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NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - REVIEW ARTICLE

Type A and B monoamine oxidases distinctly modulate signal transduction pathway and gene expression to regulate brain function and survival of neurons

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Abstract

Type A and B monoamine oxidases (MAO-A, -B) mediate and modulate intracellular signal pathways for survival or death of neuronal cells. MAO-A is associated with development of neuronal architecture, synaptic activity, and onset of psychiatric disorders, including depression, and antisocial aggressive impulsive behaviors. MAO-B produces hydrogen peroxide and plays a vital role in neuronal loss of neurodegenerative disorders, such as Parkinson's and Alzheimer's diseases. This review presents a novel role of MAO-A and B, their substrates and inhibitors, and hydrogen peroxide in brain function and neuronal survival and death. MAO-A activity is regulated not only by genetic factor, but also by environmental factors, including stress, hormonal deregulation, and food factors. MAO-A activity fluctuates by genetic–environmental factors, modulates the neuronal response to the stimuli, and affects behavior and emotional activities. MAO-B inhibitors selegiline and rasagiline protect neurons via increase expression of anti-apoptotic Bcl-2 and pro-survival neurotrophic factors in human neuroblastoma SH-SY5Y and glioblastoma U118MG cell lines. MAO-A knockdown suppressed the rasagiline-induced gene expression in SH-SY5Y cells, whereas MAO-B silencing enhanced the basal- and selegiline-induced gene expression in U118MG cells. MAO-A and B were shown to function as a mediator or repressor of gene expression, respectively. Further study on cellular mechanism underlying regulation of signal pathways by MAO-A and B may bring us a new insight on the role of MAOs in decision of neuronal fate and the development of novel therapeutic strategy may be expected for neuropsychiatric disorders.

Keywords Type A and B monoamine oxidase · Neuroprotection · Neurotrophic factor · Gene expression · Selegiline · Rasagiline

Abbreviations

ERK	Extracellular signal-regulated protein kinase
ETC	Electron transfer chain
KLF	Krüppel-like factor
MAO-A and MAO-B	Type A and B monoamine oxidase
mao-A and *mao-B* KD, KO	MAO-A and MAO-B knockdown, knockout
NHLH2	Nescient helix-loop-helix 2
NTF	Neurotrophic factor
PI3K	Phosphatidylinisitol-3 kinase
siMao-A, siMao-B, siNS	siRNA against *mao-A* and *mao-B,* and non-specific
Sp1	Specificity protein 1

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Introduction

Monoamine oxidase [monoamine: oxygen oxidoreductase (deaminating), EC 1.4.3.4, MAO] catalyzes the oxidative deamination of monoamine neurotransmitters, dietary amines, and xenobiotics, and regulates their levels and functions in the brain. Oxidative deamination by MAO produces the corresponding aldehyde and hydrogen peroxide (H_2O_2), a potent reactive oxygen species (ROS). Oxidative stress and

mitochondrial dysfunction are major risk factors common for neuronal loss in aging and age-related neurodegenerative disorders, such as Parkinson's and Alzheimer's diseases (PD and AD). MAO is classified into two classes, types A and B (MAO-A and MAO-B), according to the sensitivity to inhibitors and the affinity to substrates (Shih et al. 1999; Youdim and Bakhle 2006). MAO-A is selectively inhibited by clorgyline [3-(2,4-dichlorophenoxy)-*N*-methyl-*N*-prop-2-ylyl-propan-1-amine] and MAO-B by selegiline [(−)deprenyl, (2*R*)-*N*-methyl-1-phenyl-*N*-pro-2-ynyl-propan-2-amine] and rasagiline [(1*R*)-*N*-prop-2-ynyl-2,3-dihydro-1*H*-amine]. Serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine (NE) are oxidized by MAO-A, whereas phenylethylamine, benzylamine, and octopamine are by MAO-B. Dopamine (DA) and tyramine are the substrates for both MAO-A and MAO-B.

MAO-A and B are expressed in distinct population of neuronal cells. MAO-A occurs predominantly in catecholaminergic neurons and MAO-B in serotonergic and histaminergic neurons and astrocytes (Riederer et al. 1989; Saura et al. 1996). MAO-A level in the brain is determined before the birth, and MAO-A regulates development of neuronal architecture coordinately with its major substrate 5-HT (Buckholtz and Mayer-Lindenberg 2008; Naoi et al. 2016, 2017a). MAO-B appears only in the postnatal stage and increases with age, suggesting its association with neuronal loss in aging and neurodegenerative disorders (Fowler et al. 1997). These isoenzymes are involved differentially in the brain function at the specified life stage, even though they share 70% common amino acid sequences and the same FAD coenzyme covalently bound to cysteine in the common pentapeptide sequence.

MAO-A has been proposed as a mediator or modifier of intracellular signal pathway directly and indirectly by regulation of the substrate monoamine levels and H_2O_2 production. This review will discuss mainly the recent research advances on the role of MAO-A and B in regulation of survival and death of neurons and in neuroprotection by MAO-B inhibitors and other bioactive compounds (Naoi et al. 2012; Finberg and Rabey 2016). MAO-A and MAO-B were confirmed to regulate expression of neuroprotective Bcl-2, neurotrophic factors, and the opposite MAO isoenzyme either in a promoting or suppressive way in human neuroblastoma SH-SY5Y and glioblastoma U118MG cells, respectively (Inaba-Hasegawa et al. 2012, 2017a). MAO-A activity fluctuates in respond to genetic and environmental stimuli, and the association with psychiatric disorders, such as depression and antisocial behavior, is discussed.

MAO-A and B are involved in neuronal death by different mechanisms

MAO-A in apoptosis

In the embryonic mouse brain, MAO-A is essentially required for apoptosis for development of neuronal architecture, as demonstrated by *mao-A* knockout (KO) (Wang et al. 2011). MAO-A is directly associated with death signaling in neuronal cells. A dopaminergic neurotoxin *N*-methyl(*R*)salsolinol was shown to bind to MAO-A at the substrate-binding site and induce apoptosis in SH-SY5Y cells, which *mao-A* knockdown (KD) with short interfering (siRNA) inhibited (Yi et al. 2006a). In apoptosis induced by NGF withdrawn in PC12 cells, MAO-A expression increased by activation of p38 mitogen-activated protein kinase (MAPK) pathway (De Zutter and Davis 2001). Increased MAO-A oxidized DA, enhanced H_2O_2 production and caused apoptosis, which was prevented by clorgyline. Decrease of an MAO-A repressor transcription factor R1 (RAM2/CDCA7L/JPO2) was reported to account for increased MAO-A expression (Ou et al. 2006a). Posttranslational increase of MAO-A mRNA, protein, and activity was detected in apoptosis induced by staurosporine, serum withdrawal, and inhibitors of complexes I, III, and IV in SH-SY5Y cells. MAO inhibitors, anti-oxidants, and *mao-A* KD with micro-RNA (miRNA) suppressed the cell death, suggesting that MAO-A-dependent ROS production caused cell death (Fitzgerald et al. 2007, 2014).

