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Review article

An update on amine oxidase inhibitors: Multifaceted drugs

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ABSTRACT

Although not used as extensively as other antidepressants for the treatment of depression, the monoamine oxidase (MAO) inhibitors continue to hold a niche in psychiatry and to have a relatively broad spectrum with regard to treatment of psychiatric and neurological disorders. Experimental and clinical research on MAO inhibitors has been expanding in the past few years, primarily because of exciting findings indicating that these drugs have neuroprotective properties (often independently of their ability to inhibit MAO). The non-selective and irreversible MAO inhibitors tranylcypromine (TCP) and phenelzine (PLZ) have demonstrated neuroprotective properties in numerous studies targeting elements of apoptotic cascades and neurogenesis. l-Deprenyl and rasagiline, both selective MAO-B inhibitors, are used in the management of Parkinson's disease, but these drugs may be useful in the treatment of other neurodegenerative disorders given that they demonstrate neuroprotective/neurorescue properties in a wide variety of models *in vitro* and *in vivo*. Although the focus of studies on the involvement of MAO inhibitors in neuroprotection has been on MAO-B inhibitors, there is a growing body of evidence demonstrating that MAO-A inhibitors may also have neuroprotective properties. In addition to MAO inhibition, PLZ also inhibits primary amine oxidase (PrAO), an enzyme implicated in the etiology of Alzheimer's disease, diabetes and cardiovascular disease. These multifaceted aspects of amine oxidase inhibitors and some of their metabolites are reviewed herein.

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1. Introduction

Monoamine oxidase (MAO) inhibitors are not prescribed as widely as other antidepressants (Shulman et al., 2009), but they continue to hold an important niche in the treatment of psychiatric and neurological disorders (Blanco et al., 2010; Bortolato et al., 2008; Holt et al., 2004; Kennedy et al., 2009; Muller et al., 2005; Stewart, 2007). Interest in these drugs has increased significantly in recent years following

Abbreviations: MAO, monoamine oxidase; PrAO, primary amine oxidase; SSAO, semicarbazide-sensitive amine oxidase; TCP, tranylcypromine; PLZ, phenelzine; PEH, β-phenylethylidenehydrazine; BDNF, brain-derived neurotrophic factor; EAE, experimental autoimmune encephalomyelitis; GABA, γ-aminobutyric acid; GABA-T, GABA transaminase; AD, Alzheimer's disease.

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numerous reports of their neuroprotective/neurorescue properties (Baker et al., 2007; Gerlach et al., 1996; Magyar and Szende, 2004; Sowa et al., 2004; Tatton et al., 2003; Youdim et al., 2006b). Similarly, exciting findings with primary amine oxidase [PrAO, previously called semicarbazide-sensitive amine oxidase (SSAO)] and its inhibitors have stimulated research on amine oxidase inhibitors and increased our knowledge of the etiology of several neuropsychiatric disorders and associated diabetes and cardiovascular disease (Chen et al., 2006; Yu et al., 2003). In this review, we will provide an update on neuroprotection by amine oxidase inhibitors, on the importance of metabolism of these drugs and on possible future drug applications in this area.

