Drugs related to monoamine oxidase activity

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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.

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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:

$$R - \text{CH}_2 - \text{NH}_2 + O_2 + H_2O \rightarrow R - \text{CHO} + \text{NH}_3 + H_2O_2$$

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 a-amino acid oxidase activator; DISC1, gene for disrupted in schizophrenia 1 protein; DRD4, gene for dopamine receptor D4; 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-3, glycogen synthase kinase 3/$\beta$; HIF-1$\alpha$, HIF-1$\gamma$, hypoxia-inducible factor 1, alpha subunit; HSD10, 17$\beta$-hydroxysteroid dehydrogenase X (also 17$\beta$-HSD10, ABAD); KFL11, glucocorticoid transcription factor Krüppel-like factor 11 (also called THIE2); L-DOPA, L-3,4-dihydroxyphenylalanine, levodopa; MAO, monoamine oxidase; MAOI, monoamine oxidase inhibitor; MAPK, mitogen-activated protein kinase; MPP$^+$, 1-methyl-4-phenylpyridinium; MPTP, mitochondrial permeability transition; 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; SLC6A4, gene for dopamine transporter; SLC6A3I, gene for D-amino acid oxidase; SLC6A3I, gene for serotonin transporter; SLC6A3I, gene for dopamine transporter; SLC6A4, gene for dopamine transporter; SLC6A4, gene for serotonin transporter; SLC6A4, gene for dopamine transporter; SLC6A4, gene for serotonin transporter; SLC6A4, gene for dopamine transporter; SLC6A4, gene for serotonin transporter; TPH2, gene for tryptophan hydroxylase 2; VNTR, variable number of tandem repeat.

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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:

$$H_2O_2 + Fe^{2+} + HO^{-} + OH^- + Fe^{3+}.$$
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 underlie 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 Kruppel-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 orders (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 orders (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 orders (Grunewald et al., 2012).

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 catalyze 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
common for drugs that modulate monoaminergic neurotransmission in different direct ways.

Direct effect of drugs on MAO activity can be realized by the competitive binding of the drug to an active site for monoamines or by the allosteric modulation of the active site. However, MAOIs may also bind to other proteins (Holt and Berry, 2004). The effects of MAOIs are ranked among the direct effects on MAO activity, together with the inhibition of the reuptake of neurotransmitters and the activation or blocking of neurotransmitter receptors. The structures of the active sites of MAO-A and MAO-B are well known (Fowler et al., 2007; Edmondson et al., 2009; Binda et al., 2011), which allows the synthesis of new specific ligands. Gene polymorphisms/mutations or drug-induced changes in signaling pathways related to MAO activity represent indirect modulation of MAO activity.

3. Monoamine neurotransmission and neuropsychiatric disorders

Monoamine neurotransmitters, such as 5-HT, norepinephrine, and dopamine, are the most important neurotransmitters in the pathophysiology of major mental disorders and in the molecular mechanisms of action of many psychotropic drugs. Recent evidence includes association of disturbances in the availability of monoamines, energy metabolism, inflammatory pathways, and neuroplasticity with mitochondrial dysfunctions, oxidative stress, and inflammation in the pathogenesis of mental disorders (Fišar, 2013).

Current biological hypotheses argue that changes in MAO-A activity are included in the pathophysiology of mental disorders, considering that MAO subtypes affect each other and that MAO-A expression may be regulated by both polymorphisms of MAOA gene and mutations and polymorphisms of PARK2 gene for parkin, the SIRT1 gene for sirtuin 1, the FOXO1 gene for Forkhead box protein O1, microRNAs, the RPE1 gene for presenilin-1, and other regulatory proteins (Naoi et al., 2016).

Serotonin, norepinephrine, and dopamine are able to regulate their own release via presynaptic and somatodendritic autoreceptors. There are also many ways in which these monoamine neurotransmitters interact to regulate each other (Stahl, 2013). There are close interconnections between monoamine systems and other brain signaling pathways, and changes in monoamine neurotransmission may represent both the downstream effects of more primary abnormalities in signal transduction and upstream effects on neuron survival, neuroplasticity, and neuroprotection.

The unique ability of MAO to modulate monoaminergic neurotransmission indicates that this enzyme may be a target of drugs used in the modulation of brain functions and in the treatment of various mental diseases, including mood disorders (Rivera et al., 2009; Shulman et al., 2013), anxiety (Tyrer and Shawcross, 1988; Tadic et al., 2003), schizophrenia (Samson et al., 1995; Siever and Coursey, 1985; Sun et al., 2012), attention deficit hyperactivity disorder (Jiang et al., 2001; Wargelius et al., 2012), anorexia nervosa (Urwin and Nunn, 2005), migraine (Flici et al., 2005; Merikangs and Merikangs, 1995), and neurodegenerative disorders (Cai, 2014; Youndim et al., 2004). Furthermore, there is an association between platelet MAO-B activity and personality traits, such as sensation seeking and impulsiveness (Oreland et al., 2004) or heightened reactivity to provocative situations (Chester et al., 2015).

3.1. Depressive disorders

The inadvertent induction of depression by reserpine (a monoamine-depleting agent that irreversibly and nonselectively blocks the vesicular monoamine transporter) and the effectiveness of the first antidepressants (MAOIs and inhibitors of the reuptake of norepinephrine and serotonin) led to the monoamine hypothesis, which posits that affective disorders are due to catecholamine (Schildkraut, 1965) and/or indolamine (Coppen, 1967) deficiencies in the CNS and that the therapeutic effects of antidepressants result from increased stimulation of norepinephrine and/or serotonin receptors due to the elevation of these monoamine neurotransmitters in the extracellular space. The revised monoamine theory of depression posits that monoamine systems modulate other signaling pathways that have more primary roles in depression (van den Rot et al., 2009; Heninger et al., 1996).

According to the advanced monoamine hypothesis (Meyer et al., 2006), brain concentrations of serotonin or norepinephrine are regulated mainly by MAO-A activity, and the severity of depressive symptoms is associated with disturbances in the activity of transporters of monoamine neurotransmitters in specific brain areas. This hypothesis was supported by findings that MAO-A density is elevated during a major depressive episode (Meyer et al., 2006, 2009) and that binding to serotonin transporters is reduced (Selvaraj et al., 2011). Moreover, high-activity variants of the MAOA promoter polymorphism have been found to be associated with a higher risk of depression (Rivera et al., 2009).

The monoamine-deficiency hypothesis was broadened by the presumption of disturbances in other neurotransmitter systems and their mutual interactions; e.g., the central acetylcholine system has been implicated in the pathophysiology of mood disorders (Cannon et al., 2006, 2011). The roles of various receptors and transporters in the pathophysiology of depression are discussed with respect to the results of animal studies, genetic studies and alterations in inflammation, endocrine function and neurocircuity (Meyer, 2012; Savitz and Drevets, 2013).