MAO-B in neurodegeneration

On the other hand, mainly, MAO-B oxidizes DA in the human brain (Glover et al. 1977) and it produces toxic 1-methyl-4-phenylpyridinium ion (MPP^+) from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Heikkila et al. 1984). Therefore, MAO-B is proposed as a principal player in "oxidative stress hypothesis" for the pathogenesis of PD, AD, and other neurodegenerative disorders. MAO-B mRNA and enzymatic activity increased in the platelets from patients with PD, AD, and Huntington disease (HD) (Götz et al. 1998; Zhou et al. 2001). These results suggest the contribution of MAO-B to neurodegeneration via oxidative stress in the brain.

The toxic molecule hydrogen peroxide functions as a signaling molecule

Cytotoxicity of H_2O_2 in neurodegeneration

MAO localized at the outer mitochondrial membrane produces H_2O_2 and increases ROS levels in the mitochondrial matrix and cytosol (Fig. 1). Enzymatic oxidation of tyramine by MAO increased intra-mitochondrial H_2O_2 level to 48-folds of the basal level of H_2O_2 produced in complex II of the electron transfer chain (ETC) in the presence of antimycin A (Hauptman et al. 1996). Declined activity of complex I in the ETC in parkinsonian brain (Mizuno et al. 1989) and complexes I, III, and IV in Alzheimer's disease (Valla et al. 2006) indicates that MAO mainly contributes to oxidative stress in mitochondria and subsequent neurodegeneration in these disorders. H_2O_2 is cleaved by transition metals bond to mitochondrial DNA into hydroxyl radical ($OH^{\cdot -}$), which causes single-strand breaks in mitochondrial DNA and impairs mitochondrial function (Giorgio et al. 2007). H_2O_2 induced mitochondrial permeability transition, an initial step of apoptosis (Marcocci et al. 2002) by oxidation of vital thiol residues in adenine–nucleotide translocator (ANT), a component of the mitochondrial permeability transition pore (Costantini et al. 1996). H_2O_2 activates ataxia–telangiectasia mutated (ATM) kinase and the tumor suppressor protein p53, and induces transcriptionally growth arrest and cell death.

H_2O_2 as a modulator in signal pathway

H_2O_2 functions as a signaling molecule for physiological processes to control cellular growth and death. H_2O_2 is membrane-permeable and diffusible, longer-lived than superoxide ($O_2^{\cdot -}$) or $OH^{\cdot -}$, and serves as a redox signal and regulator of transcription factors (Marinho et al. 2014). Beneficial and harmful functions of H_2O_2 depend on the intracellular concentrations, the physiological range of which spans between 10 and 100 nM (Sies 2017). At lower concentrations about 10 nM, cells respond to H_2O_2 towards proliferation and adaptation to stress by activating signal pathways, such as the nuclear factor erythroid 2-related factor 2 (Nrf2)-antioxidant response element (ARE) (Gan and Johnson Gan and Johnson 2014). H_2O_2 activates transcription factors, such as activator protein-1 (AP-1), cAMP-response-element-binding protein (CREB), heat shock factor 1 (HSF1), hypoxia-inducible factor 1 (HIF-1), NF-κB, NOTCH, and specificity protein 1 (Sp1) (Sies 2014). The activation is mediated by multiple diverse mechanisms,

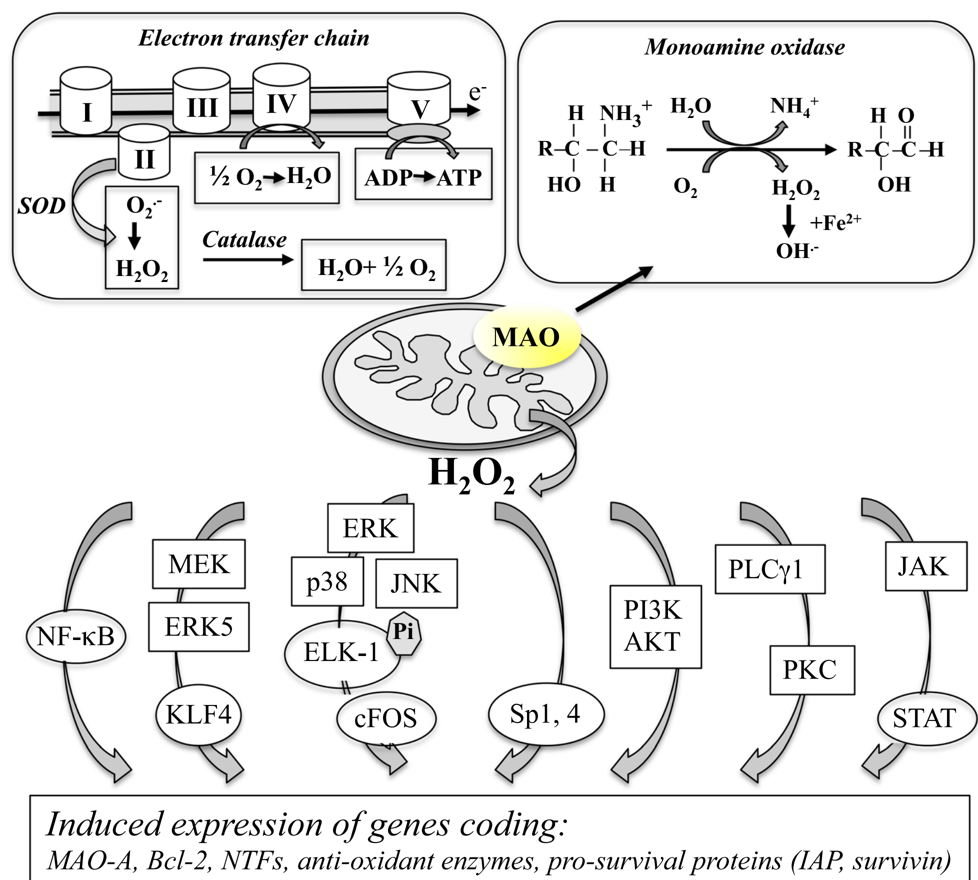

Fig. 1 H_2O_2 is produced in mitochondria mainly by the ETC and MAO, and activates various signal pathways. H_2O_2 activates receptors and enzymes (shown in boxes), and transcription factors (ovals) to increase gene expression and determine the fate of neurons. Figure presents protective signaling pathways detected in the brain, and abbreviations used here are as follows. *ELK-1* Ets-like protein-1, *ERK* extracellular signal-regulated protein kinase, *IAP* inhibitor of apoptosis, *JAK* Janus protein kinase, *JNK* c-Jun *N*-terminal kinase, *KLF* Krüppel-like factor, *MEK* mitogen-activated protein/ERK kinase, *Pi* phosphate, *PLCγ1* phospholipase C-γ1, *STAT* signal transducers and activators of transcription

leading to cell death or survival (Martindale and Holbrook 2002). Figure 1 presents signal pathways activated by H_2O_2 to protect neuronal cells.

