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Molecular mechanism of the relation of monoamine oxidase B and its inhibitors to Parkinson's disease: possible implications of glial cells

T. Nagatsu[1,2], **M. Sawada**[2]

[1] Department of Pharmacology, School of Medicine, Fujita Health University, Toyoake, Aichi, Japan
[2] Research Institute of Environmental Medicine, Nagoya University, Nagoya, Aichi, Japan

Summary Monoamine oxidases A and B (MAO A and MAO B) are the major enzymes that catalyze the oxidative deamination of monoamine neurotaransmitters such as dopamine (DA), noradrenaline, and serotonin in the central and peripheral nervous systems. MAO B is mainly localized in glial cells. MAO B also oxidizes the xenobiotic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to a parkinsonism-producing neurotoxin, 1-methyl-4-phenyl-pyridinium (MPP+). MAO B may be closely related to the pathogenesis of Parkinson's disease (PD), in which neuromelanin-containing DA neurons in the substantia nigra projecting to the striatum in the brain selectively degenerate. MAO B degrades the neurotransmitter DA that is deficient in the nigro-striatal region in PD, and forms H_2O_2 and toxic aldehyde metabolites of DA. H_2O_2 produces highly toxic reactive oxygen species (ROS) by Fenton reaction that is catalyzed by iron and neuromelanin. MAO B inhibitors such as L-(−)-deprenyl (selegiline) and rasagiline are effective for the treatment of PD. Concerning the mechanism of the clinical efficacy of MAO B inhibitors in PD, the inhibition of DA degradation (a symptomatic effect) and also the prevention of the formation of neurotoxic DA metabolites, i.e., ROS and dopamine derived aldehydes have been speculated. As another mechanism of clinical efficacy, MAO B inhibitors such as selegiline are speculated to have neuroprotective effects to prevent progress of PD. The possible mechanism of neuroprotection of MAO B inhibitors may be related not only to MAO B inhibition but also to induction and activation of multiple factors for anti-oxidative stress and anti-apoptosis: i.e., catalase, superoxide dismutase 1 and 2, thioredoxin, Bcl-2, the cellular poly(ADP-ribosyl)ation, and binding to glyceraldehydes-3-phosphate dehydrogenase (GAPDH). Furthermore, it should be noted that selegiline increases production of neurotrophins such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and glial cell line-derived neurotrphic factor (GDNF), possibly from glial cells, to protect neurons from inflammatory process.

Abbreviations: *BDNF* brain-derived neurotrophic factor, *CSF* cerebrospinal fluid, *DA* dopamine, *GDNF* glial cell line-derived neurotrophic factor, *MAO A* monoamine oxidase A, *MAO B* monoamine oxidase B, *MPDP+* 1-methyl-4-phenyl-2,3-dihydro-pyridinium, *MPP+* 1-methyl-4-phenyl-piridinium, *MPTP* 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, *NGF* nerve growth factor, *PD* Parkinson's disease, *ROS* reactive oxygen species, *TH* tyrosine hydroxylase

Correspondence: T. Nagatsu, Department of Pharmacology, School of Medicine, Fujita Health University, Toyoake, Aichi, Japan
e-mail: tnagatsu@fujita-hu.ac.jp

Parkinson's disease (PD) is an aging-related movement disorder caused by a deficiency of the neurotransmitter dopamine (DA) in the striatum of the brain as a result of selective degeneration of the nigro-striatal DA neurons (A9 neurons). DA deficiency is due to decreased number of DA neurons in the substantia nigra, and the molecular activity (enzyme activity/enzyme protein) of tyrosine 3-monooxygenase (tyrosine hydroxylase, TH) in residual DA neurons increases resulting in compensation for DA deficiency (Mogi et al., 1988). Familial PD for which the causative genes have been identified constitutes a small percentage of PD, and most PD is sporadic (idiopathic) without hereditary history. The molecular mechanism of the DA cell death in sporadic PD is unknown, but monoamine oxidase (MAO), especially type B (MAO B), is speculated to play important roles. In the brain MAO B is mainly localized in glial cells. MAO B activity in the brain increases during aging probably due to increasing numbers of glial cells (Fowler et al., 1980), and aging is a high risk factor of PD. MAO B inhibitors, such as L-(−)-deprenyl (selegiline) and rasagiline, are proved to be clinically effective for the treatment of PD. In the present review, we will examine the molecular mechanism of PD in relation to the mechanism of probable neuroprotection by MAO B inhibitors, and to possible interrelationship between DA neurons and glial cells in the inflammatory process.

Monoamine oxidases A and B (MAO A and MAO B)

Monoamine oxidase (flavin-containing) [amine:oxygen oxidoreductase (deaminating) (flavin-containing); MAO; E.C. 1.4.3.4.] catalyzes the following reaction: $RCH_2NH_2 + H_2O + O_2 = RCHO + NH_3 + H_2O_2$. MAO acts on primary

amines, and also on some secondary and tertiary amines. The monoamine substrates for MAO include physiologically and pathologically important neurotransmitters and hormones, such as DA, noradrenaline, adrenaline, and serotonin, which are slow-acting neurotransmitters in the brain and function with rapidly-acting neurotransmitters, i.e., glutamic acid and gamma-aminobutyric acid (GABA), to regulate movement, emotion, reward, cognition, memory, and learning. Thus, MAO is closely related to higher brain functions by regulating the levels of monoamine neurotransmitters and also to the pathogenesis of PD (for reviews, see Nagatsu, 2004; Nicotora et al., 2004; Riederer and Youdim, 1990; Youdim and Riederer, 1997). In the brain, MAO is thought to be important together with catechol O-methyltransferase in regulating the level of DA. The DA level decreases specifically in the nigro-striatal region in PD, which is the characteristic biochemical change (for reviews, see Cookson, 2005; Hornykiewicz, 2001; Nagatsu, 1993).