The mechanisms of action of antidepressants (including MAOIs), monoamine depletion studies, positron emission tomography studies, and genetic association studies have supported a role of monoaminergic neurotransmission in the pathophysiology of depression but have not shown evidence of a primary role of the monoaminergic system in the development of the disorder. Because direct measurements of monoamine neurotransmission did not yield definitive evidence in relation to depression, the downstream effects of monoamine neurotransmission were explored (Belmaker and Agam, 2008).

Disturbances in mitochondrial functions and major signaling pathways have been examined (Fišar and Hroudová, 2010). Functional polymorphisms in genes encoding components of these signaling pathways may participate in the development of the disease. The neurotrophic hypothesis of depression (Duman et al., 1997; Duman, 2002; Einat and Manji, 2006; Zarate et al., 2006; Pittenger and Duman, 2008) states that a deficiency in neurotrophic support may contribute to hippocampal pathology during the development of depression and that the reversal of this deficiency by antidepressants or mood stabilizers may contribute to the resolution of depressive symptoms. Over the last 15–20 years substantial evidence has emerged that stress and depression are associated with the atrophy and loss of neurons and glia as well as reduced volume of certain limbic and cortical areas (Duman, 2014). Research is focused on the signaling pathways that contribute to these morphological changes, including the regulation of neurotrophic factors and the activity of glycogen synthase kinase 3β (GSK-3β) (Gould et al., 2007), oxidative damage to the brain and metabolic changes associated with the exhaustion of energy supply, which leads to decreased ATP production by mitochondria, damage to ATP-dependent processes and thereby to changes in cellular function and sometimes apoptosis (Fišar, 2013).

The hypothesis of mitochondrial dysfunctions allows for the role of neurotoxicity and/or oxidative stress in the pathophysiology of depression. The brain is extremely vulnerable to oxidative stress damage, and mitochondria are the major source of ROS. Thus, damage due to increased oxidative and nitrosative stress and/or lowered levels of antioxidant protections is likely involved in the pathophysiology of depression (Berk et al., 2011; Maes et al., 2009, 2011, 2012).

Preclinical and clinical data indicate that monoamine neurotransmission is disturbed in mood disorders (Meyer et al., 2006, 2009; Selvaraj et al., 2011), along with dysfunctions in the energy metabolism of neurons (Kato, 2007, 2008; Kato and Kato, 2000; Stork and Renshaw, 2005), the modulation of inflammatory pathways (Maes et al., 2009), changes in the activity of transcription factors, and the expression of
neurotrophins and other components that regulate neuroplasticity and apoptosis (Duman, 2002, 2009; Duman et al., 1997; Duman and Monteggia, 2006).

3.2. Schizophrenia

The classical dopamine hypothesis of schizophrenia states that psychotic symptoms are related to disturbances in dopaminergic neurotransmission in specific brain areas. It is hypothesized that positive symptoms of schizophrenia are related to the dopaminergic hyperactivity of dopamine D2 receptors in the mesolimbic pathway and striatal areas, and negative symptoms of schizophrenia are related to dopaminergic deficit in mesocortical circuits and prefrontal areas and may involve the nucleus accumbens, which is part of the reward circuits (Stahl, 2013). Strong support for the dopamine hypothesis of schizophrenia is the fact that all currently used antipsychotics antagonize dopamine D2-type receptors. The theory, however, does not posit disturbances in the dopamine system as a complete explanation for schizophrenia. The glutamatergic hypothesis of schizophrenia holds that dopaminergic dysfunction is secondary to glutamatergic dysfunction. However, disturbances in other neurotransmitter systems may precede the onset of symptoms of schizophrenia (Fišar, 2012; Pacher et al., 2008).

Susceptibility genes for schizophrenia include the dopamine D2 and D3 receptors and MAO-A. In MAOA gene polymorphism studies, a haplotype association was found for the variable number of tandem repeat (VNTR) polymorphisms in female subjects (Sun et al., 2012), indicating that interactions between genetic variants within the MAOA gene may contribute to increased risk of schizophrenia.

3.3. Bipolar disorder

Schizophrenia and bipolar disorder overlap in many ways, including altered serotonin, dopamine, and glutamate functions. Hyperdopaminergic function is reported in both schizophrenia and bipolar disorder. A dopamine hypothesis of bipolar disorder was formulated (Berk et al., 2007) that suggested a role of increased dopaminergic transmission in mania and the converse in depression. Biomarkers for bipolar disorder are in the early stages of research (Duong et al., 2015) and include increased oxidative stress (Brown et al., 2014), increased proinflammatory markers, altered plasma neurotrophins (Scola and Andreazza, 2014, 2015), and changed dopamine transporter availability (Anand et al., 2011).

Both environmental factors and genes play an important role in the pathogenesis of bipolar disorder. Most candidate gene studies in bipolar disorder have focused on the monoamine neurotransmitter systems. A number of genes have consistently been found to be associated with bipolar disorder, such as gene for serotonin transporter (SLC6A4), tryptophan hydroxylase 2 (TPH2), dopamine receptor D4 (DRD4), dopamine transporter (SLC6A3), D-amino acid oxidase activator (DAOA), dystrophiaimyelin protein 1 (DITNBP1), neuregulin 1 (NRG1), disrupted in schizophrenia 1 protein (DISC1) and BDNF. Several polymorphisms have been suggested to play a modest role in susceptibility to the disease, including polymorphisms of the genes for MAO-A and COMT (Craddock et al., 2001; Serretti and Mandelli, 2008).

3.4. Drug addiction

The addictive process can be understood as an interaction of impairments in three functional systems: motivation-reward, affect regulation, and behavioral inhibition (Goodman, 2008). Dopamine or opioid systems play a key role in the development of addiction; however, many other neurotransmitters, neuromodulators and their receptors are involved (Di Marzo and Matias, 2005; Goodman, 2008; Hyman et al., 2006). Dopamine is a neurotransmitter in the mesolimbic and mesocortical pathways, which are the main components of the brain reward system. Repeated exposure to drugs of abuse results in a repetitive stimulation of dopaminergic neurons and subsequent desensitization of the dopamine receptors. It has been well established that the reinforcing qualities of alcohol, cocaine, methamphetamine, heroin, nicotine, marijuana, and other drugs, are mediated by its ability to raise dopamine levels in the mesolimbic system, particularly in the nucleus accumbens. Drugs that modulate dopamine availability, release or uptake may be involved in addiction control and treatment of the reward system.

