Amine oxidases and their inhibitors: what can they tell us about neuroprotection and the development of drugs for neuropsychiatric disorders?

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Although monoamine oxidase (MAO) inhibitors are not used as extensively as other antidepressants, they continue to have an important place in the armamentarium of drugs used to treat psychiatric and neurological disorders. Interest in MAO inhibitors has also increased in recent years because of numerous reports of their neuroprotective/neurorescue properties.[1–5] Such studies have resulted in a better understanding of possible mechanisms of neuroprotection; stimulated the development of new drugs, such as rasagiline; provided important clues for the development of other drugs for neuropsychiatric disorders; and contributed to the recent surge of interest in possible neuroprotective actions of psychiatric drugs in general.[6,7] Intriguingly, they have also demonstrated that the MAO inhibitors currently available are multifaceted, since, in many cases, the neuroprotection seems to be independent of their MAO inhibition. Studies on semicarbazide-sensitive amine oxidase (SSAO) and its inhibition have also provided exciting results that are relevant to neuropsychiatric disorders and associated diabetes and cardiovascular disease.[8,9] These findings are outlined briefly below.

Tranyclypromine, an irreversible, nonselective MAO inhibitor, has not been investigated as extensively as some of the other MAO inhibitors with regard to neuroprotection, but it has been reported to cause an increase in messenger ribonucleic acid (mRNA) for brain-derived neurotrophic factor (BDNF)[10] and cyclic adenosine monophosphate (AMP) response element binding protein (CREB) [11] in the rat brain hippocampus — effects that could lead to neurogenesis.[12]

l-Deprenyl (l-*N*-propargyl,*N*-methylamphetamine, selegiline), 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 on irreversible MAO-A inhibitors when foods containing tyramine are ingested. It turned out to be a poor antidepressant drug, except at higher doses, at which 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).[13] l-Deprenyl is used in Parkinson's disease[14] and has more recently been reported to be of some use in Alzheimer's disease (AD), although a recent Cochrane review did not report evidence of clinically meaningful benefit in AD.[15] 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.[1–5] A direct result of research on l-deprenyl has been the development of rasagiline, a structurally related drug (both contain an *N*-propargyl group), which has now been approved for use in Parkinson's disease in many countries.[5] Rasagiline has an advantage over l-deprenyl of not being metabolized to l-amphetamine and l-methamphetamine. The mechanisms of neuroprotective action of these *N*-propargyl drugs appear to be complex. In a recent review, Youdim and colleagues[5] 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 proposed to be the result of upregulation of antiapoptotic B-cell leukemia/lymphoma 2 (BCL2) protein. l-Deprenyl and rasagiline have also been shown to downregulate proapoptotic proteins such as BCL-associated death promoter (BAD) and BCL-associated protein X (BAX) and to prevent the activation and nuclear localization of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), an initiator of apoptotic cascades, in response to neurotoxins and reactive oxygen species.[5] Many of the effects of these *N*-propargyl drugs and the consequent neuro-

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protection appear to be independent of their MAO-inhibiting effects. The neuroprotective effects of l-deprenyl are apparently lost at high concentrations.[5]

Phenelzine (2-phenylethylhydrazine, PLZ) is an irreversible, nonselective MAO inhibitor that has been used for many years as an antidepressant drug and is also effective in treating panic disorder and social anxiety disorder. Although it is an MAO inhibitor, it inhibits gamma-aminobutyric acid transaminase (GABA-T) and produces marked increases in brain levels of GABA.[16,17] Interestingly, PLZ has been reported to be neuroprotective in a transient cerebral ischemia model in gerbils and in the N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine (DSP)-4-induced noradrenaline depletion rodent model.[18,19] Several other GABAergic agents have been reported to be neuroprotective in ischemia,[20] presumably due to their ability to counteract the excitotoxic effects of increased extracellular glutamate in such a model.[21] PLZ has been reported to decrease K^+-induced glutamate overflow in the prefrontal cortex in rats.[22] In addition, the potent ability of PLZ, a hydrazine, to sequester toxic aldehydes may be contributing to its neuroprotective actions.[18] Toxic 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 and aldehyde metabolites of catecholamines, are very reactive and can covalently modify proteins, nucleic acids, lipids and carbohydrates and activate apoptotic pathways.[23–28] Because of its hydrazine structure, PLZ is very effective at sequestering aldehydes through a direct chemical reaction.[18]

Moclobemide, an MAO-A inhibitor, has been reported to have anti-Parkinson activity and neuroprotective effects in a model of cerebral ischemia, which appear to be independent of MAO-A inhibition.[5] The irreversible MAO-A inhibitor clorgyline has been reported to be neuroprotective in vitro (it protects against apoptosis induced by serum starvation)[29] and in vivo (it protects against damage caused by the mitochondrial toxin malonate).[30] As with deprenyl and rasagiline, clorgyline contains an *N*-propargyl group.

SSAO, 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 substrates, and their metabolism results in the production of the reactive aldehydes, formaldehyde and methylglyoxal, respectively. Both aldehydes have been shown to induce beta-amyloid beta-sheet formation and subsequent fibrillogenesis in vitro,[8,9] suggesting an involvement with the etiology of AD. In addition, increased serum SSAO 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.[8,9] Jiang and colleagues[31] recently reported a strong expression of SSAO colocalized with Aβ deposits on blood vessels of postmortem brain samples from patients with AD. Interestingly, PLZ, in addition to its MAO- and GABA-transaminase- inhibitory activity, is a relatively potent inhibitor of SSAO,[32] which may be another factor contributing to its neuroprotective effects. Several specific SSAO inhibitors have been developed, and it will be interesting to see their clinical use in the future.

Several MAO inhibitors and structurally similar drugs are "in the pipeline" and are undergoing preclinical or clinical testing (see reference 5 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.[5] A series of aliphatic propargylamines have also been reported to be excellent neuroprotective agents in several toxicity models in vivo and in vitro.[33] 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*-proparglyamphetamine, may have neuroprotective properties, although there is some dispute about this.[3] l-Amphetamine has been reported to interfere with the neuroprotective action of l-deprenyl, whereas aminoindan, the major metabolite of rasagiline, is itself neuroprotective.[34] MAO inhibitors such as alphatic propargylamines were synthesized because they will not be metabolized to amphetamines.[35]

Increased MAO activity and expression of MAO mRNA have been reported in AD,[36] suggesting that MAO inhibitors should be investigated more extensively as possible adjunctive drugs in this disorder. The drug ladostigil combines the activity of rasagiline and anticholinesterase activity and is currently in clinical trials for AD.[5]

The aldehyde-sequestering actions of PLZ suggest that various analogues of this drug should be investigated as possible neuroprotective agents. By changing the length of the alkyl chain[14] or by forming the unsaturated analogue (2-phenylethylidenehydrazine, PEH),[37] the MAO-inhibiting activity or the GABA-T-inhibiting activity of PLZ can be reduced or eliminated while still retaining aldehyde-sequestering properties. Studies addressing the structure–activity relationships could then be conducted in vivo to determine the relative importance of these 3 actions on neuroprotection in models such as the transient cerebral ischemia model.

The amine oxidase inhibitors continue to be of considerable interest and the subject of extensive research. Some of them may prove useful for treating some neurodegenerative disorders and stroke, either alone or in combination with other drugs. In fact, their multifaceted nature may be an advantage, making them suitable for treating several disorders. 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 drug development. 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. Research findings to date have

demonstrated the importance of considering metabolism and the possibility that the neuroprotective actions may be reduced or lost at higher doses of the drugs.

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