H_2O_2 signaling is cellular-specific, and H_2O_2 activated the pro-survival zinc finger transcription factor Sp1 in neurons, but did not in glia (Ryu et al. 2003). H_2O_2 increased Sp1 level and its binding to DNA in nuclei of cortical neurons, and enhanced gene expression for neuroprotection. Dexamethasone activated H_2O_2–Sp1 pathway and increased MAO-A expression transcriptionally and translationally, but did not affect MAO-B (Manoli et al. 2005). H_2O_2 increased glial cell line derived neurotrophic factor (GDNF) mRNA and protein in the substantia nigra neuron-glia cell cultures by activation of phosphatidylinisitol-3 kinase (PI3K) and MAPK pathway (Saavedra et al. 2006; Fonseca et al. 2014). H_2O_2 increased Bcl-2/Bax ratio and neuronal apoptosis inhibitory protein (NAIP) in PC12 cells by activation of extracellular signal-regulated protein kinase (ERK) 5—Krüppel-like factor (KLF) 4 signaling (Su et al. 2014). H_2O_2 activated p38 MAPK, c-JUN amino-terminal kinase (JNK), and ERK, which further activated Ets-like protein-1 (ELK-1), leading to transcriptional activation of c-FOS. On the other hand, a transitional increase in intracellular H_2O_2 level activated receptor tyrosine kinases (RTKs) of epidermal growth factor (EGF) receptor and platelet-derived growth factor (PDGF) receptor and activated downstream MAPK and PI3K/Akt pathway to promote proliferation, differentiation, and chemotaxis in cancer and atherosclerosis (Catarzi et al. 2005; Truong and Carroll 2012).

MAO-B inhibitors, monoamines, and MAO-B regulate MAO-A expression

R1 a transcription repressor binds to Sp1/KLF-binding sites in *mao-A* core promoter, and inhibits MAO-A promoter and enzymatic activity (Fig. 2). Increased MAO-A in depression was mediated by R1–Sp1 pathway (Johnson et al. 2011;

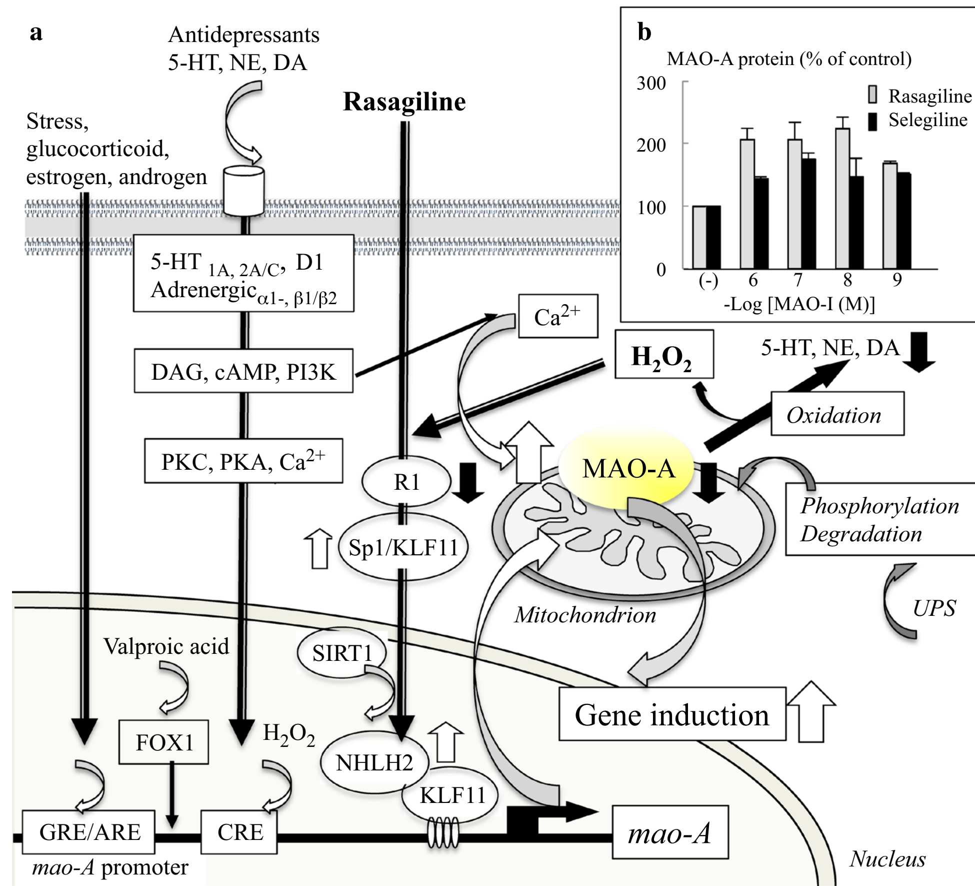

Fig. 2 In SH-SY5Y cells, various factors affect MAO-A expression. **a** Rasagiline and H_2O_2 increase MAO-A expression transcriptionally by reduction of R1 suppressor and activation of KLF11 transcription factor. MAO-A substrates, 5-HT, NE, and DA increase MAO-A by the receptors and activate signals, such as diacetyl glycol (DAG), cAMP, and PI3K. Stress, glucocorticoid, and estrogen increase MAO-A by mean of the receptors in nucleus. Modification and degradation of MAO protein by the ubiquitin–proteasome system (UPS) decrease MAO-A activity. **b** MAO-B inhibitors increased MAO-A protein. Rasagiline upregulated MAO-A mRNA, protein, and activity by R1-Sp1/KLF11 transcription pathway, but the increase by selegiline did not depend on this pathway (Inaba-Hasegawa et al. 2013)

Harris et al. 2015). KLF11 [also called transforming growth factor β-inducible early gene 2 (TIEG2)] is an *mao-A* transcriptional activator. Sp1/KLF pathway takes part in cell proliferation, apoptosis, differentiation, and neoplastic transformation. KLF11 and related transcription factors interact with histone acetyl transferase (HAT) and upregulate *mao-A* expression in chronic social defeat stress (Grunewald et al. 2012).

Rasagiline and selegiline increased MAO-A distinctly depending on MAO-A and B in neuronal and glial cells

In human neuroblastoma SH-SY5Y cells, rasagiline and selegiline (10^{-6} to 10^{-12} M) increased MAO-A mRNA, protein, and activity (Fig. 2) (Inaba-Hasegawa et al. 2013). R1–Sp1/KLF11 pathway mediated rasagiline-induced MAO-A expression, but this pathway did not mediate selegiline-increased MAO-A expression.

In SH-SY5Y cells, siRNA against MAO-A (*siMao-A*) treatment downregulated MAO-A expression, but did not affect MAO-B (Inaba-Hasegawa et al. 2013). On the other hand, in human glioblastoma U118MG cells, treatment with siRNA against MAO-B (*siMao-B*) significantly upregulated *mao-A* expression, and selegiline (10^{-6} to 10^{-10} M) synergistically increased *mao-A* expression, whereas *siMao-A* did not affect *mao-B* (Inaba-Hasegawa et al. 2017a).