Decrease in MAO activity was observed in smokers, presumably due to their exposure to tobacco constituents that possess MAO-inhibiting properties. Similar inhibition of MAO activity (that reverses when they cease to use alcohol) has been reported in subjects with alcoholism (Devor et al., 1993; van Amsterdam et al., 2006). The human MAO B promoter contains Sp/TLF-binding sites, which are responsive to ethanol-induced GAPDH (glyceraldehyde 3-phosphate dehydrogenase)/KLF11-mediated upregulation of MAO-B and subsequent neurotoxicity (Duncan et al., 2012).

The molecular mechanisms underlying the association between platelet MAO and behavior, including vulnerability for substance abuse, may include activation of common transcriptional factors, regulating both the expression of platelet MAO and components of central monoaminergic systems (Oreland et al., 2004).

The MAOA gene is an attractive candidate for exploring genetic contributions to the variation in the risk of substance use disorders because of its role in the metabolism of monoamine neurotransmitters. The MAOA gene has a functional polymorphism with a VNTR in the upstream regulatory region (MAOA-VNTR). Lower expression of the MAOA-VNTR polymorphism was associated with a history of abuse before 15 years of age in male subjects (Huang et al., 2004). The hypothesis was supported by findings that variants in MAOA account for a small portion of the variance in the risk of substance abuse disorders (Vanyukov et al., 2004).

3.5. Neurodegenerative disorders

In neurodegenerative disorders, including Parkinson’s and Alzheimer’s diseases, MAO-B has been proposed to play a primary role through generating ROS and neurotoxins. Selective MAO-B inhibitors decrease the oxidation of substrates, scaveng ROS, and induce antiapoptotic Bcl-2 and neurotrophic factors. MAO-A is also involved in neuronal loss because it is associated with apoptosis and mediates the increased expression of genes for antiapoptotic factor Bcl-2 and neurotrophic factors by MAO-B inhibitors. These results suggest an association of both MAO-A and MAO-B with neuronal death in neurodegenerative disorders (Naoi et al., 2012, 2016).

Parkinson’s disease is a common age-related progressive neurodegenerative disease, which is characterized by the death of dopaminergic neurons. Reliable biomarkers to detect early neurodegeneration in PD and to detect and monitor the effects of drug candidates on the disease process have not yet been revealed. However, some promising biomarker candidates exist, such as antibodies against neuromelanin, pathological forms of α-synuclein, and Parkinson disease protein 7 (PARK7), as well as patterns of gene expression, metabolomics and protein profiling (Gerlach et al., 2012).

MAO-B seems to play an important role in neurodegenerative disorders as an ROS producer during the oxidation of monoamine neurotransmitters. Moreover, there is positive feedback between hydrogen peroxide levels and MAO-B activity (Konradi et al., 1986). The association of MAO-B with neuronal death in PD was supported by the observation that MAO-B oxidizes the xenobiotic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) into the 1-methyl-4-phenylpyridinium ion (MPP+), a neurotoxin that causes parkinsonism in both non-human primates and humans (Heikkinen et al., 1984). MPP+ interferes with mitochondrial complex I of the electron transport chain, which leads to increased production of ROS, depletion of ATP, and cell death. Dopamine
neurons in the pars compacta of the substantia nigra are destroyed by MPP⁺.

Mitochondrial gene variations and mutations as well as nuclear gene variations and mutations contribute to the pathogenesis of PD (Andalib et al., 2014; Naoi et al., 2016). A significant association with PD was found in a polymorphism of the MAOB gene (Tan et al., 2000; Jakuabaukiene et al., 2012). However, the elevation of MAO-B in dopamine-containing neurons does not necessarily contribute to vulnerability to PD (Damiér et al., 1996).

Pharmacological treatments of PD have been based on dopamine replacement with L-DOPA, the activation of dopamine receptors by agonists, and the inhibition of dopamine catabolism, including COMT inhibitors and MAO-B inhibitors (Gallagher and Schrag, 2008). It is thought that the neuroprotective effects of MAO-B inhibitors may be related to MAO-B inhibition, the activation of multiple antioxidative and antiapoptotic factors, and increased production of neurotrophins, such as nerve growth factor (NGF), BDNF, and glial cell line-derived neurotrophic factor (GDNF) (Nagatsu and Sawada, 2006).

Parkin is a component of a multiprotein E3 ubiquitin ligase complex that participates in the ubiquitin–proteasome system; its function in the cell is thought to be protective. Parkin dysfunction represents a predominant cause of familial PD and also a risk factor for sporadic PD, AD and amyotrophic lateral sclerosis (Zhang et al., 2016). Parkin has been found to play a significant role in the degeneration of dopaminergic neurons and the regulation of MAO-B activity (Naoi et al., 2016). In cell lines, it was found that the stable transfection of the parkin-coding gene PARK2 reduced the transcription and activities of both MAO-A and MAO-B. MAO expression was increased in human B lymphocyte cell lines derived from Parkinson’s patients with a homoygous deletion of exon 4 of PARK2 (Jiang et al., 2006). These results suggest that parkin suppresses MAO expression, which may result in decreased production of ROS and may improve the survival of dopaminergic neurons. Mutations in the PARK2 gene may reduce parkin activity, which may lead to an increase in MAO-B activity, increased production of ROS, and damage to neurons. It is thought that mutations in parkin are linked to early-onset PD (Jiang et al., 2006; Naoi et al., 2016).

Alzheimer’s disease is the most common cause of dementia in older people. The formation of senile plaques, which are composed of amyloid-β (Aβ) oligomers, in the cerebral cortical regions, and intraneuronal neurofibrillary tangles, which are composed of paired helical filaments formed of hyperphosphorylated tau proteins, is thought to contribute to the etiology of AD. According to the amyloid cascade hypothesis, the primary cause of AD is an imbalance in the production and clearance of Aβ (Bayer and Wirths, 2014). However, a growing body of evidence has suggested that other factors, including neuroinflammation, glutamate excitotoxicity, metal accumulation, perturbations in cellular energy metabolism and mitochondrial dysfunctions, ubiquitin–proteasome system dysfunction, gene mutations, and increased MAO-B activity, participate in the pathophysiology of AD (Chaturvedi and Beal, 2013; Hroudová et al., 2014; Rogers and Lahiri, 2004; Ross et al., 2015). The oxidative stress-induced Alzheimer’s disease cascade hypothesis suggests that aged mitochondria are the critical cause of neurodegeneration in AD (Bonda et al., 2014), it is thought that loss of cholinergic neurons and several neurotransmitter dysfunctions are involved in the pathogenesis of AD. Depressive symptoms exacerbate pre-existing patient morbidity in up to 50% of Alzheimer’s patients (Heun et al., 2002; Lyketsos et al., 2011), which highlights the role of disturbances in monoamine systems.

