuronal cells. *N*-Propergylamine protected SH-SY5Y cells from cell death induced by neurotoxins, serum-withdrawn, and oxidative stress (Yi *et al.*, 2006b; Yogev-Falach *et al.*, 2003). Reversible MAO-A inhibitors, pirlindole and dehydropirlindole, protected primary cultured rat brain cells against cell death induced by oxidative stress (Boland *et al.*, 2002). Clorgyline reduced malonate-induced striatal damage in mice (Maragos *et al.*, 2004). In N2a cells, clorgyline prevented cell death caused by glutamate (Maher and Davis, 1996) and MPTP (De Girolamo *et al.*, 2001). Clorgyline was considered to protect cells though the MAO inhibition and reduction of ROS production.

B. MAO-A Mediates Prosurvival Bcl-2 Induction by MAO-Is

Bcl-2 protein family regulates MMPT, either in suppressive or promoting way (Shacka and Roth, 2005). The overexpression of neuroprotective *Bcl-2* suppressed the activation of death signal pathway (Maruyama *et al.*, 2001). On the other hand, in lymphocytes from patients with PD, the negative correlation was reported between Bcl-2 level and the duration and severity of the disease (Blandini *et al.*, 2004). Upregulation of proapoptotic Bak, Bad, Bcl-2, and Bcl-xL was also reported by postmortem studies of AD and PD brains (Kitamura *et al.*, 1998). However, these results may not imply a causal relationship between Bcl-2 family protein and neurodegeneration.

Bcl-2 prevents apoptosis by suppressing MMPT and Cyt *c* release (Fig. 1). Bcl-2 inhibits formation of mitochondrial pore, directly by the complex formation with proapoptotic Bax and Bak, or by the interaction with voltage-dependent anion channel (VDAC) and other components of MPP (Tsujimoto and Shimizu, 2000). In addition, Bcl-2 and Bcl-xL stabilize mitochondrial contact site, scavenge ROS–RNS, increase antioxidant enzymes, and keep the mitochondrial function (Jang and Surh, 2004). In apoptosis induced by ceramide and etoposide, Bcl-2 prevented directly caspase-2 activation and suppressed caspase-2- and -9-dependent apoptosis (Lin *et al.*, 2005).

Rasagiline and selegiline induced the mRNA and protein of antiapoptotic Bcl-2 and Bcl-xL, but not proapoptotic Bax. Neither TV1022, (*S*)-enantiomer of rasagiline, or clorgyline affected the Bcl-2 expression (Akao *et al.*, 2002b). Figure 2 shows that MAO-A is required for the induction of Bcl-2 in SH-SY5Y cells (Naoi *et al.*, 2006; Inaba-Hasegawa *et al.*, in preparation). The inhibition of *MaoA* expression with siRNA in SH-SY5Y cells reduced Bcl-2 increase by rasagiline and selegiline. Befloxatone, a reversible MAO-A-I increased Bcl-2 levels, which is consistent with the previous result with moclobemide (Chiou *et al.*, 2006). On the other hand, in MAO-B-expressing Caco-2 cells and U118MG cells, rasagiline