2. Non-selective inhibitors of MAO: phenelzine and tranylcypromine

Phenelzine (2-phenylethylhydrazine, PLZ) (Fig. 1) is an irreversible, non-selective MAO inhibitor (*i.e.* inhibits both MAO-A and MAO-B) that has been used for many years as an antidepressant drug and is also effective in treating panic disorder, social anxiety disorder, and post-traumatic stress disorder (PTSD) (Davidson, 2006; Kennedy et al., 2009; Zhang and Davidson, 2007). Although it is an MAO inhibitor, it also produces marked increases in brain levels of γ-aminobutyric acid (GABA) by inhibiting GABA transaminase (GABA-T) (Baker et al., 1991; Popov and Matthies, 1969). PLZ has been reported to be neuroprotective in a transient cerebral ischemia model in gerbils (Wood et al., 2006) and in the N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine (DSP)-4-induced noradrenaline depletion rodent model (Ling et al., 2001). Several other GABAergic agents have been reported to be neuroprotective in animal models of ischemia (Shuaib and Kanthan, 1997), presumably due at least in part to their ability to counteract the excitotoxic effects of increased extracellular glutamate in such models (Green et al., 2000). PLZ has also been reported to decrease K^+-induced glutamate overflow in the prefrontal cortex in rats (Michael-Titus et al., 2000), to alter glutamate–glutamine cycling flux between neurons and glia (Yang and Shen, 2005), to affect the GLUT-1 glutamate transporter in astrocytes and neurons, and to reverse the decreased astrocytic glutamate uptake and the alteration of the signaling kinases AKT and p38 induced by formaldehyde (Song et al., 2010). Chronic (21 day) treatment of rats with PLZ has been reported to increase brain-derived neurotrophic factor (BDNF) protein expression in the frontal cortex (Balu et al., 2008) and in the whole brain (Dwivedi et al., 2006).

In addition to these pharmacological effects, the potent ability of PLZ, a hydrazine, to sequester reactive aldehydes may contribute to its neuroprotective actions (Wood et al., 2006). Reactive aldehydes are formed from amines, from lipid peroxidation, in glycolytic pathways and through the metabolism of some amino acids. Such aldehydes, which include 3-aminopropanal, acrolein, 4-hydroxy-2-nonenal, formaldehyde and aldehyde metabolites of catecholamines, are very reactive and can covalently modify proteins, nucleic acids, lipids and carbohydrates and activate apoptotic pathways (Burke et al., 2004; Ivanova et al., 1998; Lovell et al., 2001; Marchitti et al., 2007; Seiler, 2000; Springer et al., 1997; Volkel et al., 2006; Wood, 2006). Because of its hydrazine structure, PLZ is very effective at sequestering aldehydes through a direct chemical reaction (Galvani et al., 2008; Wood et al., 2006), resulting in the formation of an inert hydrazone molecule and reduced concentrations of toxic aldehydes. Reactive aldehydes have been implicated in the pathophysiology of a number of conditions including Alzheimer's disease (AD) and various cardiovascular diseases (LoPachin et al., 2008; Matveychuk et al., 2011; Singh et al., 2010; Volkel et al., 2006; Wood, 2006). Interestingly, the reactive aldehyde acrolein has recently been suggested to be a potential factor in oxidative stress and myelin loss in multiple sclerosis (Leung et al., 2011), and was shown to induce marked myelin damage to isolated spinal cords *in vitro* (Shi et al., 2011) and to be involved in spinal cord injury *in vivo* (Hamann and Shi, 2009). Furthermore, acrolein-protein adduct levels were significantly increased in experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis, and sequestration of acrolein with hydralazine improved behavioral outcomes and reduced demyelination in the spinal cord in that model (Leung et al., 2011). PLZ has also been shown to improve behavioral outcomes in EAE mice (Musgrave et al., 2011a), possibly due to its multiple actions, including its ability to increase levels of serotonin, noradrenaline and GABA in the ventral horn of the spinal cord and some brain regions of EAE mice (Musgrave et al., 2011a,b) and its ability to sequester acrolein (Wood et al., 2006). In addition, acetaldehyde, produced from the metabolism of ethanol, is thought to play an important role in the development of alcoholic liver disease (Setshedi et al., 2010) and alcohol-related cancers (Druesne-Pecollo et al., 2009; Salaspuro, 2009); thus, sequestration of acetaldehyde may be beneficial in protecting chronic alcoholics from development or exacerbation of these alcohol-related diseases.