MAO-A substrates increased MAO-A activity

The substrate availability affects MAO-A expression. DA and NE dynamically enhanced MAO-A activity by D_2-like receptor in rat mesangial cells (Pizzinat et al. 2003). 5-HT reduction by tryptophan depletion decreased MAO-A binding in the prefrontal cortex, whereas DA increase by carbidopa–levodopa administration enhanced MAO-A in the striatum of healthy volunteers measured with [^{11}C]-harmine positron emission tomography (PET) (Sacher et al. 2012). In primary cultured astrocytes, MAO oxidized DA, produces H_2O_2, activates Ca^{2+} signaling, and increased MAO-A activity (Vaarmann et al. 2010). 5-HT, NE, and DA have been presented to activate signal pathways, increase MAO-A expression, and affect brain architecture in developmental period and adulthood neurogenesis in the hippocampus, and impact affective and aggressive behaviors (McCarthy et al. 2007; Yu et al. 2014).

However, in *mao-A* and *mao-B* KO mice, no compensatory increase in MAO-B or MAO-A was observed (Holschneider et al. 2001). Induction of *mao-A* mRNA expression by rasagiline was transit (Inaba-Hasegawa et al. 2013), suggesting that MAO-A expression and activity may fluctuate transitionally and reversely in response to changes in monoamine and H_2O_2 levels in the brain.

Genetic, biological, and environmental factors regulate MAO-A activity

MAO-A activity is regulated by gene–environment interaction

Altered expression of MAO-A is recognized in psychiatric disorders (Shih et al. 2011; Mousseau and Baker 2012; Godar et al. 2016), and even modest increase in MAO-A activity was associated with depression (Meyer et al. 2006). Association between functional polymorphism of MAO and environmental factors has been confirmed. A VNTR polymorphism of *mao-A* promoter with low transcription activity was detected in impulsive, aggressive behavior, and alcoholism (Ducci et al. 2008; Sjöberg et al. 2008). Environmental factors, such as abuse exposure in childhood, sexual abuse, and maternal stress, have been reported to decrease MAO-A activity and cause aggressive, impulsive, and antisocial behaviors (Huang et al. 2004; Fergusson et al. 2011; Byrd and Manuck 2014). Fluctuation of MAO-A activity at the distinct period of life may affect behavioral and emotional function during later life stages.

Stress and hormone affect MAO-A activity

MAO-A expression is regulated by hormonal system. Acute stress significantly decreases MAO-A activity in the human brain, and acute dexamethasone exposure decreased MAO-A protein and activity by 30–39% in SH-SY5Y and 1242-MG cells (Soliman et al. 2012). Chronic stress deregulates the hypothalamic–pituitary–adrenal (PHA) axis, activates Sp1/KLF11 signal pathway, and upregulates MAO-A and MAO-B mRNA and enzymatic activity (Chen et al. 2011; Harris et al. 2015). Glucocorticoid (GC) and androgen increased MAO-A activity by direct interaction of glucocorticoid/androgen receptors with the third glucocorticoid/androgen response element (GRE) in the promoter (Ou et al. 2006b). MAO-A expression increased in depression of postpartum or perimenopausal period by age-dependent reduction of estrogen and progesterone (Sacher et al. 2010, 2015; Rekkas et al. 2014).

Genes related to AD and PD are involved in MAO-A expression

Genes related to the familiar forms of PD and AD affect MAO-A expression. Parkin suppressed MAO-A and MAO-B activities in SH-SY5Y cells (Jiang et al. 2006). Parkin-induced degradation of estrogen-related receptors (ERRs) and inhibited MAO expression, whereas the PD-linked mutants did not affect MAO activity (Ren et al. 2011).

Wild and AD-related presenilin-1 (PS-1) variants physically interacted with MAO-A and affected the activity in mouse hippocampal HT-22 cells and PS-1 knock-in mice, and the ΔEx9, A431E, and A235V variants increased MAO-A activity (Pennington et al. 2011; Wei et al. 2012a). Increased MAO-A activity was proposed to cause depressive state in AD.

Modification of MAO protein

Modification of MAO protein also affects the enzymatic activity. Ca^{2+} increased MAO-A activity in monkey brain, mouse, and rat (Egashira et al. 2003; Samantaray et al. 2003), which might increase ROS and promote aging process (Cao et al. 2007). Ca^{2+} bound to serine 209 residue and increased MAO-A, which was inhibited by the phosphorylation with activated p38(MAPK) (Cao et al. 2009). Rines/RNF180, the RING finger-type E3 ubiquitin ligase, interacted with MAO-A, and promoted its ubiquitination and degradation, whereas Rines KO increased MAO-A activity in the locus coeruleus of mice (Kabayama et al. 2013).

MAO-B expression is elevated in PD, AD, alcoholism, and other psychiatric disorders

MAO-B in PD and AD

As discussed above, MAO-B has been proposed as a pathogenic factor of PD, but the increased activity is mainly due to massive gliosis in the substantia nigra, especially in the recessive forms of PD caused by mutation in PINK-1, parkin, and DJ-1 (Haneka et al. 2010). MAO-B activity increased in reactive astrocytes of senile plaques (Nakamura et al. 1990) and oxidative stress and loss of nigra-striatal were induced in dopaminergic neurons of PD mouse model (Liu et al. 2013). Occurrence of the intron 13 single-nucleotide polymorphism (SNPs) (rs1799836) of *mao-B* was reported in the female parkinsonian patients (Kang et al. 2006). Allele G of intron 13 has significantly higher transcriptional activity than allele A (Costa-Mallen et al. 2005), and A/G dimorphism in intron 13 sequence increased MAO-B mRNA and protein in PD and AD (Balciuniene et al. 2002; Jakubauskiene et al. 2012).

MAO-B expression increased in the brain and platelet of patients with AD (Gulyas et al. 2011; Zellner et al. 2012). MAO-B was associated with γ-secretase in the human brain, and increased with Aβ42 level in pyramidal neurons of the AD brain. Silencing MAO-B with siRNA reduced intraneuronal Aβ42 in mouse primary cultured cortical neurons, and MAO-B overexpression increased it in HerpG2 cells (Schedin-Weiss et al. 2017).

MAO-B expression in alcoholism and other psychiatric disorders

Increased platelet MAO-B activity was detected in subjects with alcohol dependence, with cognitive deficiency and loss of neurons and glia (Erjavec et al. 2014). MAO-B protein and KLF11 were upregulated in the prefrontal cortex of human alcohol dependence, leading to neuronal loss (Udemgba et al. 2014). Human *mao-B* core promoter fragment contains two clusters of overlapping Sp/KLF-binding sites separated by a CSCCC element and a TATA box, whereas *mao-A* core promoter consists of three Sp1 binding sites in reversed orientation without a TATA box. Sp1 sites contribute positively to the transcriptional activity, whereas the CACCC element negatively. Sp1 and Sp4 activate MAO-B promoter activity, and Sp3 represses (Wong et al. 2001). Decrease in methylation of the CpG sites and Sp3 upregulated MAO-B expression (Wong et al. 2003). Selegiline and rasagiline prevented the increase in KLF11–MAO-B activity by ethanol and protected SH-SY5Y cells and brain injury of rats exposed to binge ethanol (Lu et al. 2008; Duncan et al. 2016).