MAO-A is involved in the pathogenesis of AD. It was found that a promoter polymorphism of a VNTR in the MAOA gene is associated with the activity and gene expression of MAOA in the brain of Alzheimer’s patients (Takahashi et al., 2002; Wu et al., 2007). Due to the effects of MAOs on monoaminergic neurotransmission, oxidative stress, induction of neurotrophic factors, and apoptosis, MAO inhibition is part of the concept of the development of drugs with a neuroprotective effect that are intended to treat PD and AD (Benek et al., 2015; Cai, 2014; DeMaagd and Philip, 2015; Huang et al., 2012; Youdim et al., 2004; Zheng et al., 2012). The “multitarget-directed ligand” (MTDL) design strategy is based on combining pharmacophores of diverse drugs to obtain hybrid molecules. New drugs for the treatment of AD may combine cholinesterase inhibition with compounds that act on MAO activity, Aβ aggregation, γ-secretase activity, serotonin transporter activity, the production of ROS (e.g., by iron chelation activity), calcium channels, or mitochondrial permeability transition pores (mPTPs) (Bolea et al., 2013a; Weinreb et al., 2015).

3.6. Pathological aggression

Neurocircuits for different types of aggressive behavior include loops between the striatum and thalamus with frontal and prefrontal structures and important feedback to limbic and mesencephalic nuclei (Takahashi and Miczek, 2014). There is significant emphasis on the amygdala and on amygdala-frontal circuitry. The precise molecular processes that mediate aggressive behavior remain to be elucidated.

There has been focus on understanding the role of serotonin, the most intensively investigated neurotransmitter system that has been linked to aggression. The classic serotonin deficiency hypothesis associates defects in synthesis, release, reuptake, receptor activation, or metabolism to a vulnerability to aggressive behavior. This hypothesis was advanced by the inclusion of a set of various mechanisms that modulate serotonergic activity, including the nitric oxide synthase, dopaminergic and vasopressinergic systems (Bedrosian and Nelson, 2014; Morrison and Melloni, 2014; Rosell and Siever, 2015).

Impulsive aggression is significantly heritable; however, the specific pathophysiological mechanisms that mediate such behavior are not sufficiently known. Converging evidence shows that MAO-A is an important factor in the pathophysiology of violence and aggressive behavior (Brunner et al., 1993; Caspi et al., 2002; Weder et al., 2009). MAO-A-deficient males and mice exhibit a predisposition to aggressive behavior in response to stress. Particular attention has been paid to the role of functional polymorphisms in MAO-A and serotonin transporters and their impact on serotonergic signaling (Dorfman et al., 2014; Pavlov et al., 2012). It is thought that disrupted serotonergic systems, caused by low function MAO-A genotypes, predispose individuals to aggressive behavior by increasing impulsive reactive to negative affect (Chester et al., 2015).

Assuming that aggression is associated with reduced MAO-A activity, it is possible to speculate on the following approaches to the treatment of pathological aggression: (i) an increase in the synthesis of MAO-A (e.g., by transcriptional regulation or by gene therapy with siRNAs); (ii) an increase of current activity of MAO-A (e.g., by allosteric modulation via new drugs); and (iii) modification of MAO-B so that MAO-B will be able to metabolize serotonin at lower concentrations. A decrease in the intake of substrates of MAO-A in the diet and/or discontinuation of the administration of drugs that inhibit MAO-A should be involved. Another possibility is focus on other (non-serotonergic) neurotransmitters systems that mediate the role of MAO-A in pathological aggression, e.g., NMDA receptors (Bortolato et al., 2012). Further study of the physiological role of MAOs and their signaling pathways is needed to better understand their role in aggression.

MAO-A knock-out mice have elevated brain levels of serotonin, norepinephrine, and dopamine, and they manifest aggressive behavior similar to human males with a deletion of MAO-A. In contrast, MAO-B knock-out mice do not exhibit aggression and only levels of phenylethylamine are increased (Shih et al., 1999). Hypothesis has been discussed that the attenuation of the oxidative stress induced by the inactivation of either MAO isofrom may contribute to both antidepressant and antiparkinsonian actions of MAO inhibitors (Bortolato et al., 2008).

4. Inhibition of monoamine oxidase

Drug-induced inhibition of MAO is used in the treatment of depressive disorder, PD, and AD. New drugs include those with a combination
of different inhibitory functions in a single molecule. However, the mechanisms underlying both the onset of these disorders and the therapeutic and neuroprotective effects of drugs are not sufficiently understood. The effect of drug treatment on in vivo MAO activity has been confirmed by positron emission tomography; e.g., moclobemide treatment led to a 64% to 79% MAO-A blockade across brain regions (Ginovart et al., 2006). Pharmacological modulation of the monoamine system continues to be the main therapeutic strategy for the treatment of both mood disorders and schizophrenia. MAOIs have many potential therapeutic uses (Ramsay and Gravestock, 2003), including protection against oxidative stress in depressive disorder or in PD (Youdim et al., 2006).

The adverse CNS effects of MAO-B inhibitors include, depression, hallucinations, confusion, compulsive behaviors, and extrapyramidal reactions (DeMaagd and Philip, 2015). Nonspecific irreversible MAOIs can pose problems when taken concomitantly with tyramine-containing foods (“cheese reaction”). Selective irreversible MAO-B inhibitors have no such effect (unless administered at concentrations sufficiently high to inhibit MAO-A) because tyramine is effectively metabolized by intestinal MAO-A (Hasan et al., 1988). The development of reversible selective MAO-A inhibitors (RIMAs), such as moclobemide (4-chloro-N-(2-morpholin-4-ylethyl)benzamide) and lazabemide (N-(2-aminoethyl)-5-chloropyridine-2-carboxamide), avoided problems with the entrance of excess tyramine into the circulation and the potential for sympathetic cardiovascular activity by releasing norepinephrine (Youdim et al., 2006; Youdim and Bakhle, 2006). Moclobemide increases the quantity of serotonin, norepinephrine and dopamine in the brain (Haeffely et al., 1992) but does not provoke the “cheese reaction”. Several other compounds can selectively inhibit MAO (Ask et al., 1986; Flavall et al., 1986a, 1986b).

Misinformation is widespread about the potential danger of a tyramine-induced hypertensive crisis in patients treated with MAOIs. There are a few things to avoid, and in practice, diet is not a problem (Stahl, 2013). Drug–drug interactions are potentially more important clinically; drugs that can raise blood pressure by sympathomimetic actions or that cause serotonin syndrome (Boyer and Shannon, 2005) by serotonin reuptake inhibition should be avoided.