Despite its vast therapeutic potential, PLZ, like other hydrazine-containing drugs, is not without adverse effects; PLZ may produce pyridoxal phosphate depletion (Malcolm et al., 1994) [though not all studies have supported this idea (Lydiard et al., 1989)], in which case ongoing vitamin supplementation could be warranted (Gillman, 2011). Furthermore, overdoses of PLZ could potentially induce hepatotoxic and neurotoxic effects, including seizures in isolated cases (Gomez-Gil et al., 1996; Tafazoli et al., 2008). However, this drug has been available commercially for over fifty years and continues to be used clinically.

Tranylcypromine (TCP) (Fig. 1), an irreversible, non-selective MAO inhibitor, has not been investigated as extensively as some of the other MAO inhibitors with regard to neuroprotection. Yet several reports link TCP treatment with an increase in the expression of messenger ribonucleic acid (mRNA) for BDNF (Khundakar and Zetterstrom, 2006; Nibuya et al., 1995) and cyclic adenosine monophosphate (cAMP) response element binding protein (CREB) (Nibuya et al., 1996; Thome et al., 2000) in the rat brain hippocampus—effects that could lead to neurogenesis (Santarelli et al., 2003). It has also been reported that TCP increases expression of the antiapoptotic factors B-cell leukemia/lymphoma 2 (Bcl-2) and B-cell lymphoma extra large (Bcl-XL) in several brain areas (Kosten et al., 2008; McKernan et al., 2009).

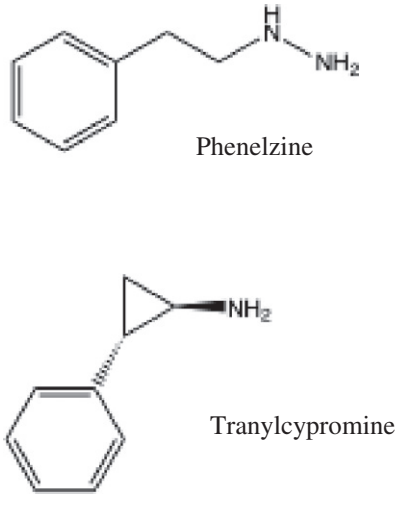

Fig. 1. Structures of the non-selective, irreversible MAO inhibitors phenelzine (PLZ) and tranylcypromine (TCP).

3. MAO-B inhibitors: l-deprenyl and rasagiline

l-Deprenyl (L-N-propargyl,N-methylamphetamine; selegiline) (Fig. 2), a selective irreversible MAO-B inhibitor, was originally developed in the hope that it would be an effective antidepressant without the pressor effect ("cheese effect") which can occur in patients that ingest tyramine-rich foods while taking irreversible MAO-A inhibitors.

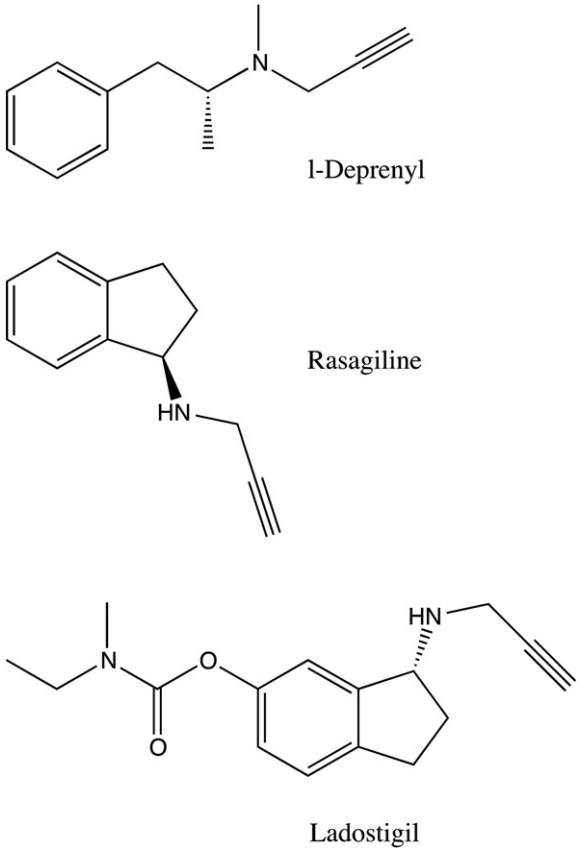

Fig. 2. Structures of the MAO-B inhibitors l-deprenyl, rasagiline and ladostigil.