MAO was first discovered as tyramine oxidase by Hare in 1928, since it catalyzed the oxidative deamination of tyramine. This enzyme was then found to oxidize various monoamines including catecholamines, i.e., DA, noradrenaline, and adrenaline, and serotonine, and was recognized as monoamine oxidase by Blashko, Zeller, Gorkin, and Quastel. The enzyme localizes in the outer membrane of mitochondria (Schneitman et al., 1967). MAO was purified from bovine liver (Gomes et al., 1969; Minamiura and Yasunobu, 1978) and bovine brain (Harada et al., 1971). The cofactor, flavin adenine dinucleotide (FAD), was identified in preparations of purified MAO (Harada and Nagatsu, 1969; Tipton, 1980). Purified MAO was discovered to contain FAD covalently bound as 8-a-cysteinyl-FAD (Walker et al., 1971).

Johnston (1968) pharmacologically discovered that the inhibitor clorgyline was able to distinguish two forms of MAO, i.e., MAO type A (MAO A) and MAO type B (MAO B). The presence of multiple forms of MAO in the human brain was also reported by Collins et al. (1970). The structures and functions of MAO A and MAO B have been elucidated by cDNA cloning, genomic DNA cloning, and genetic engineering (for review, see Shih, 2004; Shih et al., 1999).

Full-length cDNAs encoding human liver MAO A and MAO B and the genomic DNAs were cloned (Bach et al., 1988; Chen et al., 1991; Powell et al., 1991; Weyler et al., 1990). Human placental MAO A (Hsu et al., 1988), and rat liver MAO A and MAO B (Ito et al., 1988; Kwan and Abell, 1992) were also cloned and sequenced, and human and rat MAO A showed 86–88% identity. MAO B from human platelets and frontal cortex were found to have identical amino acid sequences, confirming that human MAO B is a single enzyme in various tissues (Chen et al., 1993).

Human MAO A and MAO B have subunit molecular weights of 59,700 and 58,000, respectively, consisting of 527 and 520 amino acids, respectively, and have a 70% amino acid sequence identity; and both sequences contain the pentapeptide Ser-Gly-Gly-Cys-Tyr, in which the obligatory cofactor FAD is covalently bound through a thio ether linkage to the cysteine (Bach et al., 1988; Chen et al., 1991). MAO is composed of two identical subunits (Minamiura and Yasunobu, 1978), and one FAD couples with each subunit of 60 kDa (Weyler, 1989). FAD is covalently linked to Cys-406 in MAO A and Cys-397 in MAO-B (Abell and Kwan, 2001; Edmondson et al., 2004).

The expression of functional enzymes by transfection of cells with cDNAs provides unequivocal evidence that the different catalytic activities of MAO A and MAO B reside in their primary amino acid sequences. Chimeric enzymes and site-directed mutagenesis studies contributed to elucidating the structure-function relationships of MAO A and MAO B. The enzymatic properties observed for the chimeric MAO enzymes suggest that the internal segment, but not the N- or C-terminal region, confers substrate and inhibitor specificities (Shih et al., 1998; Tsugeno and Ito, 1997; Tsugeno et al., 1995). The catalytic properties and specificity of MAO A were insensitive to substitution of both the NH_2- (up to position 112) and COOH-termini (from residue 395). The replacement of MAO A amino acids 161–375 by the corresponding region of MAO B converted MAO A catalytic properties to ones typical of MAO B; and the converted enzyme did not oxidize serotonin, a preferred substrate of MAO A, and was more sensitive to the MAO B-specific inhibitor, L-(−)-derenyl (selegiline), than to the MAO A-specific inhibitor clorgyline. These results demonstrated that amino acids 152–366 of MAO B contain a domain that confers substrate specificity and inhibitor selectivity on the enzyme (Chen and Shih, 1998; Cesura et al., 1998).

Because MAO A and MAO B are integrated proteins of the outer membrane of mitochondria, their crystallization has been difficult; and so their three-dimensional structure of human MAO B has been only recently elucidated (Binda et al., 2002a, b). Determination of the crystal structure of human MAO B allowed precise modeling of the structure of human MAO A, and preliminary models of human MAO A have been obtained by fold recognition and comparative modeling based on proteins sharing low sequence identity (Leonard et al., 2004). The 50-residue C-terminal tail of human MAO B forms an extended segment that traverses the protein surface and then folds into an alpha-helix, which protrudes from the basal face of the structure to anchor the

protein to the mitochondrial outer membrane (Binda et al., 2002a, b).

MAO A and *MAO B* genes are situated on the X chromosome, at Xp 11.23–22.1 (Chen et al., 1992; Kochersperger et al., 1986; Lan et al., 1989; Levy et al., 1989; Pintar et al., 1981). Both genes are closely located and are deleted in patients with Norrie's disease, a rare X-linked recessive neurological disorder characterized by blindness, hearing loss, and mental retardation. Human *MAO A* and *MAO B* genes consist of 15 exons and have an identical exon-intron organization. Exon 12 codes for the covalent FAD-binding site and is the most conserved exon, showing 93.9% amino acid identity between MAO A and MAO B (Chen et al., 1992; Grimsby et al., 1991).