In summary, selective inhibitors of MAO-A and nonsel ective MAOAs may be effective in the treatment of patients with depressive disorder and anxiety disorders (Stahl and Felker, 2008). MAO-B inhibition may lead to neuroprotective effects; selective inhibitors of MAO-B may be valuable in the treatment of PD and, possibly, AD (Bortolato et al., 2008; Horstink et al., 2006; Riederer et al., 2004).

5. Drugs related to monoamine oxidase activity

5.1. Current monoamine oxidase inhibitors

Every enzyme is a potential target for a drug acting as an enzyme inhibitor or activator. Enzyme inhibitors are molecules that bind to an enzyme and decrease its activity; they are the opposite of enzyme activators. There are few currently used psychotropic drugs that act primarily as enzyme inhibitors. These drugs include inhibitors of MAO, acetylcholinesterase, and GSK-3β. MAO inhibitors are discussed in more detail in this chapter.

Both the substrates and inhibitors of an enzyme are selective for that enzyme over another and bind to specific binding sites on the enzyme molecule. However, the selectivity is often lost at higher concentrations of substrate or inhibitor (Hubalek et al., 2004; Naol et al., 2016).

The binding of an inhibitor can be either reversible or irreversible. Reversible binding means that the inhibitor can be displaced from binding, e.g., by an excess of the enzyme’s substrate. An irreversible inhibitor cannot be displaced by any other molecule, and the enzyme’s activity cannot be restored unless new molecule of the enzyme is synthesized approximately 2–3 weeks later. The measurement of drug-induced changes in MAO activity (Ramsay et al., 2011) is important for the prediction of the potency, selectivity, and side effects of novel drugs.

By inhibiting MAO, nonselective MAOIs prevent the breakdown of the monoamine neurotransmitters serotonin, melatonin, norepinephrine, and dopamine, as well as trace amine neuromodulators. This process leads to an increase in the extracellular concentrations of these monoamines and therefore an alteration in neurotransmission. Drug-induced changes in the availability of monoamine neurotransmitters are a long-term approach to the modulation of mental processes and to the treatment of neuropsychiatric disorders. The widespread use of MAOIs followed the simultaneous discoveries that iproniazid caused euphoria in tuberculous patients and inhibited MAO. Consequently, MAOIs have formed an important group of drugs for the treatment of depressive disorder and PD.

MAO-A inhibitors have been used frequently in the treatment of depression. These drugs are still in clinical use, including RIMAs, such as moclobemide, befloxatone ((5R)-5-(methoxymethyl)-3-[4-[(3S)-4,4,4-trifluoro-3-hydroxybutoxy]phenyl]-1,3-oxazolidin-2-one) and toloxatone (Gareri et al., 2000), and some nonselective irreversible MAOIs, such as phenelzine and tranylcypromine. MAO-B inhibitors have been used in the treatment of PD and other neurodegenerative diseases (Youdim et al., 2006). The selective MAO-B inhibitor t-deprenyl (selegiline) was first used as an adjuvant to L-DOPA in the treatment of PD.

A wide range of MAOIs is now available (Table 1) and inhibitory effects on MAO activity are continuously discovered, both for some currently used drugs with other primary mechanisms of action and for newly synthesized multipotent drugs or isolated naturally occurring substances (Finberg, 2014).

5.1.1. Irreversible MAOIs

Iproniazid, the first clinically effective antidepressant, is a nonselective, irreversible MAOI (Fagervall and Ross, 1986). This drug was withdrawn due to a high incidence of hepatitis. Most other hydrazine antidepressants that act as nonselective, irreversible MAOIs (benoxin, iproclzoide, isocarboxazid, mebanazine, nialamide, octamoxin, phenelzine, pheniprazine, phenoxypropazine, pihvdyazine, and safrazine) have been withdrawn due to toxicity, namely hepatotoxicity, but a few remain in clinical use.

Phenelzine is a nonselective and irreversible MAOI. It is used as an antidepressant and anxiolytic in the treatment of dysthymia, bipolar depression, panic disorder, social anxiety disorder, bulimia, and post-traumatic stress disorder (Blanco et al., 2003; Fiedorowicz and Swartz, 2006).

Table 1

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reversibility</th>
<th>Selectivity</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenelzine</td>
<td>Irreversible</td>
<td>A, B</td>
<td>Antidepressant</td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td>Irreversible</td>
<td>A, B</td>
<td>Antidepressant</td>
</tr>
<tr>
<td>Isocarboxazid</td>
<td>Irreversible</td>
<td>A, B</td>
<td>Antidepressant</td>
</tr>
<tr>
<td>Iproniazid</td>
<td>Irreversible</td>
<td>A, B</td>
<td>Antidepressant</td>
</tr>
<tr>
<td>Nialamide</td>
<td>Irreversible</td>
<td>A, B</td>
<td>Antidepressant</td>
</tr>
<tr>
<td>Clorgyline</td>
<td>Irreversible</td>
<td>A</td>
<td>Antidepressant</td>
</tr>
<tr>
<td>Pargyline</td>
<td>Irreversible</td>
<td>B</td>
<td>Antidepressant</td>
</tr>
<tr>
<td>t-Deprenyl</td>
<td>Irreversible</td>
<td>B</td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>Rasagiline</td>
<td>Irreversible</td>
<td>B</td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>Ladorstigil</td>
<td>Irreversible</td>
<td>A, B</td>
<td>Parkinson’s disease</td>
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<tr>
<td>L-Deprenyl</td>
<td>Irreversible</td>
<td>A, B</td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>Moclobemide</td>
<td>Reversible</td>
<td>A</td>
<td>Antidepressant</td>
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<tr>
<td>Befloxatone</td>
<td>Reversible</td>
<td>A</td>
<td>Antidepressant</td>
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<td>Brofaromine</td>
<td>Reversible</td>
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<td>Antidepressant</td>
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<tr>
<td>Toloxatone</td>
<td>Reversible</td>
<td>A</td>
<td>Antidepressant</td>
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<tr>
<td>Pirindole</td>
<td>Reversible</td>
<td>A</td>
<td>Antidepressant</td>
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<tr>
<td>Metralindole</td>
<td>Reversible</td>
<td>A</td>
<td>Antidepressant</td>
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<tr>
<td>Toloxatone</td>
<td>Reversible</td>
<td>B</td>
<td>Parkinson’s disease</td>
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<tr>
<td>Lazabemide</td>
<td>Reversible</td>
<td>B</td>
<td>Parkinson’s disease</td>
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<tr>
<td>Safinamide</td>
<td>Reversible</td>
<td>B</td>
<td>Parkinson’s disease</td>
</tr>
</tbody>
</table>
Tranylcyprome is a nonselective (it shows a slight preference for MAO-B over MAO-A) and irreversible inhibitor of MAO. It is used as an antidepressant and anxiolytic in the treatment of mood and anxiety disorders. Chronic antidepressant treatment with tranylcypromine increased the expression of phosphodiesterase 4 in the rat frontal cortex, which may represent a compensatory response to antidepressant treatment and activation of the CAMP system (Takahashi et al., 1999). Tranylcypromine significantly increased CAMP response element (CRE)-mediated gene transcription and the phosphorylation of CRE binding protein (CREB) in several limbic brain regions thought to mediate the actions of antidepressants, including the cerebral cortex, hippocampus, amygdala, and hypothalamus (Thome et al., 2000). These results demonstrate that chronic treatment with MAOIs induces the same molecular processes that underlie the actions of other antidepressants.