It turned out to be a poor antidepressant drug, except at higher doses when its selectivity was lost and it also inhibited MAO-A [although recent reports indicate that transdermal administration allows doses of l-deprenyl to be used that are sufficient to inhibit brain MAO-A and produce an antidepressant effect without substantially inhibiting MAO-A in the gut (Frampton and Plosker, 2007)]. l-Deprenyl is used in Parkinson's disease (Rascol et al., 2011; Riederer et al., 2004) and has more recently been reported to be of some use in global ischemia, Gilles de la Tourette syndrome, narcolepsy and AD (Ebadi et al., 2006); although clinically meaningful benefit in AD continues to be a matter of debate (Birks and Flicker, 2003). l-Deprenyl is remarkable in that it has been demonstrated to have neuroprotective or neurorescue properties in a wide variety of neurotoxicity tests *in vivo* and *in vitro* (Baker et al., 2007; Gerlach et al., 1996; Magyar and Szende, 2004; Sowa et al., 2004; Tatton et al., 2003; Xiao et al., 2011; Youdim et al., 2006b). It has also been suggested that l-deprenyl has the potential to be utilized as a radiolabeled biomarker for the early detection of AD and other degenerative diseases that exhibit increased MAO-B expression (Gulyas et al., 2011).

A result of research on l-deprenyl has been the development of rasagiline (Fig. 2), a structurally related drug (also containing an N-propargyl group), which has now been approved for use in Parkinson's disease in several countries (Hauser et al., 2009; Weinreb et al., 2010; Youdim et al., 2006b). Rasagiline has an advantage over l-deprenyl in that it is not metabolized to the potentially neurotoxic products l-amphetamine and l-methamphetamine; in fact, its active metabolite, R-(−)-aminoindan, shows neuroprotective properties that are independent of MAO-B inhibition (Dimpfel and Hoffmann, 2011). The neuroprotective effects of l-deprenyl are apparently lost at high concentrations (Tatton et al., 2003; Youdim et al., 2006b), possibly due to the formation of high levels of l-amphetamine and l-methamphetamine.

The mechanisms of neuroprotective action of these N-propargyl drugs appear to be complex (Eliash et al., 2009; Tazik et al., 2009; Zhu et al., 2008). Recent evidence demonstrates that l-deprenyl, rasagiline and R-(−)-aminoindan exert concentration-dependent neuroprotective effects *in vitro* by modulating glutamatergic receptor activity in the rat hippocampus (Dimpfel and Hoffmann, 2011). Youdim et al. (2006b) indicated that l-deprenyl and rasagiline interact with the outer mitochondrial membrane, preventing neurotoxin-induced collapse of mitochondrial membrane potential and permeability transition, and the opening of the voltage-dependent anion channel; these effects are thought to reflect the upregulation of antiapoptotic Bcl-2 protein and the downregulation of proapoptotic proteins such as Bcl-associated death promoter (BAD) and Bcl-associated protein X (BAX), as well as *via* a mechanism dependent on the inactivation and nuclear localization of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), an initiator of apoptotic cascades (Akao et al., 2002; Carlile et al., 2000; Hara et al., 2006; Tatton et al., 2003; Youdim et al., 2006b). Interestingly, a recent report suggests that the increase in Bcl-2 mRNA *in vitro* induced by rasagiline is mediated by MAO-A, whereas the upregulation of Bcl-2 mRNA by l-deprenyl is not (Inaba-Hasegawa et al., 2012). l-Deprenyl has also been reported to increase levels of BDNF protein in some brain areas (Gyarfas et al., 2010), and to have anti-amyloidogenic activity *in vitro* (Ono et al., 2006). Furthermore, l-deprenyl was shown to reverse both scopolamine-induced decreases in antioxidants and increases in malondialdehyde (an important biological marker for *in vivo* lipid peroxidation) in a mouse model of AD, providing additional support for the possible utility of this drug in AD (Goverdhan et al., 2012). Indeed, increased MAO activity and expression of MAO mRNA have been reported in AD (Emilsson et al., 2002), suggesting that MAO inhibitors should be investigated more extensively as possible adjunctive drugs in this disorder. Ladostigil (Fig. 2) combines the activities described above for rasagiline with an additional anticholinesterase component and is a promising drug for AD (Bar-Am et al., 2009; Weinstock et al., 2006; Yogev-Falach et al., 2006; Youdim et al., 2006a,b).