The distribution of MAO in various tissues of various species has been investigated by use of specific inhibitors of MAO A and MAO B enzyme activities, immunohistochemistry, enzyme autoradiography, and in situ hybridization (for review, see Berry et al., 1994; Kitahama et al., 1994; Luque et al., 1998). MAO A and MAO B are distributed in various tissues including the brain of various species. Histochemical localization of MAO A and MAO B was examined in the rat brain (Willonghby et al., 1988). In the rat brain, MAO A was predominantly found in noradrenergic neurons; whereas MAO B was detected in serotonergic and histaminergic neurons and in glial cells (astrocytes) (Arai et al., 1997; Jahung et al., 1997; Levitt et al., 1982; Luque et al., 1995; Saura et al., 1994; Westlund et al., 1988a). However, DA neurons appear not to have MAO A or MAO B, in contrast to the fact that DA is a common substrate of both MAO A and MAO B activity (Arai et al., 1998; Hida et al., 1999). As another puzzling fact on the physiological role of MAO B, serotonin neurons contain only MAO B, but serotonin is a very poor substrate of MAO B (Arai et al., 1997; Levitt et al., 1982).

Most human tissues, including the brain, express both MAO A and MAO B (Konradi et al., 1988; Konradi et al., 1989; Westlund et al., 1988b). However, human placenta contains predominantly MAO A (Egashira and Yamanaka, 1981); and human platelets and lymphocytes express only MAO B (Bond and Cundall, 1997; Donnelly and Murphy, 1977). Thus platelet MAO B can be useful for estimation of brain MAO B (Oreland, 2004). mRNA transcripts of MAO A and MAO B were coexpressed in the same region in the adult human brain; and the relative concentrations of these transcripts were as follows in the decreasing order: frontal cortex, locus coeruleus, temporal cortex, posterior pensylvian cortex-supuramarginal gyri, anterior pensylvian cortex-opercular gyri, hippocampus and thalamus (Grimsby et al., 1990).

Cell-type specific expression of MAO A and MAO B were examined in cultured cells (Donnelly et al., 1976; Hawkins and Breakfield, 1978; Murphy et al., 1976; Nagatsu et al., 1981). The type of MAO activity did not vary through the stage of growth of mouse myoblast G8-1 cells, which contain mostly MAO A (95%) and a small amount of MAO B (5%) (Nagatsu et al., 1981). NG108-15 hybrid cells derived from mouse neuroblastoma $\times$ rat glioma showed both MAO A (65–90%) and MAO B (35–10%), and the total MAO A plus MAO B activity and the ratio of MAO B/MAO A activity increased as a function of time in culture. Prostaglandin E1 and theophylline, the best known combination of agents that increases the intracellular cyclic AMP content of NG-108-15 cells, caused similar increases in MAO and the MAO B/MAO A ratio in NG108-15 cells, suggesting that the activity and expression of MAO B are regulated in a cyclic AMP-dependent manner (Nakano et al., 1985). NCB 20 cells, which are a hybrid of mouse neuroblastoma N18TG-2 and Chinese hamster embryonic brain cells CHB C, had predominantly MAO B activity with a little MAO A activity (Nagatsu et al., 1981). MAO B and MAO A in hybrid NCB 20 cells were determined to be distinct enzyme molecules by peptide mapping (Nakano et al., 1986).

MAO B activity, but not MAO A activity in the brain increases during aging (Fowler et al., 1980). This increase may be due to the increase in the number of glial cells during aging. In the living human brain, MAO B can be detected by positron emission tomography (PET) using deuterium substituted [^{11}C] L-(−)-deprenyl (selegiline) (Fowler et al., 1998). The PET study indicated that MAO levels in the human brain were highest in the basal ganglia and the thalamus, intermediate in the frontal cortex and cingulate gyrus, and lowest in the parietal and temporal cortices and cerebellum. The results of PET confirm postmortem studies on increases in brain MAO B with age. The whole brain and the cortical regions and the basal ganglia, thalamus, pons, and cerebellum showed an average increase of $7.1 \pm 1.3\%$ per decade. There was also a large variability among subjects in the same age range. Interestingly, inhibition of MAO B was observed by PET study in the brain of smokers (Fowler et al., 1996). Smokers also showed low MAO B in platerets (Olerand, 2004), and are speculated to have a low incidence of PD.

MPTP-induced Parkinsonism and monoamine oxidase B (MAO B)

The discovery of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) as the first recognized synthetic neurotoxin