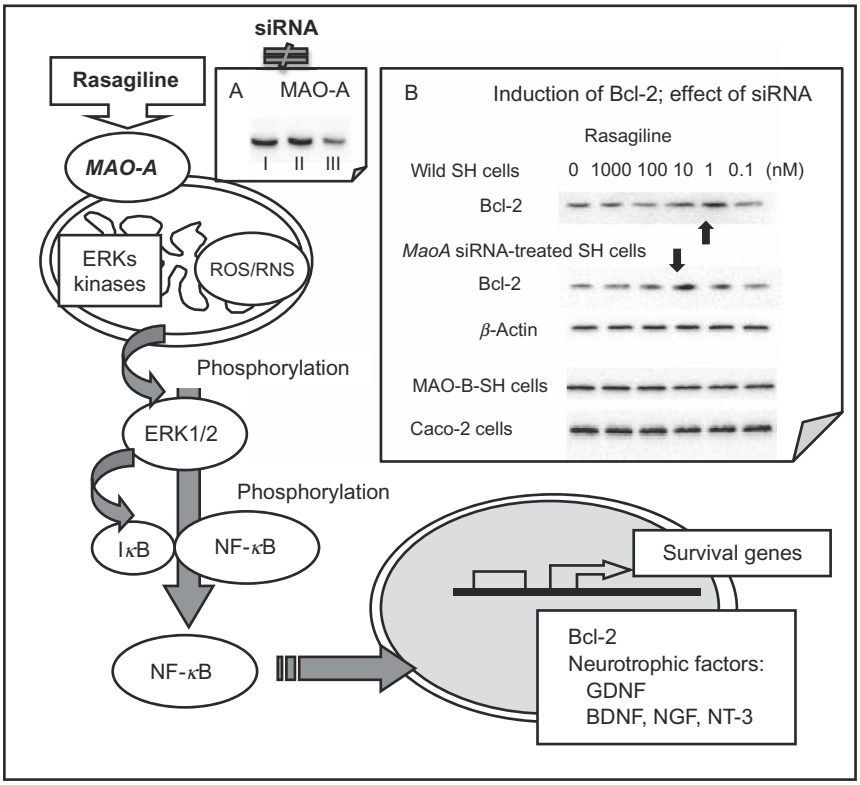

FIG. 2. Induction of Bcl-2 and prosurvival genes by rasagiline analogues and the effect of RNA interference of MAO-A. (A) MAO-A protein is decreased in cells treated with siRNA against *MaoA* (III) from wild (I) and nonspecific siRNA-treated cells (II). (B) Rasagiline increases Bcl-2 protein in wild SH-SY5Y cells, and siRNA treatment reduces the response to rasagiline, according to the reduction MAO-A protein. Rasagiline does not increase Bcl-2 in MAO-B-overexpressed SH cells or MAO-B-containing Caco-2 cells. The induction of prosurvival genes may be mediated through NF-κB activated by ROS–RNS or ERK1/2 or other kinases in mitochondria.

could not increase Bcl-2 expression. In *MaoB*-transfected SH-SY5Y cells, the response to rasagiline was markedly reduced, even though MAO-B protein was increased markedly. These results demonstrate that MAO-A is associated with increase of neuroprotective Bcl-2 protein by reversible and irreversible inhibitors of MAO-A and MAO-B.

IV. MAO-A in Induction of Neurotrophic Factors by MAO-Is

Selegiline and rasagiline increase *in vivo* and *in vitro* the expression of NTFs. NTFs are proposed as promising therapeutic tools for neurodegenerative disorders from their function in development, survival, and maintenance of specific neuronal subpopulations. Distinct NTF groups protect specified population of brain neurons, suggesting their beneficial application for different degenerative disorders and depression. NTFs comprise neurotrophin family, glial cell line-derived neurotrophic factors (GDNF) family ligands, neuropoietic cytokines, and a novel family consisting of mesencephalic astrocyte-derived neurotrophic factor (MANF; Petrova *et al.*, 2003) and cerebral dopamine neurotrophic factor (CDNF; Lindholm *et al.*, 2007). The role of MAO in the induction of neurotrophins and GDNF will be discussed in this review.

Neurotrophin family includes brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and neurotrophin-3 and -4/5 (NT-3, NT-4/5). In AD and depression, reduced BDNF levels and Val66Met polymorphism of BDNF are proposed as the pathogenic factors for selective neuronal loss (Feher *et al.*, 2009). GDNF family ligands are a member of transforming growth factor-β (TGF-β), include GDNF, neurturin, artemin, and persephin, and support dopaminergic and motor neurons in the brain (Pascual *et al.*, 2008; Sariola and Saarma, 2003). GDNF is proposed to preserve the function of DA neurons in PD and protection of nigra-striatal DA neurons was confirmed in animal PD model (Eslamboli *et al.*, 2005). However, the clinical trials to treat parkinsonian patients with GDNF could not fully prove the neuroprotective effects (Hong *et al.*, 2008; Lang *et al.*, 2006). The technical difficulties to deliver GDNF effectively in the targeted brain nuclei may account for nonbeneficial results in clinical trials. The upregulation of endogenous levels of GDNF and BDNF with brain-permeable molecules might be a more promising approach to rescue dying neurons.

Rasagiline and related propargylamine derivatives of MAO-B-Is increase NTFs and neuroprotective fibroblast growth factors in animal models. Selegiline increased the expression of basic fibroblast growth factor (bFGF) mRNA in rat brain (Biagini *et al.*, 1994), GDNF mRNA in rat striatum (Tang *et al.*, 1998) and of BDNF protein, but not CDNF, in mouse cortex (Gyarfas *et al.*, 2010). Rasagiline increased the mRNA and protein of BDNF in the rat midbrain (Weinreb *et al.*,

2009). Harmine, a MAO-A inhibitor, increased BDNF levels in rat hippocampus (Fortunato *et al.*, 2010). Rasagiline increased GDNF most prominently, followed by NGF, BDNF, and NT-3 in the cerebrospinal fluid (CSF) from nonhuman primate after the systematical administration, whereas selegiline increased BDNF in the CSF from patients with PD (Maruyama *et al.*, in preparation).

