Progress in Neuro-Psychopharmacology & Biological Psychiatry 69 (2016) 112–124

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Drugs related to monoamine oxidase activity

Zdeněk Fišar

Department of Psychiatry, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Ke Karlovu 11, 120 00 Prague 2, Czech Republic

ARTICLE INFO

Article history:
Received 2 December 2015
Received in revised form 25 February 2016
Accepted 26 February 2016
Available online 2 March 2016

Keywords:
Monoamine oxidase
Monoamine oxidase inhibitor
Neuroprotection
Mental disorder
Hybrid drug

ABSTRACT

Progress in understanding the role of monoamine neurotransmission in pathophysiology of neuropsychiatric disorders was made after the discovery of the mechanisms of action of psychoactive drugs, including monoamine oxidase (MAO) inhibitors. The increase in monoamine neurotransmitter availability, decrease in hydrogen peroxide production, and neuroprotective effects evoked by MAO inhibitors represent an important approach in the development of new drugs for the treatment of mental disorders and neurodegenerative diseases. New drugs are synthesized by acting as multitarget-directed ligands, with MAO, acetylcholinesterase, and iron chelation as targets. Basic information is summarized in this paper about the drug-induced regulation of monoaminergic systems in the brain, with a focus on MAO inhibition. Desirable effects of MAO inhibition include increased availability of monoamine neurotransmitters, decreased oxidative stress, decreased formation of neurotoxins, induction of pro-survival genes and antiapoptotic factors, and improved mitochondrial functions.

1. Introduction

Monoamine oxidases (MAOs, EC 1.4.3.4) catalyze the oxidative deamination of monoamines, including the monoamine neurotransmitters serotonin (5-hydroxytryptamine, 5-HT), norepinephrine, epinephrine, dopamine, melatonin, tryptamine, histamine, and taurine. Aldehyde, ammonia and hydrogen peroxide (H_2O_2) are formed in a MAO-catalyzed reaction:

$$R - CH_2 - NH_2 + O_2 + H_2O \rightarrow R - CHO + NH_3 + H_2O_2$$

Aldehydes are further oxidized by aldehyde dehydrogenase into carboxylic acids. In the presence of transition metals (Fe^{2+}, Cu^{+}) hydrogen peroxide may be converted to a highly reactive hydroxyl radical (HO•), e.g., by the Fenton reaction:

$$H_2O_2 + Fe^{2+} \rightarrow HO^{\bullet} + OH^{-} + Fe^{3+}.$$

MAO activity and the mitochondrial oxidative phosphorylation (OXPHOS) system are major sources of H_2O_2 in the brain. Thus, MAO significantly contributes to the production of reactive oxygen species (ROS) by mitochondria and participates in the regulation of both monoamine neurotransmission and oxidative stress in the brain (Edmondson, 2014).

Increased oxidative and nitrosative stress and/or decreased antioxidative protection are important causes of neurodegeneration, neuronal apoptosis, and lowered neurogenesis and neuroplasticity, which play a role in the pathophysiology of several neuropsychiatric disorders, including depression, Alzheimer's disease (AD), and Parkinson's disease (PD) (Leonard and Maes, 2012; Maes et al., 2009, 2011). Therefore, corresponding signaling pathways are studied as drug targets, including MAO.

MAOs belong to the family of flavin-containing amine oxidoreductases and exists as two subtypes, A (MAO-A) and B (MAO-B). Initially, subtypes of MAO were distinguished by their substrate and inhibitor specificity (Youdim et al., 2006). MAO-A specifically metabolizes serotonin, and MAO-B selectively catalyzes the deamination of benzylamine and 2-phenylethylamine. Clorgyline (3-(2,4-dichlorophenoxy)-*N*-methyl-*N*-prop-2-ynylpropan-1-amine) is an irreversible and selective MAO-A inhibitor, and L-deprenyl (selegiline, (2*R*)-*N*-methyl-1-phenyl-*N*-prop-2-ynylpropan-2-amine) is an irreversible and selective MAO-B inhibitor (Youdim and Bakhle, 2006). Of the major monoamines,