that is capable of inducing PD symptoms in humans has greatly contributed to the understanding of the molecular mechanism of sporadic PD. Calne and Langston (1983) reviewed the etiology of PD and pointed out the possibility of involvement of environmental toxic substances as being the important cause of PD, superimposed on a background of slow, sustained neuronal loss due to the process of aging. Humans are highly susceptible to MPTP, and non-human primates are also sensitive to the compound. Various non-primate animals including some strains of the mouse and even the fruit fly Drosophila also show PD-like movement disorder by administration of MPTP. The first human case of PD that appeared after intravenous injection of MPTP as a contaminant of 1-methyl-4-phenyl-piperidine-4-carboxulic acid ethyl ester (meperidine), which is a synthetic heroin, was a 23-year-old chemistry student at Bethesda, MD, USA. He synthesized that meperidine containing MPTP as a by-product and injected it intravenously into himself. L-3,4-Dihydroxyphenylalanine (L-DOPA) to supplement DA in the brain was effective in that patient as in PD patients. Kopin's group at the National Institutes of Health (NIH) identified MPTP in that meperidine preparation and reported the case in 1979 (Davis et al., 1979). Then, in 1983 in California, a group of young drug addicts acutely showed PD-like symptoms after self-administration of street batches of meperidine contaminated by MPTP. Like idiopathic PD, L-DOPA, which supplements DA in the brain as a substrate of aromatic L-amino acid decarboxylase, was an effective cure for the symptoms. These cases were reported by Langston et al. (1983), and since then the molecular mechanism of MPTP-elicited PD and investigation of similar neurotoxins in environment have been extensively studied (for review, see Nagatsu, 1997, 2002b). MPTP is highly lipophilic, and after its systemic injection, it rapidly crosses the blood-brain barrier to enter the brain. Once in the brain, MPTP, which is a pro-neurotoxin, is metabolized to 1-methyl-4-pheny-2,3-dihydro-pyridinium (MPDP+), by MAO B, which is localized in the outer membrane of mitochondria within glial cells. MPDP+ is then probably spontaneously oxidized to 1-methyl-4-phenyl-pyridinium (MPP+), the active PD-producing neurotoxin. MPP+ is then taken up via DA-transporter across the plasma membrane at the nerve terminals of the nigro-striatal DA neurons in the striatum. As acute reactions, MPP+ is taken up into synaptic vesicles from the cytoplasm by vesicular monoamine transporter type 2 (VMAT 2) to release DA from the nerve terminals; it also inhibits and inactivates tyrosine hydroxylase (TH) to decrease DA synthesis. In the chronic phase, MPP+ is transported from the nerve terminals of nigro-striatal DA neurons in the striatum to the cell bodies in the substantia nigra by retrograde axonal flow. MPP+ is also accumulated within the inner mitochondrial membrane, where it inhibits complex I (NADH ubiquinone oxidoreductase), one of the five enzyme complexes of the inner mitochondrial membrane involved in oxidative phosphorylation for ATP fromation, interrupts electron transport, releases reactive oxygen species (ROS) causing oxidative stress, and depletes ATP. Inhibition of mitochondrial complex I opens mitochondrial permeability transition pore, and subsequently triggers apoptotic cell death of the nigro-striatal DA neurons. Thus, MPP+ decreases DA acutely and chronically to produce PD-like symptoms. Oxidation of MPTP to MPP+ by mitochondrial MAO B in glial cells is essential for neurotoxicity, and selegiline as a specific MAO B inhibitor completely prevents the symptom of PD by MPTP. Mitochondrial dysfunction, especially decreased activity of complex I, is confirmed in the nigro-striatal region in the brain in sporadic PD (for review, see Mizuno et al., 1998). However, unlike sporadic PD, Lewy bodies are not observed in the remaining neurons in the substantia nigra in MPTP-induced PD.

Assuming that some MPTP-like neurotoxins in environment may trigger idiopathic PD, endogenous MPTP-like compounds have been investigated in postmortem brains and in the cerebrospinal fluid (CSF) from patients with PD. Two groups of MPTP-like compounds, isoquinolines (IQs) and beta-carbolines, were found in the human brains and CSF from patients with PD.

We found that MPP+ acutely inhibits the TH system in tissue slices of the rat striatum. In screening for various MPTP-like compounds that inhibit the striatal TH system, we found tetrahydroisoquinoline (TIQ) and its derivatives to be active inhibitors (Hirata et al., 1986). Tetrahydroisoquinoline alkaloids were first discovered in the brain as an in vivo metabolite of L-DOPA in humans by Sandler et al. (1973). Various TIQs were found in the brains of patients with PD and in those of non-parkinsonian control patients by gas chromatography/mass spectrometry: TIQ, 1-methyl-TIQ (1-Me-TIQ), N-Me-6,7-$(OH)_2$-TIQ, (N-Me-norsalsolinol), 1,N-$(Me)_2$-6,7-$(OH)_2$-TIQ (N-Me-salsolinol), 1-phenyl-TIQ, N-Me-1-phenyl-TIQ, and 1-benzyl-TIQ (1-Bn-TIQ) (for review, see Nagatsu, 1997, 2002b; Niwa et al., 1993). Exogenously administered TIQ easily crosses the blood-brain barrier and passes into the brain. However, endogenous TIQs in the brain are speculated to be enzymatically synthesized from precursor endogenous monoamines such as phenylethylamine or DA. Only the (R) enantiomer, (R)-N-Me-6,7-$(OH)_2$-TIQ (R-N-Me-salsolinol) is speculated to be enzymatically synthesized in the brain (Naoi et al., 1996). Among these TIQs in the brain, 1,N-$(Me)_2$-6,7-$(OH)_2$-TIQ (N-Me-salsolinol)

(Naoi et al., 1996), N-Me-6,7-$(OH)_2$-TIQ (N-Me-norsalsolinol) (Moser and Koempf, 1992), and 1-Bn-TIQ (Kotake et al., 1995, 1998) have been extensively investigated as probable neurotoxins to cause PD. It was also suggested that some cases of atypical PD in the French West Indies might have a link with the consumption as food of tropical plants that contain Bn-TIQs (Caparros-Lefebvre et al., 1999). Beta-carbolines have structures similar to those of MPTP/MPP+, and may be synthesized in vivo from tryptophan via tryptamine (Collins and Neafsey, 2000; Matsubara, 2000). A neurotoxic 2,9-dimethylated beta-carbonium, 2,9-dimethylated norharman, was found by gas chromatography/mass spectromrtry in CSF in half of the PD patients examined, but was not found in non-PD patients. 1-Trichloromethyl-1,2,3,4-tetrahydro-beta-carboline (TaClo) is another neurotoxic beta-carboline (Bringmann et al., 2000). TaClo can be synthesized in vivo from tryptamine and the synthetic chloral after application of the hypnotic chloral hydrate or after exposure to the widely used industrial solvent trichloroethylene, which is metabolized to chloral (Bringmann et al., 2000). However, since TaClo and the N-methylated derivative had no DA-transporter-mediated neurotoxicity in cultured cells transfected with the human DA-transporter gene, they may not cause neurotoxicity by a mechanism analogous to that of MPTP/MPP+ involving the uptake into DA neurons by DA-transporter.

