Phenelzine: An Old Drug That May Hold Clues to The Development of New Neuroprotective Agents

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ÖZET:

Fenelzin: Eski bir ilaç, yeni nöroprotektif ajanların geliştirilmesine ipuçları tutabilir

Panik bozukluk ve sosyal anksiyete bozukluğu gibi anksiyete bozukluklarının tedavisinde kullanılan monoamin oksidaz (MAO) inhibitörü bir antidepresan olan fenelzinin geçici önbeyin iskemisi olan bir hayvan modelinde nöroprotektif etkileri olduğu gösterilmiştir. Fenelzinin MAO inhibisyonu etkisi yanı sıra farmakolojik ve terapötik profiline eklenebilir çok sayıda etkisi vardır. Bu etkiler GABA transaminazın inhibisyonuyla beyin GABA düzeylerini arttırması, glutamatın işlevsel durumu üzerine etkileri, reaktif aldehitlerin tutulumu, primer amin oksidaz inhibisyonu ve beyin kaynaklı nörotrofik faktör (BDNF) üzerindeki etkilerin inhibe edilmesidir. 2-Feniletilidenehidrazin, fenelzinin önemli bir metabolit olup GABA beyin düzeylerini arttırdığı gösterilmiştir ve geçici önbeyin iskemisi modelinde reaktif aldehitlerin tutulumu ve nöroprotektif etkileri keşfedilmiştir. Fenelzin ve feniletilidenehidrazin bu etkileri nedeniyle özellikle nörodejenerasyon içeren psikiyatrik ve nörolojik bozuklukların tedavisi için gelecekte ilaç tasarımı yönünden göz önünde tutulmalıdır.

Anahtar sözcükler: Fenelzin, nöroproteksiyon, γ-aminobutirik asid (GABA), glutamat, reaktif aldehidler, primer amin oksidaz (semikarbazid sensitif amin oksidaz).

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ABSTRACT:

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The monoamine oxidase (MAO)-inhibiting antidepressant phenelzine (PLZ) is also used in the treatment of anxiety disorders such as panic disorder and social anxiety disorder and has been shown to have neuroprotective actions in an animal model of transient forebrain ischemia. Phenelzine has multiple actions in addition to inhibition of MAO that may contribute to its pharmacological and therapeutic profile. These actions include inhibition of GABA transaminase and elevation of brain levels of GABA, effects on functional availability of glutamate, sequestration of reactive aldehydes, inhibition of primary amine oxidase and effects on brain-derived neurotrophic factor (BDNF). 2-Phenylethylidenehydrazine (PEH) has been identified as a major metabolite of PLZ and has also been shown to elevate brain levels of GABA, to sequester reactive aldehydes and to exert neuroprotective effects in a transient forebrain ischemia model. The actions of PLZ and PEH should be considered when designing future drugs for the treatment of psychiatric and neurologic disorders, particularly those involving neurodegeneration.

Key words: Phenelzine, neuroprotection, γ-aminobutyric acid (GABA), glutamate, reactive aldehydes, primary amine oxidase (semicarbazide sensitive amine oxidase)

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INTRODUCTION

Phenelzine (PLZ) (Figure 1) is an irreversible, non-selective monoamine oxidase inhibitor (MAOI) used clinically for the treatment of a number of psychiatric disorders, including major depression (1), atypical depression (2-4), panic disorder (5,6), and social anxiety disorder (7). It has also been reported to reduce neuronal loss in a gerbil model of transient forebrain ischemia (8).

PLZ increases brain levels of the classical monoamine neurotransmitters (9-12) and trace amines (phenylethylamine (PEA), tyramine and tryptamine) (13). However, it also inhibits GABA-transaminase (GABA-T) (10,14,15) and markedly increases brain levels of the inhibitory amino acid transmitter Á-aminobutyric acid (GABA) (10,14-21). GABA-T requires pyridoxal phosphate (PLP) as a cofactor, and PLZ also inhibits a number of other PLP-dependent enzymes (22-25).

