Monoamine oxidase inhibitors, their structural analogues, and neuroprotection

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Monoamine oxidase (MAO) inhibitors have been used for many years in the treatment of psychiatric and neurological disorders. More recently, some of these drugs and their analogues have been shown to have neuroprotective and neurorescue effects in several models of neurologic insult, including in vitro and in vivo models of cerebral ischemia. This review will discuss current evidence regarding these aspects of I-deprenyl, tranylcypromine, phenelzine, and some structurally related drugs.

Keywords: Neuroprotection, Neurorescue, I-Deprenyl, Monoamine oxidase, Phenelzine, Phenylethylidenehydrazine, Tranylcypromine

The monoamine oxidase inhibitors (MAOIs) are often prescribed for atypical depression or depression associated with anxiety, agitation and phobias. The irreversible, non-selective MAOIs phenelzine (PLZ) and tranylcypromine (TCP) (Fig. 1) are effective antidepressants and are also useful in the treatment of anxiety disorders such as panic disorder and social phobia, but their use has been limited by a side-effect known as the "cheese effect." This side-effect is associated with ingestion of aged cheese and other foods that contain high concentrations of sympathomimetic amines, such as tyramine, by individuals who are concurrently being treated with irreversible inhibitors of MAO-A. To reduce this problem while still retaining antidepressant properties, reversible, selective inhibitors of MAO-A (RIMAs) such as moclobemide, have been developed. I-Deprenyl (also known as selegiline) (Fig. 2), an irreversible selective inhibitor of MAO-B, is not associated with the cheese effect, but is also relatively ineffective as an antidepressant at doses at which it selectively inhibits MAO-B. It has, however, been used in the treatment of Parkinson’s Disease (PD) and has demonstrated neuroprotective/neurorescue activities mediated through or associated with a variety of mechanisms.

In recent years, there has been a great deal of interest in neuroprotective actions of psychiatric drugs in general. This review will examine selected

![Chemical structures of (a) phenelzine and (b) tranylcypromine](image)

Fig. 1—Chemical structures of (a) phenelzine and (b) tranylcypromine

![Chemical structures of several MAOIs that contain the propargyl (-CH=C=H) moiety and have been reported to have neuroprotective and/or neurorescue activity: (a) deprenyl; (b) rasagiline; (c) general structure for aliphatic propargylamines (R = H or CH₃)](image)

Fig. 2—Chemical structures of several MAOIs that contain the propargyl (-CH=C=H) moiety and have been reported to have neuroprotective and/or neurorescue activity: (a) deprenyl; (b) rasagiline; (c) general structure for aliphatic propargylamines (R = H or CH₃)
MAOIs and their analogues with regard to their potential as neuroprotective agents.

**l-Deprenyl**

l-Deprenyl is a selective and irreversible inhibitor of monoamine oxidase B (MAO-B), and its pharmacology has been studied extensively. Although l-deprenyl is not an effective antidepressant at doses at which it selectively inhibits MAO-B, it has shown potential: (1) as a neuroprotective/neurorescue agent in many in vitro and in vivo experimental models of neuroprotection/neurorescue; (2) in the treatment of early PD; (3) in paradigms for improving functional recovery following ischemic stroke; (4) in the treatment of Alzheimer’s Disease in humans; and (5) in paradigms for improving functional recovery following ischemic stroke.

The neuroprotective/neurorescue activity exhibited by l-deprenyl in various models of neurologic injury is no longer believed to be due primarily to its inhibition of MAO-B but, rather, the net result of effects on several different mechanisms.

Deprenyl-associated production of neurotrophic factors (Neurotrophins)—Administration of l-deprenyl is associated with increases in the production of glial cell line-derived neurotrophic factor (GDNF) and ciliary neurotrophic factor (CNTF).

GDNF protects against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA)-induced free radical damage and prevention of the loss of nitric oxide synthase associated with use of DSP-4. l-Deprenyl was associated with increased activity of the neuroprotective enzymes superoxide dismutase (SOD), glutathione peroxidase (GPX), and lipid peroxidase (LP) relative to saline controls. The increases in enzyme activity and in GDNF mRNA levels may be components of MAO-inhibition-independent neuroprotective activity of l-deprenyl; however, these effects on GDNF, SOD, GPX and LP have not yet been shown to be completely unrelated to MAO inhibition. Kontkanen and Castrén directly compared the effects of BDNF and l-deprenyl on the growth of rat dopaminergic neurons in vitro, and showed that l-deprenyl increased the average length of neuronal branches while BDNF increased the number of new branches formed. In a study by Li et al., l-deprenyl and NGF, individually and when used in combination, increased SOD mRNA in PC-12 cells. Further, l-deprenyl actually potentiated the effect of NGF on SOD mRNA levels in these cells. Relative to control animals, striata from l-deprenyl-treated ischemic animals were shown to contain 25% higher levels of basic fibroblast growth factor (bFGF), likely due to l-deprenyl-induced astrocytic production of bFGF. As with NGF, bFGF can be secreted by glia and neurons; however, upregulation of bFGF mRNA following ischemia is seen primarily in glial cells. Taken together, these findings suggest that neurotrophic factors likely play important roles in the neuroprotective/neurorescue activity of l-deprenyl.