A sex-specific association between *mao-B* rs1799836 with increased frequency of G allele was detected in Spanish female patients with schizophrenia (Gasso et al. 2008). Platelet MAO-B activity increased in patients with post-traumatic stress disorder (PTSD) (Strac et al. 2016). Two *mao-B* SNPs, rs10521432 and rs6651806, out of 12 SNPs, were reported in negative emotionality (Dlugos et al. 2009). Platelet MAO-B activity was higher in subjects with severe agitation than non-agitated subjects, but no association was found between severe agitation and *mao-b* rs1799836 polymorphism in Caucasian male subjects (Perkovic et al. 2016).

Phorbol-12-myristale-13-acetate (PMA) is an extracellular stress inducer and increased MAO-B expression via activation of protein kinase C (PKC) and MAPK involving Sp1, Sp3, c-Jun, and early growth response 1 (Egr-1) (Wong et al. 2002). The fourth estrogen response element in *mao-B* promoter overlaps with a consensus retinoic acid receptor element (RARE), and retinoic acid activated *mao-B* promoter through activation of retinoic acid receptor α (RARα) and retinoid X receptor α (RXRα) in BE(2)C cells (Wu et al. 2009a).

Are MAO-A and B the principal player or bystander in neuroprotection by MAO-B inhibitors?

Neuroprotective activity of selegiline and rasagiline has been proved in animal and cellular models of neurodegenerative disorders. Clinical trials of selegiline and rasagiline in parkinsonian patients have been reported to prevent disease progression and ameliorate symptoms (Riederer and Laux

2011). The neuroprotective activity is mainly attributed to the direct suppression of apoptosis signaling triggered by pore formation at the mitochondrial membrane (Wu et al. 2015) and the activation of endogenous biosynthesis of anti-apoptotic Bcl-2 protein family and NTFs (Naoi et al. 2013; Bar-Am et al. 2016).

MAO-B inhibitors bind to MAO-B and also to MAO-A

However, it remains to be elusive whether MAO-B itself is involved in neuroprotection of MAO-B inhibitors. In *mao-B* KO mice, selegiline could not prevent brain damage by ischemia and age-related deficient spatial learning, suggesting the essential role of MAO-B in neuroprotection (Holschneider et al. 1999a, b). In *mao-B* KO mice, binding of [^{3}H]-L-deprenyl in the cortex, striatum and corpus callossum decreased markedly to 3.5, 4.0, and 2.7% of control, which was further downregulated by clorgyline (Ekblom et al. 1998). After daily administration of selegiline and rasagiline, MAO-A activity reduced by 70% in the plasma of patients treated with MAO-B inhibitors (Bartl et al. 2014). Systematic administration of Zydas and transdermal selegiline downregulated MAO-A to one-third of control in healthy men (Fowler et al. 2015). These results present that rasagiline and selegiline bind also to MAO-A, not only MAO-B, which may be relevant with the neuroprotection of MAO-B inhibitors in MAO-A-expressed cells.

Enzymatically "dead" MAOs may be involved in neuroprotection by MAO-B inhibitors

Inhibition of MAO-B enzymatic activity is not essentially required for the neuroprotective function of MAO-B inhibitors (Klegeris and McGeer 2000). Selegiline and rasagiline (10^{-4}–10^{-6} M) irreversibly inhibit the enzymatic activity and protected cells at these concentrations, suggesting that catalytically inactive MAO protein may be associated with neuroprotection. Substitution of aspartic acid 328 residue of MAO-A completely inhibited the enzymatic activity, but catalytic "dead" MAO-A still affected cell viability and proliferation (Wei et al. 2012b), suggesting the different effects of genetic *mao* KO and MAO inactivation with the inhibitors on regulation of neuronal viability and function.

MAO-B inhibiters bind to MAO apart from the active site and also to other protein

MAO inhibitors bind to MAO at site different from the active site and trigger downstream pro-survival signaling. TVP1022, the *S*-enantiomer of rasagiline, a very week MAO-B inhibitor, bound to imidazolines 1 and 2 (I_1 and I_2) binding sites in MAO-A and protected PC12 cells and neonatal rat ventricular myocytes, through activation of p42/44 MAPK (Barac et al. 2012). Other MAO inhibitors, clorgyline, moclobemide, transcypromine, and phenelzine, also show affinity for I_2 site (Alemany et al. 1995; MacInnes and Handley 2002). MAO inhibitors bind to other amine oxidases [semicarbazide-sensitive amine oxidase (SSAO), diamine oxidase (DAO), plasma amine oxidase (PAO)], alcohol, and aldehyde dehydrogenases (Holt et al. 2004). Clorgyline, Ro41-1049 (a reversible MAO-A inhibitor), and phenelzine have very high affinity to D_2 receptors (Levant et al. 2010). However, there is no direct evidence to support that binding to other protein can contribute neuroprotection by MAO-B inhibitors.

MAO-A mediates Bcl-2 and NTF induction by MAO-B inhibitors in SH-SY5Y cells

Neuroprotective activity of NTFs, especially brain-derived neurotrophic factor (BDNF) and GDNF, has been demonstrated in clinical studies and also in cellular and animal models of neurodegenerative disorders. BDNF, a member of the neurotrophin family (BDNF, NGF, and 3-NT), activates tropomycin-related kinase (Trk) receptor B (TrkB), and promotes neurogenesis, synaptic plasticity, and cell survival. Reduced BDNF levels and BDNF functional polymorphism in major depressive disorder are proposed to account for impaired neurogenesis in the hippocampus (Michel et al. 2008). GDNF family (GDNF, neurturin, artemin, and persephin) functions in cellular growth, differentiation, and survival, and the activity is mediated by a multicomponent receptor complex composed of GDNF family receptor α1 (GFRα1), RET (rearranged during transfection) receptor tyrosine kinase (TK), and phosphatidyl inositol-linked protein. GDNF is expressed in the striatum (caudate putamen) and thalamus and protects selectively dopaminergic neurons.