As summarized in Table I, MAO-Is increase NTFs in cellular models. Rasagiline increased mRNA and protein of GDNF in SH-SY5Y cells (Maruyama *et al.*, 2004a) and mRNA of BDNF and GDNF in serum-deprived cells PC12 and SH-SY5Y (Bar-Am *et al.*, 2005; Weinreb *et al.*, 2004; Yogev-Falach *et al.*, 2002, 2003). Selegiline increased mRNA of a ciliary neurotrophic factor (CNTF) in cultured rat astrocytes (Seniuk *et al.*, 1994), NGF in cultured rat cortical astrocytes (Semkova *et al.*, 1996), and BDNF and NT-3 in embryonic stem cells (Esmaeli *et al.*, 2006). Selegiline and desmethylselegine increased mRNA of NGF, BDNF, and GDNF in cultured mouse astrocytes (Mizuta *et al.*, 2000). *R*-(−)-1-(Benzofuran-2-yl)-2-propyl-aminopentane [(−)-BPAP], a MAO-A-I (Knoll *et al.*, 1999) and an antiapoptotic agent (Maruyama *et al.*, 2004b), increased NGF, BDNF, and GDNF in cultured mouse astrocytes (Shimazu *et al.*, 2003). Rasagiline and selegiline preferentially increased the mRNA and protein of GDNF and neurotrophins (BDNF, NGF. 3-NT), respectively, in SH-SY5Y cells (Maruyama *et al.*, in preparation). Recently, we confirmed that MAO-A in SH-SY5Y cells is required for MAO-I-dependent synthesis of BDNA, NGF, and GDNF, but they are not increased in MAO-B-overexpressing cells, as in the case with Bcl-2 induction.

The effects of MAO-Is on NTFs have been studied *in vitro* using only limited types of cultured cell lines: SH-SY5Y and related neuroblastoma cells and astrocytes and related glioblastoma cells (Table I). These cell lines were used for the NTF induction by other small molecules. Antidepressants increased mRNA of neurotrophins and GDNF (Henkel *et al.*, 2008) and an antipsychotic olanzapine enhanced BDNF mRNA in SH-SY5Y cells (Lee *et al.*, 2010). In astrocytes, monoamine neurotransmitters increased NTFs (Mele *et al.*, 2010), and apomorphine (Ohta *et al.*, 2000) and cabergoline, a D2 agonist, simulated the synthesis of NGF, BDNF, and GDNF in cultured mouse astrocytes (Ohta *et al.*, 2004). At present, it remains to be clarified whether these compounds require MAO for the NFT induction.

V. Is MAO-A the Binding Site of MAO-Is for Induction of Neuroprotective Genes?

The binding site of rasagiline analogues in MAO-B has been intensively studied (Binda *et al.*, 2004), but it remains elusive how MAO-Is bind to MAO-A and induce prosurvival genes in nuclei. Rasagiline and selegiline inhibit MAO-A activity in a noncompetitive way to substrate and befloxatone and moclobemide are reversible MAO-A-Is, and all these MAO-Is induce Bcl-2 through binding to

Table I
Induction of Prosurvival Neurotrophic Factors by Rasagiline, Selegiline, and the Related Compounds.

MAO-Is	Induced gene product	Cell type	Type of MAO	Reference
Rasagiline	GDNF mRNA, protein	SH-SY5Y cells	MAO-A	Maruyama *et al.* (2004a)
	BDNF mRNA	PC12 cells	MAO-A	Yogev-Falach *et al.* (2002) Weinreb *et al.* (2004)
Rasagiline	BDNF, GDNF mRNA	SH-SY5Y cells	MAO-A	Bar-Am *et al.* (2005)
Rasagiline/selegiline	BDNF, NGF, NT-3, GDNF Protein, mRNA	SH-SY5Y cells	MAO-A	Maruyama *et al.* (in preparation) Inaba-Hasegawa (in preparation)
Selegiline	CTNF mRNA	Rat cortical astrocytes	MAO-B	Seniuk *et al.* (1994)
Selegiline	NGF mRNA, protein	Rat cortical astrocytes	MAO-B	Semkova *et al.* (1996)
Selegiline	NGF, BDNF, GDNF mRNA	Mouse astrocytes	MAO-B	Mizuta *et al.* (2000)
Selegiline	BDNF, NT-3	Embryonic stem cells	*	Esmaeli *et al.* (2006)
N-Propargylamine	GDNF, BDNF mRNA	SH-SY5Y cells, serum-deprived	MAO-A	Bar-Am *et al.* (2005)
(−)-BPAP, selegiline	NGF, BDNF, GDNF	Mouse astrocytes	MAO-B	Shimazu *et al.* (2003)
DA, NE, E	NT-3	Rat cortical astrocytes	*	Mele *et al.* (2010)

* MAO type was not mentioned.