Administration of PLZ to rodents increases brain GABA levels up to 3-4 times control values (19), but GABA-T activity is not inhibited in vivo by more than 50% even at doses as high as 60 mg/kg (15), suggesting that other, as yet unidentified mechanisms may also be involved in PLZ's GABA-elevating effect. PLZ has been reported to produce a transient decrease in brain levels of glutamine and glutamate (26,27), a decrease in glutamate-

glutamine cycling flux between neurons and glia (27), and a reduction in KCl-evoked glutamate release (28). However, while studies consistently report that PLZ causes transient decreases in whole brain glutamine levels, the effects of PLZ on glutamate are much less robust, with some (27), but not all (17) studies reporting a decrease in whole brain glutamate levels. In this regard, it is of interest that researchers in the Neurochemical Research Unit have recently found that PLZ decreases glutamate release from astrocytes (Song, Baker, and Todd, unpublished). PLZ may reverse the activity of the GABA transporters (GATs), thus exporting GABA from the presynaptic neuron.(29).

ß-PHENYLETHYLIDENEHYDRAZINE (PEH)

PLZ is interesting in that not only is it a MAOI, it is also a substrate for MAO (30). In rats, inhibition of MAO prior to PLZ administration markedly reduces the inhibition of GABA-T activity and the elevation of brain GABA (15,21), suggesting that a metabolite produced by the action of MAO on PLZ is responsible for these actions on GABA. This metabolite has subsequently been demonstrated to be ß-phenylethylidenehydrazine (PEH) (Figure 1) (MacKenzie, Knaus and Baker, unpublished), a compound shown by us to transiently decrease whole brain glutamine levels and to increase extracellular GABA in the striatum (31). Unlike PLZ, PEH has only weak inhibitory effects on MAO (32), suggesting that PEH could be an interesting therapeutic alternative to PLZ in some disorders since it has the GABAergic actions of the parent drug, but would be unlikely to the produce the "cheese effect", a problematic food-drug interaction associated with irreversible inhibitors of MAO . PEH has also been reported to reduce epileptic activity in rat hippocampal slices (29) and, like PLZ, to be neuroprotective in a gerbil transient forebrain ischemia model (33).

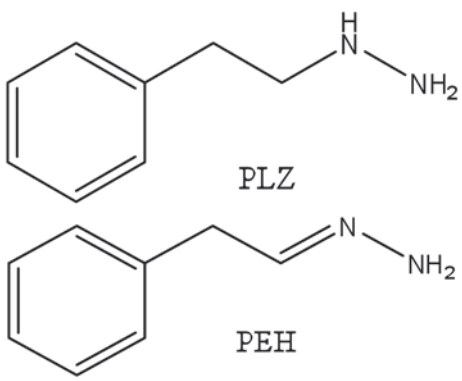

Figure 1: The chemical structures of PLZ and PEH

NEUROPROTECTIVE MECHANISMS OF ACTION OF PLZ

The neuroprotective action of PLZ could potentially not only lead to a reduction in the disability that so often occurs following stroke in humans, but also provide insight into novel therapeutic interventions for a number of neurodegenerative conditions. There are several properties of PLZ that could account for its neuroprotective actions.

Phenelzine elevates brain GABA levels

PLZ produces a marked and long-lasting increase in brain levels of GABA, and this elevation may counteract the excitotoxicity associated with excessive activity of glutamate which is thought to be an important contributor to the neurodegeneration observed in stroke and a number of other neurological and psychiatric conditions. Many studies have reported marked increases in brain glutamate levels following ischemia (34-37), and a reduction in glutamatergic activity has been shown to be neuroprotective in this context. Initial concomitant increases in brain levels of glutamate and GABA in cerebral ischemia have been reported. However, the increase in GABA is usually much more transient than that of glutamate, with the initial increase in brain GABA followed by a longer-lasting decrease in brain levels and function of this inhibitory neurotransmitter (38-45). This decrease in GABAergic activity likely exacerbates the neuronal damage induced by excitotoxicity in the long term, since the opposing actions of the GABAergic system on the hyperactive glutamatergic system are reduced (42).