Anti-apoptotic activity—Several recent studies have shown that glyceraldehyde-3-phosphate dehydrogenase (GAPDH), in addition to its role in glycolysis, is involved in many non-glycolytic processes, including apoptosis. GAPDH is believed to serve as an initiation signal for the apoptotic process. CGP 34660, several neuroprotective aliphatic propargylamines, l-deprenyl and N-desmethylddeprenyl, all of which have in common the presence of a propargyl (-CH2-C=CH) moiety (Fig. 2), are known to bind to GAPDH at a common site. Neuroprotective aliphatic propargylamines prevent the increase in GAPDH mRNA that is known to occur in the nucleus following a pro-apoptotic insult. This increase in nuclear GAPDH may initiate a sequence of events characterizing cellular apoptosis.

Other effects of l-deprenyl—Li et al. reported that l-deprenyl and another MAO-B inhibitor decrease the amount of mRNA for glial fibrillary acidic protein (GFAP), an indicator of activation of astrocytes, in C6 glioma cells, and hypothesized that this reduction in GFAP mRNA may account in part for the neuroprotective effects of l-deprenyl. Yu et al. found that pretreatment of rodents with l-deprenyl or 2-HxMP (an aliphatic propargylamine) not only protected against the loss of hippocampal noradrenaline levels produced by the neurotoxin DSP-4 [N-(2-chloroethyl), N-ethyl-2-bromotetrazylamine], but prevented the loss of nitric oxide synthase associated with use of DSP-4.

The role of l-deprenyl in the scientific literature and in medical practice has evolved over time. This drug was originally developed as a potential antidepressant but has since yielded invaluable information about mechanisms that may be involved in neuroprotection/neurorescue in the settings of chronic and acute neurotoxicity. Investigations of this drug...
have led to the development of several new, structurally related drugs, such as the aliphatic propargylamines\(^5\), based on the key functional noities found in \(l\)-deprenyl. Continued development and examination of \(l\)-deprenyl-related drugs will allow us to describe further the pathophysiology of neuronal death in the setting of ischemia and to identify and target mechanisms by which we may affect robust neuroprotection.

**Tranylcypromine**

Tranylcypromine (TCP) is a non-selective, reversible MAOI antidepressant medication that, in addition to its utility as an antidepressant, possesses activities that may provide it with neuroprotective activity after cerebral ischemia.

As was seen to be the case with \(l\)-deprenyl, TCP induces synthesis of neurotrophic factors. The discussion that follows will address the reported effects of TCP on mRNA for brain-derived neurotrophic factor (BDNF) and how this may affect neuroprotection.

Several antidepressant medications, including TCP, have been linked to upregulation of BDNF mRNA\(^7\). This is significant, with respect to the mechanism of TCP's antidepressant effect, because infusion of BDNF into the midbrain has been shown to have an antidepressant-like effect in animal models\(^50,51\). The upregulation of BDNF following treatment with antidepressants has been shown to occur in the same regions of the brain where upregulation of cyclic AMP response element binding protein (CREB), a transcription factor, has been demonstrated. One prediction that has been put forth is that these observations suggest possible involvement of cAMP-dependent intracellular signalling pathways in the regulation of BDNF synthesis\(^52\). This possibility is supported by the observation of a potentiating effect of phosphodiesterase (PDE) inhibitors on the upregulatory effect of antidepressants on BDNF\(^53\).

**Antidepressant treatment-associated increases in BDNF mRNA levels**—BDNF is involved in neuronal survival, development, maintenance and plasticity\(^52,53\) and also has an effect on glutamatergic signalling\(^52,54,55\).

Chronic, but not acute, administration of the antidepressants TCP, desipramine, sertraline and mianserin has been reported to be associated with upregulation of BDNF mRNA in rat hippocampus\(^7\), and TCP treatment also resulted in an increase in BDNF mRNA in the frontal cortex. The upregulation of BDNF mRNA was specific to antidepressants, and was not seen with drugs, such as morphine, from other classes. In the same study\(^5\), chronic treatment with all of the antidepressant drugs except mianserin also resulted in an increase in mRNA for the BDNF plasma membrane receptor, trkB. As mentioned above, recent work suggests that CREB (and therefore cAMP-dependent signalling pathways) may play a role in the chronic antidepressant treatment-associated increase in BDNF mRNA levels.

The nature of the relationship between antidepressant treatment and upregulation of neurotrophic factors such as BDNF remains largely undetermined. It could be argued that drug treatment directly induces changes in levels of neurotrophins or that antidepressant treatment leads to upregulation of neurotrophin levels by affecting some aspect of cellular stress. There is little information regarding the efficacy of TCP in animal or in vitro models of cerebral ischemia or in chronic neurodegenerative disorders. Accordingly, further studies on TCP and related compounds will be required to determine the effectiveness of these agents in models of acute and/or chronic neuronal cell death.