4. MAO-A and its inhibitors

Much of the work on neuroprotection provided by MAO inhibitors has focused on selective MAO-B inhibitors such as L-deprenyl and rasagiline, but selective MAO-A inhibitors may also exert protective effects (Naoi et al., 2006). Moclobemide (Fig. 3), a reversible MAO-A inhibitor, has been reported to have anti-Parkinson activity and neuroprotective effects in a model of cerebral ischemia, but these effects appear to be independent of MAO-A inhibition (Youdim et al., 2006b).

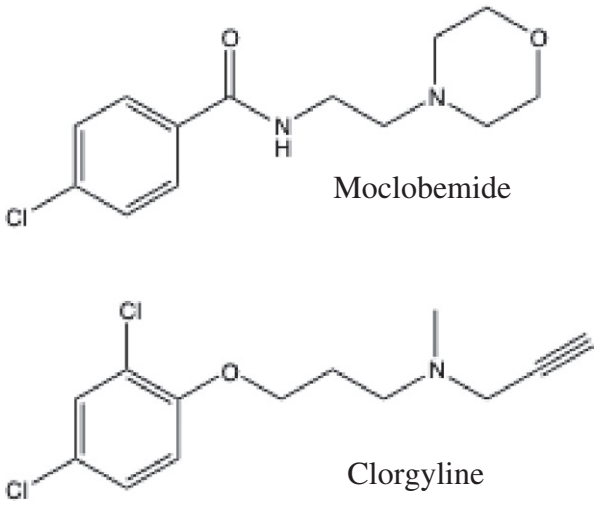

Fig. 3. Structures of the MAO-A inhibitors moclobemide and clorgyline.

It has also been suggested that moclobemide may facilitate selected differentiation of stem cells into functional neurons (Egan, 2006). Verleye et al. (2007) reported that moclobemide reduced anoxia- and glutamate-induced neuronal damage in neuronal–astroglial cultures from rat cerebral cortex *via* a mechanism independent of its interaction with glutamate receptor subtypes. The irreversible MAO-A inhibitor clorgyline (Fig. 3) has been reported to be neuroprotective *in vitro* (protective against apoptosis induced by serum starvation) (Egan, 2006) and *in vivo* (protective against damage caused by the mitochondrial toxin malonate) (Malorni et al., 1998). As with l-deprenyl and rasagiline, clorgyline contains an N-propargyl group. Recent research has also suggested that MAO-A may have a role in the induction and regulation of apoptosis (Chiou et al., 2006; Egan, 2006; Jiang et al., 2008; Maragos et al., 2004; Naoi et al., 2006, 2011; Ou et al., 2006) and that MAO-A activity and function could rely on its physical interaction with certain AD-related presenilin-1 variants (Wei et al., 2012).