While antagonism of glutamate NMDA receptors can reduce cell loss in both in vitro and in vivo models of excitotoxicity, increasing GABAergic transmission can also counteract excitotoxic damage, probably with fewer

adverse side-effects than observed with NMDA receptor antagonists. GABAergic agents, including tiagabine and vigabatrin (gamma-vinyl GABA), have been reported in preclinical studies to reduce the extent of ischemia-mediated neuronal damage in vivo and in vitro (40,46,47), and thus it is not surprising that PLZ has been shown to reduce neuronal damage in an animal model of ischemia (8). It is also interesting to note that glutamate-associated excitotoxicity is also thought to play a role in the neurodegeneration observed in Alzheimer's disease (48-50) and GABAergic deficits have been reported in AD, although these latter findings are conflicting and complicated by variables such as illness severity and post-mortem handling of brain tissue (51). Facilitation of GABAergic transmission has been reported to result in neuroprotective effects both in vivo and in vitro against ß-amyloid (Aß) mediated toxicity, suggesting that PLZ and PEH should be considered as possible adjunctive drugs in the treatment of AD.

Phenelzine and reactive aldehydes

There has been a great deal of interest in recent years in possible neurotoxic effects of reactive aldehydes such as 3-aminopropanal (3-AP), acrolein, and formaldehyde in neurodegenerative disorders. Metabolism of the polyamines spermidine and spermine, catalyzed by polyamine oxidase, produces putrescine (another polyamine) and 3-AP and acrolein as by-products (52). The metabolism of methylamine (MA) and aminoacetone, via the action of semicarbazide-sensitive amine oxidase (SSAO) (now called primary amine oxidase), results in production of FA and methylglyoxal, respectively (53). Aldehydes, such as acrolein, 4-hydroxynonenal (4-HNE) and malondialdehyde, are products of lipid peroxidation [oxidative damage to lipids by reactive oxygen species (ROS)] (54,55), and high aldehyde concentrations are considered to be biological markers of oxidative stress (56).

Free reactive aldehydes can bind rapidly to amino acids, proteins, nucleic acids and lipids, forming irreversible adducts that can cause inhibition of synthesis of protein, RNA and DNA, and can interfere with the functioning of enzymes, membrane transporters and cell membranes (54,57). Acrolein can induce apoptosis via direct toxic effects on mitochondria (58), and 3-AP has been shown to cause lysosomal leakage or rupture, resulting in mitochondrial damage and activation of apoptotic cascades (and often cellular necrosis as well) (59-61). Several aldehydes have been reported to deplete levels of the endogenous antioxidant glutathione, exacerbating oxidative damage (62,63).

Theoretically, antioxidants counteract the actions of ROS and therefore reduce lipid peroxidation and the generation of the resultant aldehyde byproducts, but antioxidants have not been particularly effective in preventing aldehyde-mediated cytotoxicity either in animal models (8) or clinically (64). An effective alternative method for reducing aldehyde-mediated toxicity is "sequestering" through direct chemical interaction with the aldehyde, producing non-reactive and non-toxic products, thus reducing the reactive "aldehyde load." For example, N-benzylhydroxylamine, cyclohexylhydroxylamine and t-butylhydroxylamine sequester 3-AP, presumably forming inert oximes, and decrease aldehyde-mediated neurodegeneration in vitro (8). Aminoguanidine sequesters FA in vitro and in vivo (65), and acrolein and 3-AP have been shown to be sequestered by hydralazine, dihydralazine and PLZ, producing inert hydrazones (8,66). PLZ was also shown to sequester 4-HNE in vitro (67). The free hydrazine group of PLZ interacts with the aldehyde to produce a hydrazone molecule (Figure 2). PEH should also have the same property, and indeed has been shown recently to sequester FA (MacKenzie and Baker, unpublished). Both drugs also elevate brain levels of ornithine (68), an amino acid that is converted into polyamines, the source of potent reactive aldehydes; the reason for this elevation is not yet established, but it will be of interest to determine if it reflects a reduction in brain levels of polyamines.

High levels of free aldehydes and/or protein adducts formed by acrolein, 4-HNE, malondialdehyde and methylglyoxal (all products of lipid peroxidation) have been reported in AD brains, often colocalized with