Like MPTP, the neurotoxicity of 1-Bn-TIQ (Kotake et al., 1998), N-methyl-(R)-salsolinol (Naoi et al., 1996), and beta-carbolines (Collins and Neafsey, 2000; Matsubara, 2000) are suggested to be precursor neurotoxins, and to be protected by MAO B inhibitors. These compounds inhibit complex I to reduce ATP synthesis in agreement with low complex I activity in the brain in PD and may produce ROS.

Rotenone is a naturally occurring, lipophilic compound from the roots of certain plants (Derris species) with the structure not related to amines, and is used as the main component of many insecticides. Rotenone is a specific inhibitor of complex I, and in Lewis rats by the chronic systemic administration causes highly selective degeneration of the nigro-striatal DA neurons with behavioral PD symptoms of hypokinesia and rigidity and with formation of intracytoplasmic inclusions like Lewy bodies, which are mainly composed of alpha-synuclein and a characteristic feature of sporadic PD (Betarbet et al., 2000). The relation of rotenone to MAO B remains to be investigated.

Specific inhibitory activity towards complex I of IQs and beta-carbolines suggests that they might be the possible neurotoxins producing PD. However, the concentrations of IQs and beta-carbolines in postmortem brain and CSF are low (in the order of ng/g tissue), and their in vivo toxicity and clinical significance in human PD remain to be further examined. Also, the question remains; is there any relation between clinical efficacy of MAO B inhibitor L-deprenyl (selegiline) in PD patients, as describes below, and complete prevention of PD symptoms in animal PD-models produced by MPTP- or MPTP-like neurotoxins by the inhibitor?

Clinical efficacy of monoamine oxidase B inhibitors in Parkinson's disease

L-Deprenyl (R-(−)-deprenyl, the generic name selegiline) was the first discovered MAO B specific inhibitor (for review, see Knoll and Magyar, 1972; Knoll, 1980). Selegiline is a suicide inhibitor, i.e., the compound acts as a substrate for the target enzyme MAO B and results in irreversible inhibition (Riederer and Youdim, 1990). Clinical efficacy of the MAO B inhibitor, selegiline, for addition of L-DOPA that supplements deficient DA in PD was first reported by Birkmayer et al. (1985). In a long term (9 years) study of treatment of PD patients with L-DOPA alone or in combination with selegiline, a significant increase of life expectancy in L-DOPA-selegiline group was observed. The results were interpreted as indicating selegiline's ability to prevent or retard the degeneration of striatal DA neurons. This hypothesis was not far fetched since selegiline selectively prevents the degeneration of nigrostriatal DA neurons in animal PD models induced by MPTP, as described above. After the first work on the clinical efficacy of selegiline on Parkinson's disease (Birkmeyer et al., 1985), the Parkinson Study Group in USA (1989) preliminarily reported that the use of selegiline (10 mg per day) delays the onset of disability associated with early, other untreated cases of PD. The Parkinson Study Group (1993) further reported the results of the multicenter controlled clinical trial of Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (the ''DATATOP'' study). Selegiline and tocopherol (vitamin E as an antioxidant) clinical trial from 1987 for 5 years (the US DATATOP study, selegiline momotherapy) suggested that deprenyl (10 mg per day) but not tocopherol (2000 IU per day) dalays the onset of disability associated with early, otherwise untreated PD. However, this remains controversial (Lang and Lees, 2002). Further uncertainty arose in 1995, when a study by the Parkinson's Disease Research Group of the United Kingdom (UK-PDRG) found 57% higher mortality in patients receiving combined selegiline and L-DOPA treatment compared with patients on L-DOPA alone (Lees on behalf of the Parkinson's Disease Research

Group of the United Kingdom, 1995). Other clinical trials have, however, failed to show any increase in mortality and showed neuroprotective effects of selegiline (Counsell, 1998; Olanow and Riederer, 1996; Olanow et al., 1995). Furthermore, another MAO B inhibitor, rasagiline (N-propargyl-R-aminoindan) that is a selsective, irreversible, second-generation MAO B inhibitor, has shown effectiveness in early PD when given as once-daily treatment without dose titration (Parkinson Study Group, 2002). To clarify the role of MAO B inhibitors in the treatment of PD, Ives et al. (2004) did a meta-analysis of data from all published trials, and reported that MAO B inhibitors (selegiline, lazabemide, or rasagiline) with or without L-DOPA, versus placebo, L-DOPA, or both, reduce the need for L-DOPA, and the incidence of motor fluctuations, without substantial side effects or increased mortality. This study supported the efficacy and safety of monotherapy of early PD by MAO B inhibitors such as selegiline.

Molecular mechanism of neuroprotective effects of L-deprenyl (selegiline) against Parkinson's disease

Stimulated by clinical efficacy of selegiline as a MAO B inhibitor for the treatment of early PD as described above, mechanisms of possible neuroprotection by selegiline have been extensively studied. The early hypothesis on the mechanism of clinical efficacy of selegiline in the treatment without or with L-DOPA was the prevention of degradation of DA, which is produced endogenously from tyrosine by TH or from exogenously administered L-DOPA for treatment, by MAO B inhibition (symptomatic effect). However, accumulating results indicate that selegiline may also have neuroprotective effects by several mechanisms that are related or not related to MAO B inhibition.