Rasagiline, selegiline, and related compounds increased Bcl-2 and NTFs

Selegiline, rasagiline, *N*-propargylamine, aminoindan (a rasagiline metabolite), and befloxantine (a reversible MAO-A inhibitor) increased Bcl-2 expression and suppressed apoptosis (Akao et al. 2002; Yi et al. 2006b; Weinreb et al. 2004, 2010). In cultured cells, selegiline and rasagiline enhanced the levels of GDNF, BDNF, and other NTFs (Tatton et al. 2002; Maruyama et al. 2004; Nakaso et al. 2006). Rasagiline and selegiline (10^{-7} to 10^{-10} M) increased GDNF mRNA and protein more markedly than BDNF in SH-SY5Y cells (Maruyama et al. 2004; Maruyama and Naoi 2013). Oral administration of selegiline (5 mg/day for 7–8 weeks) to parkinsonian patients and subcutaneous injection of rasagiline (0.25 mg/day for 4 weeks) in non-human primates increased BDNF and GDNF in the cerebrospinal fluid (CSF)

(Maruyama and Naoi 2013). Rasagiline increased BDNF and GDNF also in the rodent brain (Gyarfas et al. 2010; Ledreux et al. 2016). MAO inhibitors permeable though the blood–brain barrier (BBB) may be applicable for the NTF supplement therapy in neurodegenerative disorders.

Rasagiline, aminoindan, and MT-031 (an MAO-A and acetylcholine esterase inhibitor) induced TrkB receptor, activated downstream cell signal mediators, and increased PI3K protein in animal models of PD, inflammation, and aging (Mandel et al. 2007; Badinter et al. 2015; Liu et al. 2017). However, binding of rasagiline or selegiline to Trk receptors and GFRα has been not reported.

MAO-A mediates gene induction by rasagiline and selegiline

MAO-A mediates Bcl-2 and NTF induction by rasagiline in SH-SY5Y cells. MAO-A KD with siRNA inhibited rasagiline-dependent Bcl-2 protein and *BDNF* and *NGF mRNA* expression, whereas selegiline (10^{-6}–10^{-10} M) increases *BDNF* expression more markedly in *mao-A* KD cells than cells treated with non-specific (*NS*) siRNA (Fig. 4). In *mao-B*-overexpressed SH-SY5Y cells, MAO-B was found to mediate Bcl-2 induction by selegiline, but not by rasagiline (Inaba-Hasegawa et al. 2012). Rasagiline and selegiline increased Bcl-2 protein and *NTF* mRNA expression either in MAO-A dependent or independent way (Inaba-Hasegawa et al. 2017a, b).

MAO-B represses the constitutional and selegiline-enhanced expression of genes in U119MG cells

Glial cells induce cell death in neurons by production of pro-inflammatory cytokines and chemokines, and phagocytosis. However, protoplasmic astrocytes contain also protective NTFs and glutathione and inhibit disease progression (Halliday and Stevens 2011). Various neuroprotective compounds, such as selegiline (Mizuta et al. 2000), dopamine agonists (Ohta et al. 2010), memantine (Wu et al. 2009b), valproate (Chen et al. 2006), amantadine (Ossola et al. 2011), and antidepressant (Hisaoka et al. 2008), induced NTF expression in astrocytes.

In U118MG cells, MAO-B was involved in constitutional expression and induction by selegiline and rasagiline of Bcl-2 and NTFs (Inaba-Hasegawa et al. 2017a, b). Figures 3, 4 show that *mao-B* KD with *siMao-B* increased the basal expression of Bcl-2 mRNA and protein, *BDNF, NGF,* and *GDNF* mRNA, whereas *mao-A* KD decreased them. In control U118MG cells, selegiline (10^{-6}–10^{-10} M) and rasagiline (10^{-7}–10^{-10} M) enhanced *BDNF* and *GDNF*. In *siMao-B* treated cells, selegiline (10^{-6} to 10^{-10} M) further increased Bcl-2, *BDNF,* and *GDNF* expressions, but rasagiline did not, suggesting that selegiline and rasagiline-activated distinct signal pathways to increase gene expression.

As summarized in Fig. 4, rasagiline induced pro-survival genes by activation of signal pathways mediated by MAO-A in neuronal cells. In glial cells, MAO-B functioned as a repressor of *mao-A, bcl-2,* and *NTFs* and the gene induction by selegiline, whereas *mao-A* KO suppresses it.

MAO-A substrates, 5-HT, NE, and DA, induce BDNF and GDNF expressions

MAO-A substrates, 5-HT and NE, stimulate BDNF synthesis and affect neuronal plasticity in aging and neurodegenerative disorders (Mattson et al. 2004). β-Adrenergic receptors mediated NE-dependent BDNF induction by exercise and antidepressants, and 5-HT_{1A} and $5\text{-HT}_{2A/C}$ were associated with antidepressant-induced BDNF expression (Ivy et al. 2003). NE and nitric oxide (NO) promoted BDNF level and survival of cultured hippocampal neurons through activation of cAMP-response element binding (CREB) and Akt-MAP signal pathways (Patel et al. 2010). NE induced BDNF in embryonic rat hippocampal neurons by PI3K and MAPK cascades (Chen et al. 2007).

In astrocytes, monoamine receptors are also expressed (Pav et al. 2008), and DA and NE stimulated biosynthesis of endogenous BDNF (Juric et al. 2006). In cultured rat cortical astrocytes, DA upregulated BDNF protein level (Miklic et al. 2004). NE increased BDNF through binding to α_1- and β_1/β_2-adrenergic receptors, and activation of ligand-G-protein-coupled receptor-PI3K–ERK–CREB cascades or Ca^{2+}-dependent protein kinase (Juric et al. 2008). NE, epinephrine, and DA increased 3-NT expression in primary cultured cerebellar astrocytes by cAMP/PKA and PKC pathways and Ca^{2+} mobilization (Mele et al. 2010). However, little is known about the expression of BDNF transcripts by 5-HT in astrocytes.

DA increased also GDNF via activation of D_1 receptors in human fetal astrocytes (Kinor et al. 2001). 5-HT increased GDNF in C6 glioblastoma cells by binding to 5-HT_{2A} and activation of MEK–MAPK pathway (Hisaoka et al. 2004, 2008), and also via fibroblast growth factor (FGF) receptor 2 (FGFR2) (Tsuchioka et al. 2008). In contrast to BDNF, GDNF induction by NE has been not reported in astrocytes.

Epigenetic regulation of MAO-A expression in gene–environmental interaction

Recently, genotype-dependent environmental influence has been proposed as the pathogenic factor for effective disorders (Ludwig and Dwivedi 2016). Epigenetic regulation