**Phenelzine**

Phenelzine (PLZ) has been used clinically for many years in the treatment of depression and anxiety disorders\(^5\). In addition to its MAOI activity, PLZ inhibits GABA transaminase (GABA-T), in addition to other transaminases\(^56\) and causes marked, relatively long-lasting elevations of brain GABA levels\(^57,58\). Studies have demonstrated that PLZ also has neuroprotective/neurorescue properties in transient forebrain ischemia\(^59,60\), an animal model of human strokes which occur following cardiac arrest, hypotension, drowning or anaesthesia accidents.

Transient forebrain ischemia causes increases in hippocampal and striatal extracellular levels of the excitatory amino acid glutamate and of the inhibitory amino acid GABA\(^61\). The increase in extracellular GABA, which appears to be relatively transient, results in a relatively rapid feedback reduction of the synthesis and release of that neurotransmitter. In light of increased extracellular glutamate levels and inhibition of GABA\(_A\) receptor activity that occur in conditions of excess glutamate\(^62\), the cellular environment in ischemic brain favours glutamatergic excitation (and eventual excitotoxicity) over GABAergic inhibition\(^63,64\). Shuaib et al\(^65,66\) reported a relationship between the decrease in GABA levels in
global ischemia in gerbils and the onset of neuronal damage in the substantia nigra. They also demonstrated that a number of drugs that enhance GABA receptor activity, either directly or as modulators, are neuroprotective in the hippocampus and substantia nigra in the same model. Further arguments in favour of elevating brain GABA levels as a means to attenuate glutamatergic excitotoxicity have been discussed previously. Although much of the work examining drugs such as PLZ (and its analogues) as neuroprotective agents focuses on their use as monotherapies, the most efficacious use of these agents may turn out to be in combination with other drugs that act by complementary mechanisms. One such combination, the rationale for which has been discussed above, is that of other GABAergic drugs (GABA receptor agonists, positive modulators of GABA receptors) and glutamate receptor antagonists. Other interesting combinations would be with hypothermia, clot-dissolving agents such as rtPA, or both, and these combinations will undoubtedly receive more attention, clinically and preclinically, in the future.

Phenelzine analogues—A metabolite of PLZ is responsible, at least in part, for the GABA-elevating effects of this drug. Two putative metabolites, phenylethylidenehydrazine (PEH) and N²-acetyl-PLZ (AcPLZ) are shown in Fig. 3.

PEH is similar to its parent compound, PLZ, in that both drugs inhibit GABA-T and are associated with elevation of brain GABA levels. Unlike PLZ, a potent MAOI, PEH only weakly inhibits MAO. N²-Acetylphenelzine, on the other hand, has no effect on GABA-T or brain GABA levels, but retains the MAO-inhibiting properties of its parent drug, PLZ.

Treatment of gerbils with PEH (good inhibitor of GABA-T and weak inhibitor of MAO) or PLZ (good inhibitor of both GABA-T and MAO) results in increased neuronal survival in the ischemia-sensitive hippocampal CA1 region when either drug is administered 3 hours after the ischemic insult and then once daily thereafter for 7 days. This suggests that, in the gerbil model of transient forebrain ischemia, the GABA-elevating action of PLZ may contribute more to the drug’s neuroprotective efficacy than its MAO-inhibitory potency—if, indeed, either of these mechanisms is to any degree responsible for neuroprotection. The 4-fluoro analogue of PEH (Fig. 3) which, like PEH, displays good GABA-T inhibition and only weak MAO-I activity, has also been shown to be neuroprotective in the gerbil model of transient forebrain ischemia when administered hours after reperfusion and then once daily for 7 weeks.

One preliminary test for identification of potential neuroprotective agents involves protection against DSP-4-induced noradrenaline (NA) depletion mouse hippocampus. l-Deprenyl and many of its analogues, including aliphatic propargylamines, are efficacious in this test. PLZ (Fig. 1), AcPLZ (Fig. 3) and some N¹- and N²-propargyl analogues of PLZ (Fig. 3) also protect against DSP-4-induced NA depletion. All of these drugs inhibit MAO-B to some extent, but it has been suggested that the MAO-B-inhibiting effects of such drugs are not critical for their neuroprotective actions in this test, although this still remains a matter of debate. PEH and its analogues have not yet been tested in this model.

Conclusion

The scarcity of good therapeutic agents for treatment of stroke necessitates further investigation of the mechanisms responsible for cell death in this setting of cerebral ischemia and the development of new therapeutic and investigational agents based on these findings.
the knowledge gained thus far. As has been discussed, drugs which have MAO inhibition as their primary therapeutic mechanism have not only provided us with hope with regard to their potential utility in the treatment of ischemic stroke, but also serve as tools for investigating the role of GABA in neuroprotection in the setting of ischemic stroke. An important caveat to the use of such non-specific MAO inhibitors in treatment of stroke and other disorders is the risk of pharmacokinetic food-drug and drug-drug interactions with these drugs. Studies with these drugs are providing us with important clues for the development of future neuroprotective agents which could be useful for treatment of a wide variety of neurological and psychiatric disorders. With good fortune, these investigations will lead to the development of more drugs, such as the PEH analogues, with therapeutic efficacy in addition to tolerable or at worst medically manageable side-effect profiles.

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