Abbreviations: AD, Alzheimer's disease; Bcl-2, B-cell lymphoma 2 protein; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; COMT, catechol-*O*-methyltransferase; CREB, cAMP response element-binding protein; *DAOA*, gene for D-amino acid oxidase activator; *DISC1*, gene for disrupted in schizophrenia 1 protein; *DRD4*, gene for dopamine receptor D_4; *DTNBP1*, gene for dystrobrevin-binding protein 1; *FOXO1*, gene for Forkhead box protein O1; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GDNF, glial cell line-derived neurotrophic factor; GSK-3β, glycogen synthase kinase 3β; HIF-1α, HIF-1α, hypoxia-inducible factor 1, alpha subunit; HSD10, 17-β-hydroxysteroid dehydrogenase X (also 17β-HSD10, ABAD); KFL11, glucocorticoid-transcription factor Krüppel-like factor 11 (also called TIEG2); L-DOPA, L-3,4-dihydroxyphenylalanine, levodopa; MAO, monoamine oxidase; MAOI, monoamine oxidase inhibitor; MAPK, mitogen-activated protein kinase; MPP^{+}, 1-methyl-4-phenylpyridinium; MPT, mitochondrial permeability transition; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NGF, nerve growth factor; *NRG1*, gene for neuregulin 1; OXPHOS, oxidative phosphorylation; *PARK2*, gene for parkin; PARK7, Parkinson disease protein 7; PD, Parkinson's disease; PK, protein kinase; *PSEN*, gene for presenilin-1; RIMA, reversible and selective inhibitor of MAO-A; ROS, reactive oxygen species; *SIRT1*, gene for sirtuin 1; *SLC6A3I*, gene for dopamine transporter; *SLC6A4*, gene for serotonin transporter; *SRY*, sex-determining region Y gene; *TPH2*, gene for tryptophan hydroxylase 2; VNTR, variable number of tandem repeat.

E-mail address: zfisar@lf1.cuni.cz.

http://dx.doi.org/10.1016/j.pnpbp.2016.02.012
0278-5846/

MAO-A generally metabolizes serotonin, norepinephrine, dopamine, and tyramine; in the human brain, MAO-B mainly metabolizes dopamine (Glover et al., 1977).

MAO subtypes have been definitively demonstrated by cloning the cDNAs encoding MAO-A and MAO-B subunits (Bach et al., 1988). Both *MAOA* and *MAOB* gene are located on the X chromosome (Lan et al., 1989). The primary, secondary and tertiary structures of MAO-A and MAO-B are well known; these enzymes exhibit ~70% sequence identity. Both enzymes are dimeric in their membrane-bound forms. Crystallographic and biochemical data of both isozymes have confirmed differences in the structures of their active sites (Fowler et al., 2007; Edmondson et al., 2009; Binda et al., 2011).

Studies of the transcriptional regulation of the *MAOA* and *MAOB* genes showed that different promoter organizations may underline different tissue- and cell-specific expressions of MAO subtypes (Shih et al., 2011). Different transcription factors, components of intracellular signaling pathways, and hormones also participate in the regulation of *MAOA* and *MAOB* expressions. *MAOA* expression can be activated by the transcription factor Sp1 and suppressed by transcription repressor R1 (Chen et al., 2005). The functions of MAO-A and its repressor R1 have been demonstrated in apoptotic signaling pathways. It was found that MAO-A and R1 are downstream of p38 kinase and Bcl-2 but upstream of caspase-3 and that inhibition of MAO-A prevents cell apoptosis. In addition, MAO-A and R1 are involved in the c-Myc-induced proliferative signaling pathway (Ou et al., 2006a). Glucocorticoids and androgens induce *MAOA* expression through R1 and Sp1 (Ou et al., 2006b). *MAOA* (X-located gene) is a putative target gene directly regulated by a transcription factor encoded by the sex-determining region Y (*SRY*) gene located on the Y chromosome; *SRY* activates both *MAOA*-promoter and catalytic activities in a human neuroblastoma cell line. Sp1 synergistically enhances the *SRY* activation of *MAOA* promoter (Wu et al., 2009). Chronic stress-induced increases in MAO-A were found to be mediated by the glucocorticoid-transcription factor Krüppel-like factor 11 (KLF11, also called TIEG2) pathway, which may play a crucial role in modulating distinct pathophysiological steps in stress-related disorders (Grunewald et al., 2012). MAO-B is activated by the protein kinase C (PKC) and mitogen-activated protein kinase (MAPK) cascades. MAO-A and MAO-B are distinctly regulated by diverse hormones. This differential regulation may contribute to the differences in the temporal/spatial expression and physiological functions between these two isoenzymes. Modulation of endogenous levels of transcription factors of MAO genes could be considered as an alternative approach to regulate MAO activity in addition to using MAOIs (Shih et al., 2011).

MAOs are mainly bound to the outer mitochondrial membrane. Both isoenzymes are expressed in most tissues, including brain. In the central nervous system (CNS), intraneuronal MAO is dominant in the metabolism of monoamine neurotransmitters, regulates the storage of monoamines, and protects neurons from exogenous monoamines. The distribution of MAO-A and MAO-B in the brain is not random; MAO-A occurs mainly in catecholaminergic neurons, whereas serotonergic and histaminergic neurons and astrocytes contain predominantly MAO-B (Saura et al., 1996; Shih et al., 1999; Tong et al., 2013). Due to the loss of selectivity of MAO isoenzymes at high concentrations of substrates, serotonin is metabolized by MAO-B in presynaptic areas when it is present at high concentrations.