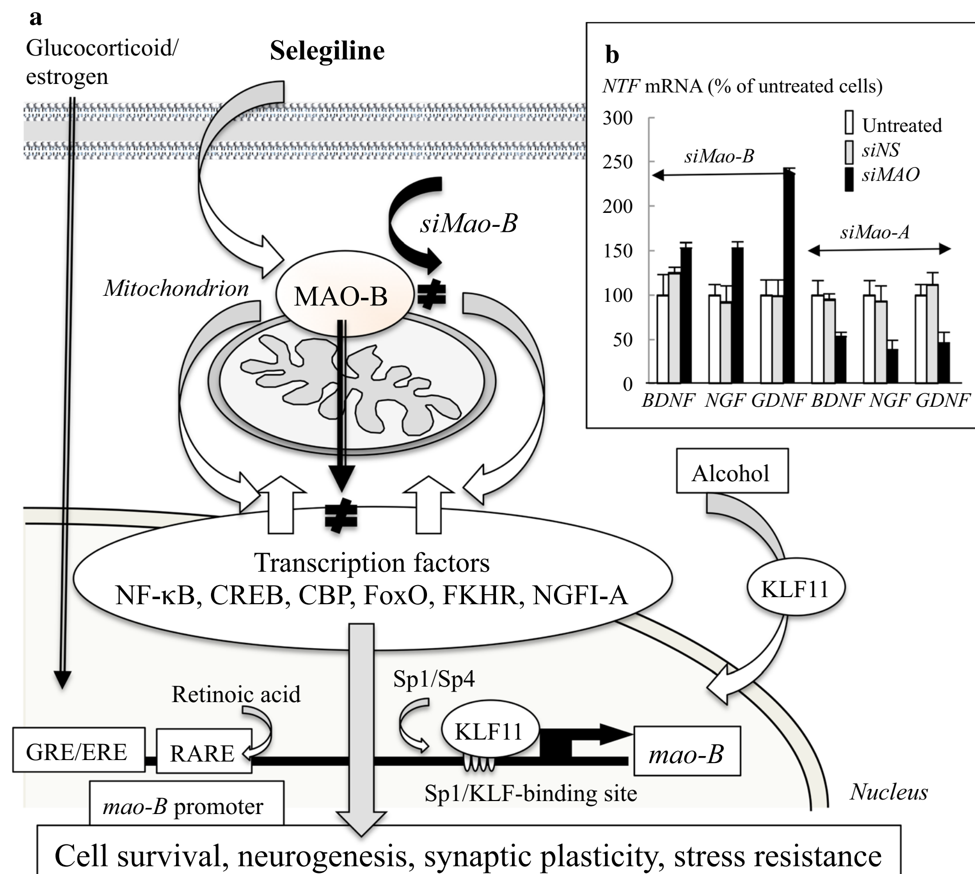

Fig. 3 In U118MG cells, MAO-B functions as a repressor of gene expression coding Bcl-2, BDNF, and other NTFs. **a** MAO-B suppressed the basal expression of *Bcl-2*, *BDNF*, *NGF*, and *GDNF*, and MAO-B silencing with *siMao-B* enhanced it. Selegiline increased these genes synergistically. Selegiline triggers MAO-B-mediated signal pathways, and monoamines activate the receptors and downstream transcription factors, including NF-κB, CREB, CREB-binding protein (CBP), FoxO, forkhead in rhabdomyosarcoma (FKHR), and NGF-inducible factor A (NGFI-A). Finally, increased Bcl-2 and NTFs increase cell survival, neurogenesis, and synaptic plasticity. Ethanol activates KLF11 and upregulates *mao-B* expression. MAO-B expression is regulated also by glucocorticoid, estrogen, and retinoic acid via their receptor element, GRE/estrogen response element (ERE), and retinoic acid receptor element (RARE). **b** *siMao-B* treatment enhanced the constitutional expression of *BDNF*, *NGF,* and *GDNF* in U118MG cells, whereas *siMao-A* suppressed it (Inaba-Hasegawa et al. 2017a, b)

of MAO activity influences the vulnerability to environmental stress, and affects social cognition, learning and memory, and stress-related behaviors (Roth and Sweatt 2011). In depression, high levels of MAO-A expression are proposed to impair neurogenesis in the hippocampus and cause molecular changes. However, MAO-A genotype did not fully correspond to MAO-A activity in the brain (Fowler et al. 2007), suggesting involvement of epigenetic modification of MAO-A activity. By epigenetic modification, specific gene is manipulated in the interaction through DNA methylation, hypomethylation, histone modifications, and non-coding RNAs.

DNA methylation in epigenetic regulation of MAO-A

The CpG site-specific methylation state of *mao-A* promoter predicts MAO-A activity in the brain of healthy men (Shumay et al. 2012). Alteration of DNA methylation in *mao-A* promoter was reported in female patients with depression and panic disorder (Domschke et al. 2012; Melas and Forsell 2015; Ziegler et al. 2016) and antisocial personality disorder (Checknita et al. 2015), and with nicotine and alcohol dependence (Philibert et al. 2008). Increased level of methylation at the CpG residues in *mao-A* promoter

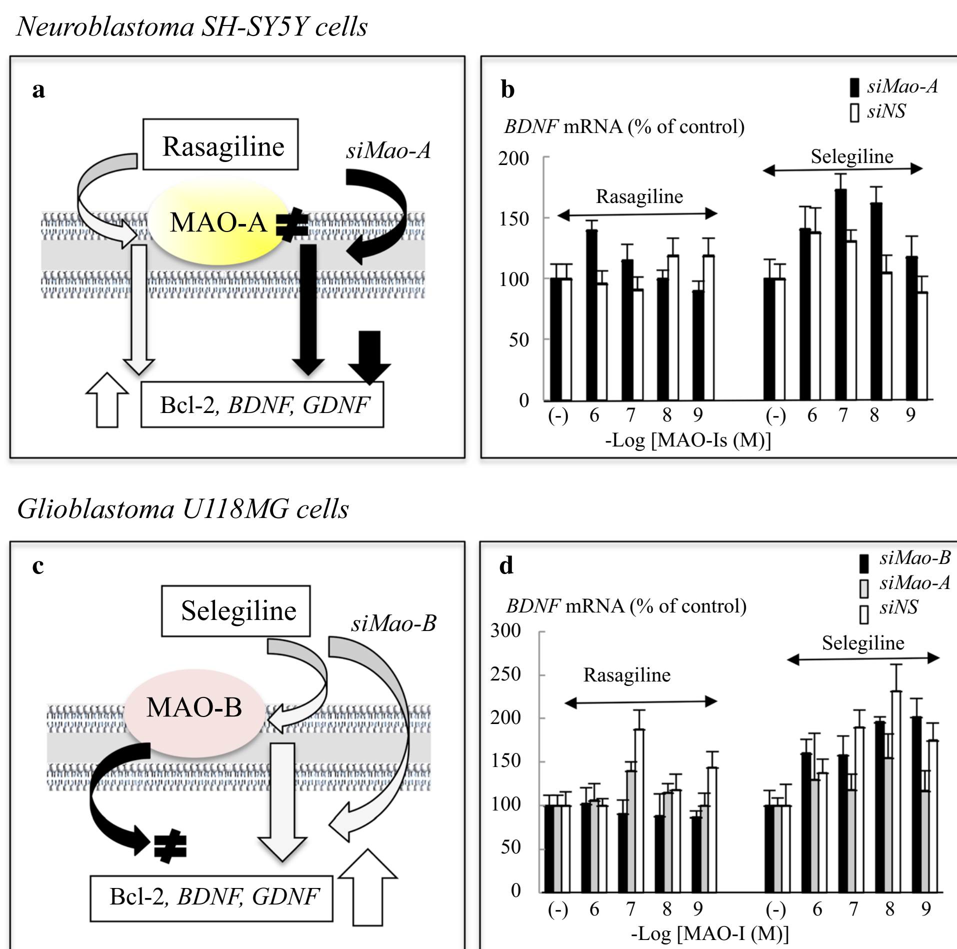

Fig. 4 Contrasting effects of *mao-A* and *mao-B* KD on the gene induction by rasagiline and selegiline in SH-SY5Y and U118MG cells. **a**, **b** In SH-SY5Y cells, MAO-A mediates the induction of Bcl-2, *BDNF*, and *GDNF*. Rasagiline and selegiline increased *BDNF* mRNA, and *siMao-A* decreased *BDNF* expression by rasagiline, but enhanced that by selegiline. **c**, **d** In U118MG cells, MAO-B represses signal pathways to gene expression. Rasagiline and selegiline increased *BDNF* mRNA and *siMao-B* treatment synergistically enhanced selegiline-dependent induction, whereas *siMao-A* reduced selegiline and rasagiline-induced *BDNF* level (Inaba-Hasegawa et al. 2017a, b)

