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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.

Contents

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).

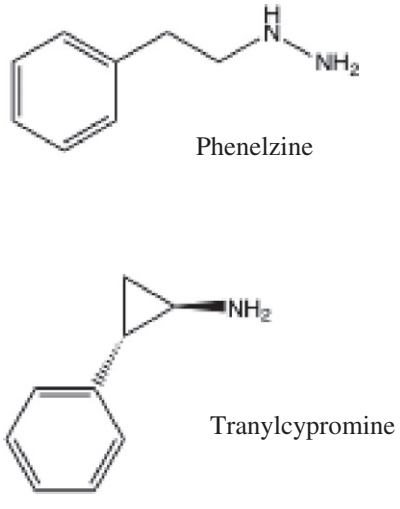

Fig. 1. Structures of the non-selective, irreversible MAO inhibitors phenelzine (PLZ) and tranylcypromine (TCP).

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.