MAO-A. These results suggest that the binding of neuroprotective MAO-Is to MAO-A may occur at the site other than the substrate-binding site. Imidazoline-binding domain is localized in MAO-B at the residues between K148 and M222 (Raddatz, *et al.*, 1997), and the imidazoline I_2-site ligands inhibit MAO-A and MAO-B activities in rat liver and adipocytes (Bour *et al.*, 2006; Ozaita *et al.*, 1997). However, an I_2 ligand guanabenze induced apoptosis in SH-SY5Y cells, which was inhibited by rasagiline, suggesting that rasagiline binds to MAO-A at the site different from the imidazoline-binding site (Inaba-Hasegawa *et al.*, in preparation). On the other hand, agmatine an endogenous I_2 ligand showed neuroprotective effects by *in vivo* and *in vitro* experiments (Qiu and Zheng, 2006), but the role of MAO was not studied in these studies.

TSPO is an MPP component, and PK11195 and other TSPO ligands inhibit the activity of MAO-A in preference to MAO-B and induce apoptosis in cells through MPP opening, which rasagiline can suppress completely. However, TSPO ligands do not increase Bcl-2 in SH-SY5Y cells and rasagiline does not bind to TSPO, suggesting that TSPO is not associated with the induction of prosurvival genes (Naoi *et al.*, in preparation). MAO-Is can bind to other proteins: D_2 DA receptor in rat striatal membrane (Levant, 2002), GAPDH (Ou *et al.*, 2009; Tatton *et al.*, 2003), and semicarbazide-sensitive amine oxidase (SSAO, EC 1.4.3.4; Holt *et al.*, 2004). However, it is not clear whether these proteins mediate MAO-I-dependent increase of prosurvival genes.

VI. Signal Pathway for Induction of Prosurvival Genes by MAO-Is

The signal pathway to increase the Bcl-2 and NTF transcription is another interesting issue. The constitutive Bcl-2 expression is regulated by extracellular signal-regulated kinases1/2 (ERK1/2)–nuclear factor-κB (NF-κB) pathway as proved by selective inhibitors of these kinases (Naoi *et al.*, 2007). Rasagiline increased NTFs and Bcl-2 through this ERK1/2–NF-κB pathway (Maruyama *et al.*, 2004a). Rasagiline and structurally related TV3326 [(*N*-propargyl-(3*R*)-aminoindan-5-yl)-ethyl methyl carbamate] and its (3*S*)-enantiomer TV3279 activated protein kinase C (PKC), MAPK, and tyrosine kinase-dependent pathway (Bar-Am *et al.*, 2004; Sagi *et al.*, 2003; Weinreb *et al.*, 2004; Yogev-Falach *et al.*, 2002). As alterative pathways, selegiline activated protein kinase A (PKA)-ERK1/2-c-Myc pathway to induce thioredoxin (Andoh *et al.*, 2005), and selegiline also activated phosphoinositol-3-kinase (PI3K)–nuclear factor-E2-related factor-2 (Nrf2) pathway to induce antioxidant enzymes in SH-SY5Y cells (Nakaso *et al.*, 2006). It has not been confirmed which signal pathway is primarily activated by MAO-Is, and the receptor or binding site of rasagiline and selegiline on the cell surface is not identified.

How does MAO on mitochondrial outer membrane mediate the signals to nuclei? Recently, several factors are proposed as the signals from mitochondria to nuclei. ROS and RNS activate mitochondrial kinases and mediate stress signaling from mitochondria to nuclei through activation of ERK1/2–NF-κB pathway (Biswas *et al.*, 2003; Dagda *et al.*, 2009; Horbinski and Chu, 2005). Activation of ERK1/2–NF-κB pathway in mitochondria functions either prosurvival or proapoptotic signaling, and NF-κB activation promotes cell survival through induction of antioxidant genes with a few exceptions (Morgan and Liu, 2011). It should be further studied whether rasagiline analogues activate prosurvival signal pathway in nuclei via regulation of redox state or through the activation of ERK–NF-κB signal pathway in mitochondria.