Isocarboxazid is a nonselective, irreversible MAOI used as an antidepressant (Fagervall and Ross, 1986). It is primarily used to treat mood and anxiety disorders, but it was tested in the treatment of PD and other dementia-related disorders.

Clorgyline is an irreversible inhibitor preferential for MAO-A. Clorgyline is structurally related to parergline (MAO-B inhibitor) and is used in research into MAOs (Fišar et al., 2010). l-Deprenyl (selegiline) is a selective irreversible MAO-B inhibitor; its action results in increased availability of dopamine at central synapses and the subsequent prolongation of dopamine activity. Selegiline increased spatial memory performance in aged male rats; this increase may be related to the suppression of lipid peroxidation and alleviation of the age-related decrease in the number of neurons in the hippocampus (Király et al., 2006). The combined effects of selegiline may lead to protection of the homeostatic regulation of the neuro-immuno-endocrine axis of an organism against aging (Kitani et al., 2002).

Selegiline was tested in the treatment of PD both as an adjuvant to l-DOPA and as monotherapy (DeMaagd and Philip, 2015). Neither selegiline nor lazabemide delays disease progression, but they both have a positive effect on motor fluctuations (Macleod et al., 2005). It seems that inhibition of both forms of MAO is required to increase dopamine activity (Youdim et al., 2006). Selegiline does not have amphetamine-like properties, but it is a molecule similar to methamphetamine and can be metabolized to l-amphetamine or l-methamphetamine. The ability of l-deprenyl to prevent MPTP-induced nigrostriatal dopaminergic neurodegeneration led to the development of other MAO-B inhibitors for the treatment of PD.

Rasagiline ((1R)-N-prop-2-ynyl-2,3-dihydro-1H-inden-1-amine) is a selective irreversible MAO-B inhibitor used as a monotherapy in early and late PD and for adjunctive therapy in patients with moderate to advanced disease (Oldfield et al., 2007; Youdim, 2003). The effectiveness of rasagiline for both motor and non-motor symptoms has been described in both early and advanced PD patients. Rasagiline displayed a placebo-like tolerability profile in several studies. Rasagiline is a valuable therapeutic option for use in all stages of PD (McCormick, 2014; Pistacchi et al., 2013; Stocchi et al., 2015). Unlike selegiline, rasagiline is not metabolized to a neurotoxic l-methamphetamine derivative. Rasagiline prevents cell death and the opening of mitochondrial permeability transition pores. As a result, rasagiline, its metabolite and other propargylamines may regulate apoptosis and exhibit neuroprotective effects realized by the support of mitochondrial viability and stabilization of permeability transition by regulating Bcl-2 family proteins (Naoi et al., 2003; Weinreb et al., 2004). Rasagiline and its derivatives also affect amyloid precursor protein. Novel bifunctional neuroprotective iron-chelating and MAO-inhibiting drugs are synthesized with a propargyl group before being tested for the treatment of neurodegenerative diseases (Mandé et al., 2005).

Studies on AD and PD suggest that selegiline and rasagiline are the most promising neuroprotective agents to date. The neuroprotection is ascribed to the stabilization of mitochondria and the induction of pro-survival genes, including those for the antiapoptotic factor Bcl-2 and neurotrophic factors (NGF, BDNF, neurotrophin 3, and GDNF), which is followed by activation of neurotrophic receptors and protein kinase systems (Weinreb et al., 2004, 2007a; Naoi and Maruyama, 2010; Naoi et al., 2016).

Lazabemide is a reversible and selective inhibitor of MAO-B that was under development as an anti-parkinsonian agent (Henriot et al., 1994). Safinamide is a reversible and selective MAO-B inhibitor indicated for the treatment of PD alone or in combination with other drugs. Safinamide acts by multiple mechanisms; it reduces the degradation and reuptake of dopamine, acts as a glutamate release inhibitor, and blocks sodium and calcium channels (Caccia et al., 2006).

5.1.2. Reversible MAOIs

Moclobemide is a selective reversible MAO-A inhibitor that has shown both antidepressant (Lotufo-Neto et al., 1999) and antiparkinsonian activity (Sieradzan et al., 1995; Youdim and Riederer, 2004). Administration of moclobemide results in improved vigilance, attention, and memory (Allain et al., 1992), which may be attributed to the regulation of hippocampal neuropaclipity.

Eprobemide is a noncompetitive reversible inhibitor of MAO-A. It was used as an antidepressant. Brofaromine is a reversible selective inhibitor of MAO-A, which was primarily tested in the treatment of depressive disorder and anxiety. Brofaromine is also a serotonin reuptake inhibitor; it was found to be as effective as tricyclic antidepressants (Lotufo-Neto et al., 1999). Carboxazone is a reversible MAOI with preference for MAO-B (Moretti et al., 1981). It was used as an antidepressant. Piribedil and metralindole are reversible inhibitors of MAO-A that were used as antidepressants (Andreeva et al., 1991). Toloxatone is a reversible inhibitor of MAO-A that was used for the treatment of depression (Berlin et al., 1990). Metralindole and minaprine are reversible inhibitors of MAO-A, which were investigated as a potential antidepressants.

5.1.3. Other MAOIs

In addition to drugs that act primarily as MAO inhibitors, there are many substances that are weak MAOIs or inhibit MAO at higher concentrations as a side effect (Fišar, 2010; Fišar et al., 2010, 2011). Whether it is a desirable or undesirable effect of treatment depends on potential drug–drug interactions and on the symptoms of the disease. For example, amphetamine is a weak reversible MAOI. Amphetamine can be utilized as an augmenting agent to boost the therapeutic effects of MAOIs. Some MAOIs, such as tranylcypromine have amphetamine-like dopamine-releasing properties. Zonisamide is an antiseizure drug. Many mechanisms are postulated for zonisamide, including a reduction in levodopa-induced quinone formation, protection against mitochondrial impairment, an increase in astroglial cysteine transport, inhibition of microglial activation, MAO-B inhibition, increased dopamine release, and blockade of calcium channels (Grover et al., 2013). Zonisamide has potential efficacy for several neuropsychiatric disorders, including migraine, neuropathic pain, Parkinson’s disease, essential tremor, stroke, obesity, and anxiety. Another example is rafinamide, a multimodal drug that is under investigation for the treatment of neuropathic pain and other pain conditions (Di Stefano et al., 2013). This drug acts as a mixed voltage-gated sodium channel blocker, N-type calcium channel blocker, noncompetitive NMDA receptor antagonist, and MAO-B inhibitor. Linezolid is an antibiotic; it is also a weak MAOI and should not be used concomitantly with other MAOIs (Lawrence et al., 2006). Methylen blue has been shown to be a multiaacting drug that affects many cellular targets, including reversible inhibition of MAO-A. Moreover, azure B, a metabolite of methylene blue, is also a potent MAO-A inhibitor (Petzer et al., 2012; Ramsay et al., 2007).