Neuroprotection due to inhibition of dopamine degradation by MAO B inhibitor selegiline

DA is a common substrate of MAO B and MAO A. However, in PD only MAO B inhibitor is clinically effective. Selegiline may increase the level of DA in the synaptic cleft in the DA nerve endings in the striatum after release from presynaptic terminals by inhibiting MAO B. DA as a substrate of MAO B produces H_2O_2 and 3,4-dihydroxyphenylacetaldehyde as neurotoxic products. However, since presence of MAO activity is not observed in DA neurons (Arai et al., 1998), DA released from DA neurons or produced from exogenously administered L-DOPA in L-DOPA therapy may be oxidized in the outside of DA neurons possibly in glial cells that contain MAO B to produce cytotoxic H_2O_2 and the aldehyde metabolite. Then H_2O_2 may get into the nigro-striatal DA nerons, and may be oxidized to produce cytotoxic oxygen radicals (reactive oxygen species, ROS) by iron presumably catalytically with neuromelanine. Iron accumulates in the DA neurons in the substantia nigra in PD (Dexter et al., 1987; Hirsch et al., 1991; Jellinger et al., 1992; Sofic et al., 1988). ROS may cause lipid membrane peroxidation and finally cell death of DA neurons (Dexter et al., 1993; Youdim et al., 1993). MAO B inhibitors can prevent this neurotoxic process to protect DA neurons.

Another possible mechanism of selegiline related to MAO B inhibition is an amphetamine-like tonic effect due to increased accumulation of phenylethylamine. Phenylethylamine is a good substrate of MAO B and may be produced in glial cells. Phenylethylamine at high concentrations were found in the striatum in the postmortem brain from PD patients treated with selegiline, and may have an endogenous ''amphetamine-like activity'' to stimulate DA neurons (Gerlach et al., 1992).

Selegiline's neuroprotective mechanism that is not related to MAO B inhibition

It has been known for many years that neuroprotective effects of selegiline can be observed in cell culture experiments at lower concentrations than those for MAO B inhibition, suggesting that selegiline's neuroprotective effects may also be caused by some other mechanisms than MAO B inhibition.

Riederer and Lachenmayer (2003) pointed out the possibility of neuroprotection by selegiline independent from MAO B inhibition by re-examining the clinical studies such as the DATATOP study (1993) based on the half life of selegiline in vivo in humans. In those clinical studies, the efficacy of selegiline was evaluated at the end-point between baseline and the end of the study (14 months including a 2 months wash-out period). Reported data on the half life of seligiline were between about 2–10 days (Gerlach et al., 2003; Youdim and Tipton, 2002) and 40 days (Fowler et al., 1994). Even the slow recovery of MAO B activity as determined by Fowler et al. (1994) would indicate only a 20% recovery of MAO B activity after a 2-week wash-out period and less than 50% recovery after a 4-week period. However, a significant increase in amine neurotransmitter concentrations can only be demonstrated after the MAO activity has been inhibited by at least 80% (Green et al., 1977). Thus a recovery of only 20% of the MAO B activity is already sufficient to prevent an increase in the neurotransmitter concentration. These results would suggest that

a safe period of 4 weeks for wash-out of selegiline would be perfectly adequate for avoidance of any residual symptomatic effects by in vivo MAO B inhibition and that the residual efficacy indicates its neuroprotective effectiveness of this class of drugs as a cornerstone of drug development not only for PD but also for neurodegenerative disorders in general (Riederer and Lachenmayer, 2003). In experimental animals selegiline was shown to be protective against the damaging effects of several neurotoxins, including the dopaminergic neurotoxin MPTP and 6-hydroxydopamine (6-OHDA) and the noradrenergic neurotoxin N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine (DSP-4), again suggesting that selegiline may show neuroprotective mechanism of action which is independent of its action on MAO B (Gerlach et al., 1992). Furthermore, selegiline dose-dependently attenuated ethylcholine aziridinium ion-induced memory impairment, and co-administration of selegiline and donepezil, a selective acetylcholinesterase inhibitor, at doses that do not exert efficacy individually, significantly ameliorated scopolamine + p-chlorophenylalanine-induced memory deficits (Takahata et al., 2005a).

There have been several suggestive findings on the molecular mechanism of neuroprotection by MAO B inhibitor selegiline.

First, selegiline and the metabolite desmethylselsegiline stimulated synthesis of neurotrophins, i.e., nerve rrowth factor (NGF), brain- derived neurotrophic factor (BDNF), and glial cell line-derived neurotrophic factor (GDNF), which act for neuroprotection and anti-apoptosis, in cultured mouse astrocytes (Mizuta et al., 2000). Selegiline as well as BDNF showed trophic effects on cultured DA neurons (Kontkanen and Castren, 1999). Besides neuroprotection for DA neurons, in mixed primary cultures of hippocampal neuronal and glial cells, selegiline increased NGF protein content and protected hippocampal neurons from excitotoxic degeneration, suggesting that astrocyte-derived NGF could contribute to the neuroprotective activity (Semkova et al., 1996).