was reported in male patients with paranoid schizophrenia (Chen et al. 2012).

Chromatin modification in MAO-A expression

Posttranslational reversible modification of histone, such as acetylation, phosphorylation, ubiquitination, and sumoylation, rearranges chromatin and affects the transcription. SIRT1 an NAD^+-dependent deacetylase regulates gene expression through histone acetylation, and enhances memory and learning, cognitive function, and synaptic plasticity (Michan et al. 2010). It showed neuroprotective activity in animal models of AD and amyotrophic lateral sclerosis (ALS) (Chen et al. 2005; Kim et al. 2007). SIRT1 activated MAO-A in the brain and induced anxiety and exploratory drive, whereas SIRT1 KO mice showed less susceptibility to depression (Libert et al. 2011). SIRT1 deacetylated nescient helix–loop–helix 2 (NHLH2), a brain-specific transcription factor, and increased the transcriptional activity on *mao-A* promoter. Micro-RNA-142 (miR-142) was shown to suppress SIRT1–NHLH2 pathways and decrease MAO-A mRNA, protein, and the activity in BE(2)M17 cells, and might be associated with the pathogenesis of several neurodegenerative disorders and HIV-associated cognitive deficient (Chaudhuri et al. 2013). SIRT1 regulates MAO-A activity, but not MAO-B, and serves as a stress sensor signaling for MAO-A to respond to environmental stimuli.

Diet and food-derived phytochemicals regulate MAO activity and affect behavior and emotion

Dietary habits and food factors regulate lifespan, age-dependent decline of cognition and incidence of neuropsychiatric disorders (Mattson et al. 2002). Food-derived polyphenolic compounds, such as (−)-epigallocatechin-3-gallate (EGCG), and genistein (4′,5,7-rihydroxyisoflavone), inhibited DNA methyltransferase and reactivated genes (Yang et al. 2008). Bioactive phytochemicals inhibit MAO activity and show NTF-mimic activity (Vina et al. 2012; Naoi et al. 2017b). Flavonoids with catechol structure, such as quercetin (3′,4′,5,7-tetrahydroflavonol), ginkgolide B, and EGCG, inhibit MAO-A and induces BDNF expression,

whereas non-flavonoid phytochemicals, resveratrol (*trans*-3,4′,5-trihydroxstilbene) and curcumin [(1*E*, 6*E*)-1,7-bis(4-hydroxy-3-methoxypheny-hepta-1,6-diene-3,5-dione), inhibit MAO-B and increase GDNF. Phytochemicals affect MAO expression and vice versa MAO-A and MAO-B regulate pro-survival gene induction by phytochemicals. Ginkgolide B and curcumin increase *mao-A* expression, and tetrahydrocurcumin and sesamin *mao-B* expression in U118MG cells (Inaba-Hasegawa et al. 2017b). Ginkgolide B, EGCG, and curcumin increase the expression of neuroprotective *Bcl-2*, *GDNF, NGF,* and *NT-3* mRNA (Naoi et al. 2017b), which was synergistically enhanced by *mao-B* KD, but inhibited by *mao-A* KD, as in the case with selegiline. Phytochemicals capable of inhibition of MAO and selective induction of GDNF or BDNF may be expected as neuroprotective and antidepressant compounds for the therapy in neurodegenerative disorders, cognitive decline, and depressive disorders.

Discussion

This review presents the fluctuation of MAO-A activity by genetic and environmental factors and the association with neurodevelopment and brain functions, including mood, motor, cognition, substance abuse, and aggressive and asocial behaviors. Transient and reversible changes in MAO-A activity in combination with the substrates and H_2O_2 modulate intracellular signaling systems and expression of genes related to neuronal survival and death. For this study, the in vivo assay for MAO-A enzyme activity is essentially required. PET imaging can demonstrate in situ MAO activity using a [^{11}C]-labeled irreversible propargylamine MAO inhibitors, clorgyline, and reversible MAO-A inhibitors, harmine and befloxatone, and [^{18}F]fluoroethyl-harmol, and MAO-B activity with [^{11}C]-selegiline, and [^{18}F]fluororasagiline (Dolle et al. 2003; Fowler et al. 2005; Nag et al. 2012; Kersemans et al. 2013; Maschauer et al. 2015). Human PET studies demonstrated in vivo the effects of MAO-A substrates on MAO-A activity (Sacher et al. 2012), inhibition of MAO-A and -B by smoking (Leroy et al. 2009), MAO-B elevation in aging, and AD (Gulyas et al. 2011), the distribution in the brain, and binding of rasagiline to MAO-B (Freedman et al. 2005). PET imaging of MAO activity and genotype analysis in peripheral samples are expected to present the fluctuation of MAO activity and clarify its role in gene–environment interaction and neuropsychiatric disorders.

Genes coding *mao-A* and *mao-B* exhibit the identical exon–intron organization and are derived from duplication of a common ancestral gene (Grimsby et al. 1991). The two isoenzymes share the common protein structure and function in many aspects, even though they are expressed in different types of cells. Mainly MAO-A and B protein and activity are expressed in SH-SY5Y and U118MG cells, respectively, but mRNA of both MAO isoenzymes is detected in either cells. Crosstalk between the MAO isoenzymes has been shown by the substrates, inhibitors, and H_2O_2 between neuronal and glial cells. In glial cells, MAO-A expression was found to be suppressed by MAO-B and this issue should be further clarified to find role of MAO-A and B in the brain.

MAO-A gene and environmental factors determine the MAO expression and enzymatic activity, which may be associated with development of neural architecture and brain function throughout the life stages. MAO-B was found to repress the constitutional expression and selegiline- and phytochemical-sensitive increase of *Bcl-2* and *NTFs*, and *mao-A* itself in glial cells. Further studies on these novel functions of MAOs should bring us new strategy for elucidation of the pathogenesis and development of new therapy for neuropsychiatric disorders.

Compliance of the ethical standards

Conflict of interest The authors declare that there are no competing financial interests in relation to the work described.

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