MAO inhibitors (MAOIs) prevent the breakdown of monoamine neurotransmitters and thereby increase their availability. MAOIs were among the first antidepressants to be clinically used. Reversible and selective inhibitors of MAO-A (RIMAs) have antidepressant potential and a good safety margin regarding the tyramine effect; they are used in the treatment of depressive disorder and social phobia (Fulton and Benfield, 1996; Bonnet, 2003) and are associated with fewer dropouts because of adverse effects compared with other antidepressants (Linde et al., 2015). Some irreversible inhibitors of MAO-B have shown therapeutic value in the treatment of several neurodegenerative conditions, including PD and AD (Youdim et al., 2006). Lowered metabolism of monoamine neurotransmitters and decreased production of hydrogen peroxide are both understood as principal primary biochemical processes related to the therapeutic effects of MAOIs. The neuroprotective effects of some MAOIs seem to be related to their antiapoptotic activity and modulation of gene expression leading to increased neuroplasticity and neuronal survival (Naoi et al., 2016). New drugs for the treatment of major depressive and other neuropsychiatric disorders are developed to function as multitarget-directed ligands, with the selective reversible inhibition of MAO as one target.

2. Drug-induced regulation of monoamine neurotransmission

Monoamine neurotransmitters and, consequently, MAO activities are involved in processes associated with chronic stress, various neuropsychiatric disorders and the effects of many psychotropic drugs. In general, various drugs could affect monoaminergic neurotransmission via the regulation of the synthesis of neurotransmitters (Moranta et al., 2004), the regulation of the catabolism of monoamine neurotransmitters (Fišar et al., 2012), the inhibition of the release or reuptake of neurotransmitters, changes in the activity of components of intracellular signaling pathways (Fišar and Hroudová, 2010), and neuroplasticity.

The term neuroplasticity (also known as brain plasticity, cortical plasticity, or cortical re-mapping) describes functional and structural changes in brain cells that occur both during development and in response to external or internal stimuli (Mesulam, 1999; Nestler et al., 2002). Neuroplasticity is a fundamental mechanism of neuronal adaptation to environmental inputs, including long-term treatment with psychotropic drugs. The term synaptic plasticity includes the development of new synapses and changes in the strength or elimination of existing synapses (Citri and Malenka, 2008; Rebola et al., 2010; Chaudhury et al., 2016). It is apparent that the activation/inhibition of intracellular signaling pathways by monoamines plays an important role in neuroplasticity; the activation of the cyclic AMP/cAMP response element-binding protein/brain-derived neurotrophic factor (cAMP/CREB/BDNF) pathway seems important in the formation of new synaptic connections and memory traces etc. (Nestler et al., 2002; Reichardt, 2006).

The specific effects of monoamine neurotransmitters are due to the activation of the monoamine system in the brain and processes associated with this. The primary biochemical effects of drugs that affect the monoaminergic system includes the activation or inhibition of monoamine receptors, the inhibition of enzymes participating in monoamine catabolism, and changes in the activity of membrane neurotransmitter transporters. Long-term treatment with monoaminergic drugs induces adaptive changes in the monoamine system and related neurotransmitter systems. These changes involve regulation of the density and sensitivity of membrane receptors and the activity of specific neurotransmitter transporters; the activation of intracellular signaling pathways; the activation of transcription factors; increases in the gene expression of neurotrophic factors; the activation of neurotrophic signaling pathways; feedback effects on neurotransmission; increases in functional and structural neuroplasticity (synaptogenesis and formation or changes in axons, synapses, dendrites, and dendritic spines); antiapoptotic effects; support of neurogenesis, cellular resilience and neuron survival; anti-inflammatory effects; HPA axis regulation; protection against the neurotoxic effects of cellular stress; the synchronization of biological rhythms; and epigenetic changes (Fišar, 2013).

The actions of monoamine neurotransmitters on target cells are terminated by the active transport of neurotransmitters from the extracellular space into the synapse (reuptake) and/or by the enzymatically catalyzed degradation of neurotransmitters. The major enzymes involved in the catabolism of dopamine or norepinephrine is MAO or catechol-*O*-methyltransferase (COMT); serotonin is metabolized in the brain mainly by MAO. Drugs that directly inhibit monoamine transporters or catabolize enzymes cause rapid changes in the availability of monoamine neurotransmitters and in the activation of the corresponding receptors. Consequently, there is an increased availability of monoamine neurotransmitters, and long-term processes may be