VII. Discussion

The association of MAO-A with neuronal death in PD is shown by the fact that MAO-A is a target of dopaminergic neurotoxins. However, we should be cautious to apply the results to neurodegenerative disorders and depression in general, since the cell death is regulated by various genetic and environmental factors. On the other hand, rasagiline and related MAO-B-Is are now proposed as neuroprotective agents in PD and AD, whereas selegiline and reversible MAO-A-Is are used as antidepressants. However, the role of MAO in promoting neuronal survival and ameliorating functional deterioration has not been well clarified. Recent advances in gene engineering to express *Mao* in specified neurons of brain region (Chen *et al.*, 2007) will bring us new insight on the function of MAO at the distinct phase of brain aging.

MAO-A may be associated with the fate of neuronal cells through regulation of 5-HT levels in the brain. 5-HT reduced apoptosis induced by *N*MM*R*Sal through inhibiting the binding of the neurotoxin to MAO-A (Yi *et al.*, 2006a). In MAO-KO mice, proliferation of neuronal stem cells was diminished in the developing telencephalom and the deficit persisted in adult mice (Cheng *et al.*, 2010). Inhibition of MAO-A induced the differentiation of neural stem cells into serotonergic cells (Chiou *et al.*, 2006). These results show that MAO-A regulates neuronal development though controlling 5-HT level, which promotes proliferation and inhibits differentiation.

The induction of Bcl-2 and NTFs is clearly associated with MAO, as shown in Fig. 2. Considering that NTF signaling regulates Bcl-2 expression, the NTF induction may be the most vital for the neuroprotective activity of MAO-Is. BDNF binds to its tyrosine kinase receptor, TrkB, and activates prosurvival signal pathways, MAPK/ERK and PI3-kinase/Akt kinase cascade to increase neuroprotective genes (Almeida *et al.*, 2005). NGF downregulates Bim, the proapoptotic BH3-domain-only number of Bcl-2 family, by phosphorylation through MEK/MAP kinase

pathway in PC12 cells (Biswas and Greene, 2002). Previous papers present that NTFs are increased by irreversible and reversible MAO-Is only in MAO-A- or MAO-B-expressing cells, suggesting that MAO-A or MAO-B is required for the induction of NTFs. However, this issue also should be further studied in details.

In addition to propargylamine derivatives of MAO-B-Is, various reversible and irreversible inhibitors of MAO-A and MAO-B have been developed for the application as neuroprotective agents for AD and PD. VK-28 and M30, 8-hydroxyquinoline derivatives, are inhibitors of MAO-A and MAO-B and iron chelators, and they protected *in vivo* and *in vitro* neuronal cells from neurotoxins and oxidative stress (Gal *et al.*, 2005; Shachar *et al.*, 2004). A MAO-B-I, PF9601N [*N*-(2-propyl)-2-(5-benzyloxy-indolyl) methylamine] protected SH-SY5Y cells against MPP^+ toxicity (Sanz *et al.*, 2008). However, the association of MAO with their neuroprotective functions has not well been confirmed.

Upregulation of *MaoA* expression was observed in apoptosis, suggesting that *MaoA* may be an apoptogenic gene. NGF- or serum-withdrawal increased *MaoA* expression in PC12 or SK-N-BE(2)-C cells, and MAO-A was proposed as a target of proapoptotic p38 MAP kinase (De Zutter and Davis, 2001; Ou *et al.*, 2006). MAO-A synthesis is activated by Sp-1 and regulated by a repressor R1 (Zhu *et al.*, 1994; Chen *et al.*, 2005). However, we recently found that rasagiline increased *MaoA* expression through decrease of R1 in SH-SY5Y cells, whereas selegiline did not increase the expression, as reported in 1242 MG glioma cells (Ekblom *et al.*, 1996). The different effects of rasagiline and selegiline on *MaoA* expression are now studied.

As a conclusion, MAO-A regulates cellular signaling systems, especially ERK-NF-κB pathway, and plays a decisive role in the survival, death, and differentiation of cells in physiological conditions and neuropsychiatric disorders, PD and AD. In depression, MAO-A and BDNF may be not only associated with the etiology but also the response to the treatment (Balu *et al.*, 2008; Domschke *et al.*, 2008). MAO-A variants may determine the treatment responses, which may be ascribed to the difference in MAO-A-mediated BDNF induction by antidepressants. Our recent results on the different induction of neurotrophins and GDNF analogues by selegiline and rasagiline suggest the opportunities to increase endogenous NTFs specific for selective neuronal system: BDNF in depression and GDNF in PD. Compounds with high affinity to MAO-A should be screened for the induction of prosurvival genes and new therapeutic strategy will be developed for protection of neuronal cells in neurodegenerative disorders and depression.

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