5.2. Novel drugs that affect monoamine oxidase activity

Current treatments for neurodegenerative disorders, such as AD, are based on alleviating the symptoms of the disease, not on treating the
progression of the disease (Francis et al., 2012). Current pharmacological treatments for depressive disorder aim to enhance serotonergic and/or noradrenergic neurotransmission; however, between 30% and 50% of individuals treated with a given antidepressant do not show a response (Baghai et al., 2006). No reliable biochemical, physiological or genetic predictors of treatment efficiency are available. Among others, polymorphisms in genes for monoamine transporters, monoamine receptors, tryptophan hydroxylase, COMT, and MAO are thought to explain inter-individual variability in response to treatment (Fabbri et al., 2013).

A series of new potent and selective MAO inhibitors have been synthesized, whereas molecular docking provided insight into the binding mode and potency (Lühr et al., 2010; Shi et al., 2010; Strydom et al., 2010). Several new pharmacological approaches are under investigation, which include the modulation of intracellular signaling pathways controlling mitochondrial functions, neuroplasticity, apoptosis, oxidative and nitrosative stress, and neuroinflammation (Maes et al., 2012). Based on the recognition of new intracellular processes associated with the development of affective and neurodegenerative diseases, new drugs aimed at these new targets are synthesized and tested. MAO activity is frequently affected, either directly or indirectly, by these novel drugs (Song et al., 2013).

### 5.2.1. Hybrid drugs

A new family of dual inhibitors of acetylcholinesterase (AChE) and MAO have been synthesized as multitarget drug candidates with potential impacts on AD therapy. The rivastigmine- (AChE inhibitor) and rasagiline- or selegiline- (selective inhibitors of MAO-B) related series were designed to have combined inhibitory activities by virtue of their carbamate and propargylamine pharmacophores (Maruyama et al., 2003; Sterling et al., 2002; Weinstock et al., 2001). Ladostigil has been tested as a reversible cholinesterase inhibitor and a brain-selective irreversible MAO inhibitor that combines the mechanisms of action of rivastigmine and rasagiline into a single molecule (Weinreb et al., 2015). This drug has been investigated for the treatment of neurodegenerative disorders such as AD, Lewy body disease, and PD (Weinstock et al., 2000). Ladostigil and rasagiline enhance the activity of BDNF and GDNF (Weinreb et al., 2007a). Ladostigil also has antidepressant and antiapoptotic effects (Martinez and Castro, 2006; Weinstock et al., 2000). Ladostigil prevented gliosis, oxidative and nitrosative stress, and memory impairment in rat model of AD (Shoham et al., 2007; Weinstock et al., 2011) and reversed the effect of aging on the expression of various mitochondrial and key regulator genes involved in neurodegeneration, cell survival, synaptogenesis, oxidation, and metabolism (Weinreb et al., 2007b).

A novel series of tacrine–selegiline hybrids with AChE and MAO inhibition activities exhibited high inhibitory activity, and some compounds seem to have the potential to be candidates for AD treatment (Lu et al., 2013).

A series of other multitargeted molecules able to interact with both AChE and MAO have been designed as combinations of the benzylpiperidine moiety of the donepezil that inhibits cholinesterases and the MAO-inhibiting propargyl group (Bolea et al., 2011). Among these multitarget hybrid compounds, AS2324 (N-[5]-[3-[1-benzylpiperidin-4-yl]propoxy]-1-methylindol-2-yl[methyl]-N-methylprop-2-yn-1-amine) has been shown to have an impact on different processes involved in AD pathogenesis, such as inhibition of Aβ1-42 self-aggregation, reduction of Aβ1-42-mediated toxicity through the prevention of the mitochondrial apoptosis pathway activation, and capturing of free-radical species (Bolea et al., 2013b; Esteban et al., 2014).

Memooquin (2,5-bis[6-ethyl-[2-methoxyphenyl]methylamino] hexylaminocyclohexa-2,5-diene-1,4-dione), a quinone-bearing polyamine compound, represents a multi-targeted drug without inhibitory effect on MAO; it acts as an AChE and β-secretase-1 inhibitor, and also possesses antioxidant and anti-Aβ aggregation properties. Memooquin is effective as a cognitive enhancer, and its action supports a multi-target strategy of AD treatment (Bolognesi et al., 2009; Capurro et al., 2013).

Recently, hybrids were reported for AD treatment obtained as a result of the juxtaposition of a selective AChE inhibitor (donepezil), a potent brain-selective MAO-A/B inhibitor, and a neuroprotective biometal-chelator (Wang et al., 2014).

Based on the assumption that a more effective therapy for AD would result from multitarget-directed drugs, Youdim et al. have developed a series of non-toxic brain permeable multifunctional hybrid compounds with potential therapeutic value for pathological aging and AD (Weinreb et al., 2015). Multifunctional chimeric propargylamine-derivatives were developed, such as M30 (5-[[methyl[(prop-2-ynyl)amino]methyl]quinolin-8-ol], VAR10303 (5-[(2-[(methyl-prop-2-ynyl)-amino]-ethyl]quinolin-8-ol), and HLA20 (5-[(4-prop-2-ynylpiperazin-1-yl)methyl]quinolin-8-ol) with iron chelating, brain-selective MAO-A/B inhibitory, and neuroprotective activities. M30 and VAR10303 were found to be highly potent brain selective MAOIs with little effect on peripheral MAO activity, thus limiting the adverse tyramine effect on the cardiovascular system (Bar-Am et al., 2015). Molecular mechanisms of action of neuroprotective effects of these drugs include decreasing the toxicity of H2O2-Fe2+ reactivity, increasing the antioxidant activity, regulation of transcription factor HIF-1α (hypoxia-inducible factor 1, alpha subunit), and stimulation of neurite outgrowth and antiapoptotic activity. P30 induced also reduction of Aβ1 levels as a result of regulation of amyloid precursor protein expression (Avramovich–Tirosh et al., 2010; Weinreb et al., 2015; Youdim and Oh, 2013).