5. Primary amine oxidase and its inhibition

PrAO, an enzyme containing copper and quinine as cofactors and located on the outer membrane of vascular smooth muscles and endothelial cells, catalyzes the oxidation of several primary amines to produce the corresponding aldehyde as well as hydrogen peroxide and ammonia. Methylamine and aminoacetone are examples of PrAO substrates, and their metabolism results in the production of the reactive aldehydes formaldehyde and methylglyoxal, respectively. Both aldehydes have been shown to facilitate the conversion of β-amyloid to the hydrophobic β-sheet conformation and subsequent fibrillogenesis *in vitro* (Chen et al., 2006; Yu et al., 2003), suggesting an involvement with the etiology of AD. In addition, increased serum PrAO activity, relative to control subjects, has been reported in various vascular disorders, including complications of diabetes and in congestive heart failure, atherosclerosis, multiple cerebral infarctions and AD (Chen et al., 2006; Yu et al., 2003). Jiang et al. (2008) reported a strong expression of PrAO co-localized with β-amyloid deposits on blood vessels of postmortem brain samples from patients with AD. Interestingly, PLZ, in addition to its ability to inhibit MAO and GABA-T and to sequester reactive aldehydes, is a relatively potent inhibitor of PrAO (Holt et al., 2004; MacKenzie, 2009; Wang et al., 2006), which could certainly contribute to its neuroprotective effects. Several specific PrAO inhibitors have been developed and it will be interesting to determine their efficacy in the clinical setting in the future (Elovaara et al., 2011).

6. Metabolism of amine oxidase inhibitors and its relevance

The possible importance of metabolites of N-propargyl drugs should be taken into consideration with regard to contributions to neuroprotective properties and adverse effects. Two metabolites of l-deprenyl (l-amphetamine and l-methamphetamine) are potentially neurotoxic, whereas another metabolite, N-propargylamphetamine, may have neuroprotective properties, although the latter conclusion remains contentious (Magyar and Szende, 2004). l-Amphetamine has been reported to interfere with the neuroprotective action of l-deprenyl, whereas aminoindan and hydroxyaminoindan, major metabolites of rasagiline and ladostigil, are neuroprotective themselves (Bar-Am et al., 2004, 2007, 2010). MAO inhibitors such as aliphatic propargylamines were synthesized because they are not metabolized to amphetamines (Yu et al., 1992). PLZ is metabolized to β-phenylethylidenehydrazine (PEH) (Fig. 4), (MacKenzie, 2009; MacKenzie et al., 2010) and this metabolite appears to contribute significantly to the neurochemical and pharmacological effects of the parent drug, including elevation of brain GABA (MacKenzie et al., 2010; Parent et al., 2002; Paslawski et al., 2001), sequestration of reactive aldehydes (MacKenzie, 2009), inhibition of PrAO (MacKenzie, 2009) and conferring neuroprotection in a model of transient cerebral ischemia (Tanay et al., 2002; Todd et al., 1999).

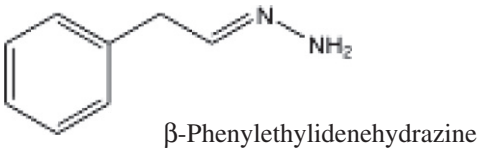

Fig. 4. Structures of ß-phenylethylidenehydrazine (PEH).