Second, selegiline increased the activity of catalase and Mn-superoxide dismutase (Mn-SOD; SOD 2) in the striatum of 25-week-old rats. In slice cultures, selegiline increased Cu, Zn-superoxide dismutase (Cu, Zn-SOD; SOD 1) and Mn-SOD activities with a maximal effective concentration of 10^{-8} and 10^{-10} M, respectively. Furthermore, selegiline significantly increased glutathione level (Takahata et al., 2005b). Selegiline, at 1 μM or less, induced thioredoxin for protection against oxidative injury caused by MPP + in human SH-SY5Y neroblastoma cells and also in primary neuronal culture of mouse midbrain DA neurons. The redox cycling of thioredoxin may mediate the protective action of selegiline. Thioredoxin at 1 μM increased the expression of mitochondrial proteins Mn-SOD and Bcl-2 supporting cell survival (Andoh et al., 2002). Thus selegiline without modifying MAO B activity may augment the gene induction of thioredoxin leading to elevated expression of anti-oxidative Mn-SOD and anti-apoptotic Bcl-2 protein in the mitochondria for protecting against MPP +-induced neurotoxicity. The induction of thioredoxin was blocked by a protein kinase A (PKA) inhibitor and mediated by a PKA-sensitive phospho-activation of MAP kinase ERK 1/2 and transcription factor c-Myc. Selegiline-induced thioredoxin and associated neuroprotection were concomitantly blocked by the antisense against thioredoxin mRNA (Andoh et al., 2005). These results suggest that selegiline can decrease oxidative stress in the nigro-striatal region by augmenting various anti-oxidant systems.

Third, selegiline was found to alter the cellular poly(ADP-ribosyl)ation response to gamma-irradiation. Because poly(ADP-ribose) formation is catalyzed by the 113-kDa nuclear enzyme poly(ADP-ribose)polymerase 1 (PARP-1), this result suggests that altered cellular PARP-1 activity may contribute to the neuroprotective potential and/or life span extention afforded by selegiline (Brabeck et al., 2003).

Fourth, selegiline and other propargylamines were found to bind to glyceraldehydes-3-phosphate dehydrogenase (GAPDH). The GAPDH binding was associated with decreased synthesis of pro-apoptotic protein, and thus may contribute to neuroprotection (Tatton et al., 2003).

All these results suggest anti-oxidative and anti-apoptotic activity of selegiline, which neuroprotective mechanism may not be related to MAO B inhibition.

Novel MAO B inhibitors as anti-parkinsoian and anti-neurodegenerative drugs

Rasagiline (N-propargyl-1R-aminoindan) is a novel, potent, irreversible MAO B inhibitor designed for use as an anti-perkinsosonian drug. As described above, rasagiline is clinically effective as monotherapy or as an adjunct to L-DOPA for PD (Ives et al., 2004). Youdim et al. (2005) have reported that the neuroprotective activity of rasagiline is associated with the propargylamine moiety, which protects mitochondrial viability and mitochondrial permeability pore by activating Bcl-2 and down-regulating the Bax family of proteins, and that rasagiline processes amyloid precursor protein (APP) into the neuroprotective-neurotrophic soluble APP-alpha by protein kinase C-dependent and mitogen-activated protein kinase-dependent activation of alpha-secretase, and increases expression and proteins of

NGF, GDNF, and BDNF, suggesting its efficacy also in Alzheimer's disease.

Youdim et al. (2004) also reported novel bifunctional drugs targeting MAO inhibition and iron chelation as an approach to neuroprotection in PD and other neurodegenerative diseases. The authors suggest that bi-functional brain penetrable drugs with iron chelating property and MAO inhibitory activity could be the most feasible approach for neuroprotection in neurodegenerative diseases owing to the protection of elevated iron in oxidative stress and also neuroprotective effect by propargylamine moiety.

R-(−)-(Benzofuran-2-yl)-2-propylaminopentane [R-(−)-BPAP], which is a new sensitive enhancer of the impulse propagatin of action potential mediated release of catecholamines and serotonin in the brain (Knoll et al., 1999), was reported to protect apoptosis induced by N-methyl(R)salsolinol, an endogenous DA neurotoxin (Maruyama et al., 2004).

Considering the development of these new neuroprotective drugs, we would be able to expect development of new drugs which are effective against PD, Alzheimer's disease, and various neurodegenerative diseases in preventing or retarding the progress of such diseases.

Neuroprotective effects of MAO B inhibitors and neural growth factors (neurotrophins) and cytokines produced from glial cells in the inflammatory process in Parkinson's disease

Neuroinflammation, especially accompanied by activated microglia in the brain, has been recently noted in PD (for review, see Hirsch et al., 2003; Nagatsu and Sawada, 2005). As the first features of inflammation in PD, McGeer and the collaborators reported an increased number of major histocompatibility complex (MHC) class II antigen [human leukocyte antigen-DR (HLA-DR)]-positive microglial cells in the substantia nigra (McGeer et al., 1988; McGeer and McGeer, 1995). We and other investigators found increased levels of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-alpha (Mogi et al., 1994a), interleukin (IL)-1beta and IL-6 (Mogi et al., 1994b), and decreased levels of neurotrophins such as BDNF and NGF (Mogi et al., 1999a) in the nigro-striatal region of postmortem brains and/or in the ventricular or lumber cerebrospinal fluid (CSF) from patients with sporadic PD, and in animal models, such as MPTP- and 6-hydroxydopamine-induced PD (for review, see Mogi and Nagatsu, 1999b; Nagatsu et al., 1999, 2000a, b; Nagatsu, 2002a). These changes in cytokine and neurotrophin levels may be initiated by activated microglia, which may then proceed to apoptotic cell death and subsequent phagocytosis of DA neurons.