### 5.2.2. Drugs that affect mitochondrial enzymes

Considering the key role of mitochondria in cellular metabolism and neuron survival, drug-induced mitochondrial dysfunction (mitochondrial toxicity) as one of the causes of drug toxicity is studied in the development of new drugs for the treatment of neurodegenerative disorders (Mattson et al., 2008). Mitochondria can be damaged by drugs by the inhibition of mitochondrial electron transport chain complexes, uncoupling of oxidative phosphorylation, opening of the mitochondrial permeability transition pores, increase in oxidative stress by the formation of ROS and/or depletion of antioxidative protection, changes in calcium homeostasis, inhibition of fatty acid β-oxidation, depletion of mtDNA, and inhibition of various transporters and enzymes of the citric acid cycle or electron transfer system (Nadanaciva and Will, 2009). On the other hand, clinically applicable pharmacotherapies may include the drug-induced inhibition of MAO, upregulation of mitochondrial biogenesis, modulation of Ca2+ homeostasis, enhancement of mitochondrial fusion and fission, support of mitochondrial respiration, and elimination of the burden of mutant mtDNAs via cytoplasmic transfer (Schohn et al., 2010).

To date, mechanisms leading to the development of neurodegenerative diseases are poorly understood; however, it is clear that protein misfolding and/or increased production of reactive oxygen and nitrogen species are tightly linked to the emergence and development of neurodegenerative diseases. The pharmacological modulation of cellular stress response pathways has emerging implications for the treatment of neurodegenerative disorders, cardiovascular disease, and cancer (Calabrese et al., 2010).

Mitochondrial enzymes seem to be appropriate targets for newly developed drugs for the treatment of neurodegenerative disorders. Only a few mitochondrial enzyme modulators have been published and their design, synthesis and evaluation will be highly progressive in the near future. Early in drug development, it is necessary to test for drug-induced changes in mitochondrial function, including MAO activity, which may induce both therapeutic and adverse effects of drugs. For example, it is assumed that the mitochondrial enzyme 17-/3-hydroxysteroid dehydrogenase X (HSD10, 17-/3-HSD10, also called amyloid beta binding alcohol dehydrogenase, ABAD) may contribute to the neuronal
dysfunction associated with AD by interacting with intracellular Aβ (Van et al., 1997; Yang et al., 2014). Thus, inhibition of the interaction of HSD10 with Aβ can be associated with the therapeutic effects of drugs on AD progression (Lim et al., 2011; Valasaari et al., 2014). In preliminary in vitro experiments, we found that newly synthesized modulators of HSD10 (ten compounds derived from fentizoxole) appear to be relatively safe in terms of influencing monoaminergic neurotransmission through the inhibition of MAO (IC₅₀ approximately 10⁻¹⁰ μM for MAO-A, 10⁻¹⁰ – 10⁻¹² μM for MAO-B); however, attention must be paid to their inhibitory effects on the activity of mitochondrial respiratory chain (IC₅₀ approximately 10⁹ μM for complex I-linked respiration).

6. Conclusion

The role of monoamine neurotransmitters and related processes in the pathophysiology of certain neuropsychiatric disorders is well documented. Brain monoamines are involved in signaling processes affected by both neuropsychiatric disorders and different psychotropic drugs. An increase in monoamine neurotransmitters availability, decrease in hydrogen peroxide production, and the neuroprotective effects evoked by MAOIs represent important approaches in the development of new drugs for the treatment of affective disorders and neurodegenerative diseases.

The design of new drugs for psychiatric and neurodegenerative disorders is based on new knowledge about (1) the intracellular signaling pathways involved in the survival or death of neurons, (2) the specific intracellular processes that cause a disorder, and (3) the molecular mechanisms of action of existing drugs that are effective in the treatment of a disorder. Various mental disorders are characterized by abnormalities in a series of interconnected cellular pathways and processes, such as changes in the availability of neurotransmitters and the expression of their receptors and transporters, proinflammatory cytokine production, activation of immune cells, increased production of reactive oxygen and nitrogen species and reduced antioxidant protection, disruption of mitochondrial function, increased apoptosis, and reduced neurogenesis and neuroplasticity. Specific to a particular disease may be the degree of damage of normal neuronal functions, affected neural circuits or brain area, and the molecular cause of damage to normal brain function.

One promising treatment options for mental disorders and neurodegenerative diseases is the modulation of mitochondrial functions and processes related to them, such as the metabolism of monoamines, calcium homeostasis, bioenergetics, apoptosis, oxidative stress, and antioxidant protection.

Abundant evidence suggests that the therapeutic potential of MAO-A inhibitors is related to their antidepressant effect, and MAO-B inhibitors can have neuroprotective properties in the treatment of neurodegenerative diseases. The therapeutic action of MAO-A inhibitors in the treatment of mood disorders is linked mainly to the modulation of serotonergic neurotransmission. The therapeutic action of MAOIs used in the treatment of neurodegenerative disorders has been linked to the reduction of the oxidative stress and induction of antiapoptotic and pro-survival factors. This is a simplified view because the effects of MAO-A and MAO B inhibitions overlap significantly, e.g., some RIMAs may also have neuroprotective properties and are effective in the therapy of PD, and some MAO-B inhibitors exhibit antidepressant effects. Novel anti-Parkinson’s and anti-Alzheimer’s drugs have been synthesized that act as multitarget-directed ligands with MAO as one target.

In addition to a direct influence on the activity of MAOs by binding to the active site for substrate or allosteric inhibition, targeting the regulation of gene expression of MAO-A and regulatory processes of neuronal survival and death appears to be a possibility. Specificity of action and/or individual effectiveness could provide drugs that affect the activity of regulatory proteins whose gene mutations or polymorphisms are associated with the onset of the disease.

Many drugs, both currently used and newly synthesized, have MAO-inhibitory activity. The desirable effects of MAO inhibition include increased availability of monoamine neurotransmitters, which underlies their antidepressant action, decreased production of hydrogen peroxide, which contributes to lowering of oxidative stress, decreased formation of neurotoxins, which facilitates their antiapoptotic and neuroprotective effects, induction of pro-survival genes, and increased ability to clear damaged mitochondria. The undesirable effects of MAO inhibition include vascular effects, which may be associated with the application of irreversible non-selective MAOIs. It should be kept in mind that the MAOI-induced increased availability of monoamine neurotransmitters may be undesirable for certain drug interactions, including selective serotonin reuptake inhibitors, tricyclics, opioids, amphetamines, and tetryphoton supplements.

Conflict of interest statement

The author declares that there is no conflict of interest.

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