7. Other effects of MAO inhibitors

As discussed herein, MAO inhibitors may be useful in treating psychiatric and neurologic disorders other than depression, including panic disorder, social anxiety disorder, PTSD, Parkinson's disease, Gille de la Tourette's syndrome, and possibly AD (Ling et al., 2001; Naoi et al., 2011; Rubinstein et al., 2006; Wood et al., 2006). MAO inhibitors have also been reported to be useful in treating bulimia nervosa and various pain disorders (Kennedy et al., 2009). Pharmacologically, both PLZ and TCP can affect the uptake and release of neurotransmitter amines as well as alter the metabolism of a number of drugs through inhibition of cytochrome P450 (CYP) enzymes (Baker et al., 2000 for review; London and Milne, 1962; Salsali et al., 2004; Smith et al., 1980). Both of these MAO inhibitors can also alter the activity of a number of other enzymes (Baker et al., 2000; Holt et al., 2004). TCP has been reported to alter levels of endogenous ligands of the endocannabinoid system and to increase CB_1 receptor binding in various rat brain regions (Hill et al., 2008). There is a close association between imidazoline binding sites and MAO binding sites (although the nature of this association is still a matter of debate), and some amine oxidase inhibitors also appear to interact with sigma receptors (Holt, 2003; Holt et al., 2004). It is well known that MAO inhibitors can cause a marked increase in brain levels of the so-called "trace amines" β-phenylethylamine, tyramine, octopamine, and tryptamine (Boulton et al., 1984; Sabelli and Mosnaim, 1974), all of which can alter uptake and release and receptor sensitivity of the classical biogenic amine neurotransmitters. Interest in the trace amines has increased markedly in the last few years with the discovery of a family of G-protein coupled receptors, some of which appear to be selectively activated by trace amines (Berry, 2007; Borowsky et al., 2001; Holt et al., 2004; Lindemann and Hoener, 2005); these receptors have since been termed "trace amine-associated receptors". It has been proposed that the amphetamines exert their effects, at least in part, through these receptors (Bunzow et al., 2001), and given the structural similarities between the amphetamines and TCP, PLZ and l-deprenyl, it is conceivable that these MAO inhibitors may also act on these receptors directly in addition to indirect effects caused by their ability to dramatically elevate brain levels of the trace amines.

8. Future applications and drug development

Several MAO inhibitors and structurally similar drugs are "in the pipeline" and are undergoing preclinical or clinical testing (see Kennedy et al., 2009; Youdim et al., 2006b for review). Some of these are propargylamines, and they may also prove to be useful for treatment of several neurodegenerative disorders. For example, rasagiline and CGP 3466 (a propargylamine which does not inhibit MAO) have been reported to be beneficial in an animal model of amyotrophic lateral sclerosis (Youdim et al., 2006b). A series of aliphatic propargylamines have also been reported to be excellent neuroprotective agents in several toxicity models *in vivo* and *in vitro* (Berry and Boulton, 2002). The aldehyde-sequestering actions of PLZ suggest that various analogs of this drug should be investigated as possible neuroprotective agents. By changing the length of the alkyl chain, the GABA-T-inhibiting activity and/or the MAO-inhibiting activity of PLZ can be altered (Popov and Matthies, 1969) while still retaining aldehyde-sequestering properties. Studies addressing the structure–activity relationships could then be conducted *in vivo* to determine the relative importance of sequestering

aldehydes on neuroprotection in models such as the transient cerebral ischemia model. The utility of MAO inhibitors in drug withdrawal has been considered; recent work has suggested that MAO-A inhibitors may be useful in the early stages of withdrawal from heavy cigarette smoking (Bacher et al., 2011). In addition, Gatch et al. (2006) found that several MAO inhibitors modulated the discriminative stimulus effects of cocaine and suggested that they may be useful for the treatment of cocaine abuse. GABAergic drugs have also been suggested as potentially useful drugs in management of cocaine and methamphetamine dependence (DeMarco et al., 2009; Karila et al., 2008; Peng et al., 2008), and PLZ and PEH should be tested in this regard. PEH has been reported to reduce epileptiform activity in rat hippocampal slices (Duffy et al., 2004), and studies on its potential as an anticonvulsant are warranted. Galvani et al. (2008) have suggested that hydrazines, including PLZ, could be useful therapeutic agents for atherosclerosis and its cardiovascular complications because of their ability to neutralize reactive carbonyl components like reactive aldehydes.

9. Conclusion

The amine oxidase inhibitors continue to be of considerable interest and the subject of extensive research. Some of them may prove useful for treating specific neurodegenerative disorders, stroke and drug abuse, either alone or in combination with other drugs. In fact, their multifaceted nature may be an advantage, making them suitable for treating several disorders. Investigations to date have demonstrated that the neuroprotective actions of such drugs are complex and, in many, but not all, cases are independent of MAO inhibition. They continue to be valuable pharmacological tools that have done much to increase our knowledge of mechanisms involved in neuroprotection and have provided important clues for future development of neuroprotective drugs.

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