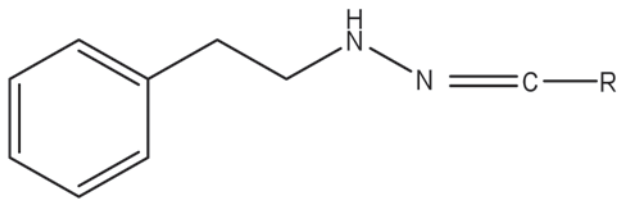

Figure 2: General structure of a hydrazone formed by the reaction of PLZ with a reactive aldehyde

neurofibrillary tangles (57,69-71). Elevated acrolein levels may contribute to mitochondrial dysfunction in AD (72), and several aldehydes, including FA, have been reported to induce Aß aggregation and fibrillogenesis in vitro (73). FA has also been reported to be involved in the production of amyloid-like complexes (61), and to induce polymerization of tau protein both in vitro and in vivo (74). Importantly, the expression of primary amine oxidase, the enzyme responsible for the conversion of MA to FA, has been reported to be increased in AD brains (75), and primary amine oxidase-mediated deamination has been proposed to play a role in the pathogenesis of AD (76). Sequestration of FA with aminoguanidine was shown to prevent FA-induced A, aggregation both in vivo and in vitro (65); this drug is not useful clinically due to its harmful side effects, but these findings highlight the importance of identifying other aldehyde-sequestering drugs able to protect against FA-mediated pathology.

Phenelzine inhibits MAO and primary amine oxidase activity

Increased MAO-B activity has been reported in aged individuals and in several neurodegenerative disorders (77,78), and increased intracellular Ca^{2+} (observed in AD and other neurodegenerative diseases) has been reported to contribute to increased MAO-A activity (79) (although findings regarding changes in MAO-A activity in AD and other degenerative disorders are conflicting). The toxic products of MAO-catalyzed reactions (which include reactive aldehydes and H2O2) probably contribute to the neurodegeneration observed in these individuals. PLZ and other MAOIs would be expected to provide neuroprotective effects by inhibiting production of these toxic products, particularly in conditions where MAO activity is increased. H2O2, a major ROS, can be converted to toxic hydroxyl free radicals in the presence of transition metal ions, possibly contributing to oxidative stress (80).

PLZ also inhibits the activity of primary amine oxidase (MacKenzie, Holt, and Baker, unpublished, 81,82), an enzyme located primarily on the outer membrane of vascular endothelial cells, smooth muscle cells and adipose cells, and also found circulating in the blood. In the brain it is found solely in the cerebral vasculature (82,83). This enzyme deaminates MA and aminoacetone (endogenous amines), resulting in production of FA and methylglyoxal, respectively (53). Interestingly, the activity and expression of primary amine oxidase is reportedly elevated in serum and brains respectively of AD subjects (75,84), suggesting that inhibition of this amine oxidase could potentially lead to neuroprotective effects by reducing the formation of toxic products.

Effects of PLZ on neurotrophic factors

Brain-derived neurotrophic factor (BDNF) is the most prevalent neurotrophic factor in adult brain and is important for neuronal survival and activity (85). The actions of BDNF depend on two secreted forms, the precursor (pro-BDNF) and the mature (BDNF) forms, which activate two distinct receptors, the p75 neurotrophin receptor and the tropomysin related kinase B (TrkB) receptor, respectively. Abnormalities involving BDNF have been reported in various psychiatric and neurological disorders, and several antidepressants, including PLZ, are known to elevate brain BDNF levels (86,87), partly via the activation of CREB (cAMP response element binding protein), a transcription factor (88). We have recently observed PLZ can alter the expression and release of BDNF in astrocytes and neurons (Song, Baker, and Todd, unpublished).

SUMMARY

There has been increased interest in MAOIs in general in recent years because of their possible neuroprotective properties. Much of that research has focused on the N-propargyl drug l-deprenyl and related analogues (89), but PLZ, a hydrazine drug, should also be considered in this regard. PLZ is a multifaceted drug with regard to both its therapeutic profile and its neuropharmacological mechanisms of action. Factors which could be contributing to its neuroprotective effects include the following: inhibition of MAO-A and –B; elevation of brain GABA levels; sequestration of reactive aldehydes; and inhibition of primary amine oxidase. Its major metabolite, PEH, also elevates brain GABA levels and sequesters reactive aldehydes and should also be considered as a neuroprotective drug in its own right.

In summary, studies on the mechanisms of action and

metabolism of PLZ suggest that the clinical application of PLZ should be wider than it already is (e.g. should it be used in post-stroke depression and in AD?) and that analogues of PLZ and PEH should be developed as potential new drugs for treating psychiatric and neurologic disorders, particularity those involving neurodegeneration.

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