Cytokines such as IL-6, Il-1beta, or TNF-alpha are pleiotropic factors, and promote signals that either exert neuroprotective effects or neurotoxic effects leading to cell death. Neurotrophins such as BDNF and GDNF are strongly neuroprotective for DA neurons. In order to address the question as to whether microglia activation is neurotoxic or neuroprotective in vivo in PD, we examined activated microglia in the autopsy brain from patients with PD by immunohistochemistry using HLA-DR antibody. We (Imamura et al., 2003) found 2 types of activated microglia, one associated with and one without neuronal degeneration: the former was found in the nigro-striatum; and the latter, in the hippocampus and cerebral cortex. We (Imamura et al., 2005) also observed activated microglia in Lewy body disease (LBD), in which neurodegeneration is observed both in the nigro-striatum and hippocampus (Kosaka, 2002), in the nigro-striatum and hippocampus. In normal controls, neuronal loss and activated microglia were not observed in the hippocampus, and neurons were strongly BDNF-positive. In the hippocampus in PD, BDNF-positive neurons were only slightly decreased. In LBD, the number of activated microglia increased more than those in PD, and all neurons were very weakly stained by anti-BDNF. The results suggest activated microglia in the hippocampus to be probably neuroprotective in PD, but in the nigro-striatum to be neurotoxic. As another evidence supporting this hypothesis, two subsets of microglia were isolated from mouse brain by cell sorting: one subset with high production of ROS and the other with no production of ROS. On the other hand, Sawada with coworkers found that a neuroprotective microglia clone in a co-culture experiment converted to a toxic microglia clone by transduction of the HIV-1 Nef protein with increasing NADPH oxidase activity (Vilhardt et al., 2002). Based on these results, we speculate that activated microglia may change in vivo from neuroprotective to neurotoxic subsets as degeneration of DA neurons in the substantia nigra progresses in PD and that the cytokines from activated microglia in the substantia nigra and putamen may be, at least initially, neuroprotective, but then become neurotoxic during the progress of PD (Sawada et al., 2005).

Another interesting question is the possible interrelationship between familial PD and neuroinflammation. Recent discoveries of the causative genes of familial PD (PARK), starting from discoveries of alpha-synuclein in PARK 1 (Polymeropoulos et al., 1997) and parkin in PARK 2 (Kitada et al., 1998) gave a fresh insight to the molecular mechanism of sporadic PD (for review, see Cookson,

2005). Although the function of alpha-synuclein is not yet clear, alpha-synuclein is a main component of cytoplasmic inclusions called Lewy bodies, which are frequently observed in the residual DA neurons in the substantia nigra in PD. The term Lewy body disease (LBD) is proposed by Kosaka (2002) for neurodegenerative diseases with intracellular Lewy bodies. The parkin gene encodes a ubiquitin ligase E3 (Shimura et al., 2000), and the mutated parkin gene results in a faulty ubiquitin-proteasome system. Since misfolded or unfolded proteins in cells are normally degraded by the ubiquitine-proteasome system, dysfunction of the ubiquitine-proteasome system causes accumulation of misfolded proteins, suggesting that PD as well as other neurodegenerative diseases such as LBD and Alzheimer's disease may also be ''protein-misfolding diseases''. A puzzling question is that Lewy bodies are not observed in PARK 2. Misfolded substrate proteins of parkin accumulated by loss of function, such as Pael receptor (parkin-associated endothelin receptor-like receptor), which is rich in the nigral region, may accumulate in the endoplasmic reticulum (ER) and cause ER stress (Imai et al., 2001). Although the molecular link is not completely clear, ER stress may cause oxidative stress as observed in idiopathic PD, and may ultimately trigger the cascade of apoptotic cell death. A causal link is speculated between oxidative stress and neuroinflammation in sporadic and familial PD (Hald and Lotharius, 2005).

In another experiment using a primary mesencephalic neuron-glia co-culture system, aggregated alpha-synuclein activated microglia, and microglial activation enhanced DA neurodegeneration induced by aggregated alpha-synuclein depending on phagocytosis of alpha-synuclein and activation of NADPH oxidase with production of ROS (Zhang et al., 2005). NADPH activation in activated microglia agrees with the concept of toxic change of activated microglia proposed by Sawada and coworkers (Vilhard et al., 2002).

In addition to microglia, astrocytes are thought to contribute, although to a lesser extent, to the neurodegenerative process in PD (McNaught and Jenner, 1997). Although astrocytes release neurotrophins or small antioxidants with free radical-scavenging properties (reduced glutathione, ascorbic acid, GDNF, BDNF, NGF, basic fibroblast growth factor (bFGF)), in certain disease conditions they may also produce toxic products such as NO, and pro-inflammatory cytokines (Mena et al., 2002).

Astrocytes contain MAO B (Levitt et al., 1982), but the presence of MAO B in microglia has not been examined yet.

The interrelationship between neuroinflamation and the neuroprotective effects of MAO B inhibitors remains to be further elucidated. However, since selegiline, a MAO B inhibitor, increases the production of neurotrophins like BDNF and NGF probably from glial cells, MAO B inhibitors would be expected to prevent the progress of toxic injury by activated toxic microglia or astrocytes and also the progress of the inflammatory process in PD.

Conclusion

MAO, especially MAO B, may play important roles in the pathogenesis of PD. MAO B inhibitors such as selegiline and rasagiline have been shown to prevent the progress of PD either in combination with L-DOPA or alone (monotherapy). Further study on the mechanism of neuroprotection by MAO B inhibitors would contribute both to elucidation of molecular mechanism of PD and to the development of new neuroprotective drugs against PD which could prevent the onset and progress of PD. Such drug development would also be useful not only against PD but also against Alzheimer's disease and other neurodegenerative diseases.

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