

Monoamine Oxidase Inhibitors and Neuroprotective Mechanisms

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ÖZET:

Monoamin oksidaz inhibitörleri ve nöroprotektif mekanizmalar

Son yıllarda monoamin oksidaz inhibitörleri üzerindeki ilgide bir canlanma gözlenmektedir. Bunun başlıca nedeni in vivo ve in vitro çeşitli toksik durumlarda bu ilaçların bazılarının nöroprotektif ve / veya sinir kurtarıcı (neurorescue) etkileri olduğunun gösterilmesidir. Psikiyatrik ilaçların nöroprotektif etkilerine yönelik ilginin artması, glia-nöron etkileşimlerinin daha iyi anlaşılmasını sağlamış ve gerek psikiyatrik gerekse nörolojik bozuklukların tedavisine yönelik yeni ilaçların geliştirilmesi için önemli ipuçları elde edilmiştir. Bu editoryalde bu alanla ilgili bazı çalışmaların kısa özeti sunulmuştur.

Anahtar sözcükler: Monoamin oksidaz, monoamin oksidaz inhibitörleri, nöroprotektif ajanlar, primer amin oksidoredüktazlar, l-deprenil, phenelzin, selegiline, tranilsipromin, rasagiline

Klinik Psikiyatri Bülteni 2012;22(4):293-6

ABSTRACT:

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There has been a resurgence of interest in recent years in monoamine oxidase inhibitors, primarily because of the demonstrated neuroprotective and/or neurorescue properties of several of these drugs in a variety of toxic situations in vivo and in vitro. The consequence has been an increased interest in possible neuroprotective effects of psychiatric drugs in general, an improved understanding of glia-neuron interactions, and the provision of important clues to development of future drugs for treating psychiatric and neurological disorders. A brief overview of some relevant studies in this area is provided in this editorial.

Key words: Monoamine oxidase, monoamine oxidase inhibitors, neuroprotective agents, primary amine oxidoreductases, l-deprenyl, phenelzine, selegiline, tranilcypramine, rasagiline

Bullet in of Clinical Psychopharmacology 2012;22(4):293-6

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Gönderme ve kabul tarihleri / Dates of submission & acceptance: 30 Ekim 2012 / October 30, 2012

Bağıntı beyanı:

G.B.B., D.M., E.M.M., S.M.D., D.D.M.: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Declaration of interest:

G.B.B., D.M., E.M.M., S.M.D., D.D.M.: The authors reported no conflict of interest related to this article.

Monoamine oxidase (MAO) inhibitors, although not used as first line antidepressants, continue to have a niche in the treatment of psychiatric and neurological disorders. Interest in these drugs has also increased markedly in recent years following numerous reports of their neuroprotective actions in vivo and in vitro (1-6). Although MAO inhibitors might be expected to be neuroprotective because of their ability to reduce the formation of hydrogen peroxide and ammonia, potentially toxic products of the catabolism of amines by MAO, often the neuroprotection/neurorescue produced by MAO inhibitors appears to be independent of inhibition of MAO.

l-Deprenyl (1-N-propargyl, N-methylamphetamine; selegiline) a selective, irreversible MAO-B inhibitor, was

originally developed as an effective MAO inhibitor without the pressor effect ("cheese effect") sometimes seen with irreversible MAO-A inhibitors when foods containing tyramine or related sympathomimetic substances are taken concomitantly. However, it is a poor antidepressant except at higher doses at which it also inhibits MAO-A; interestingly, recent studies suggest that it is an effective antidepressant when given transdermally (7). l-Deprenyl has been used in Parkinson's disease and has been reported to be of some utility in global ischemia, Tourette syndrome, narcolepsy and possibly Alzheimer's disease (8). Perhaps the most exciting aspect of l-deprenyl is the fact that it has neuroprotective/neurorescue properties in a remarkable variety of neurotoxicity tests in vivo and

in vitro (1-6,9-11). Indeed, research on the neuroprotective actions of this drug appears to have stimulated research on possible neuroprotective actions of numerous other psychiatric drugs, including antidepressants and antipsychotics. One of the results of the interest in the neuroprotective/neurorescue studies 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 (5,12,13) and been shown to be neuroprotective in a variety of models (5,14-17). Unlike l-deprenyl, rasagiline is not metabolized to l-amphetamine or l-methamphetamine. It has been proposed that l-deprenyl and rasagiline interact with the outer mitochondrial membrane, preventing neurotoxin-induced collapse of mitochondrial membrane potentials, mitochondrial permeability transition and the opening of the voltage-dependent anion channel; these actions may be result of upregulation of anti-apoptotic BCL2 protein (5). These drugs have also been shown to downregulate pro-apoptotic proteins such as BAD and BAX and to prevent the activation and nuclear localization of glyceraldehyde-3-phosphate dehydrogenase (GADPH), which can initiate apoptotic cascades in response to neurotoxins and reactive oxygen species (5,18-21). Many of these effects may be independent of the MAO-inhibiting effects of these drugs. Research on rasagiline eventually led to synthesis of the novel drug ladostigil, which combines inhibition of cholinesterase and MAO-B and has potential for treatment of Alzheimer's disease (AD) (5,22-24). Ladostigil protects against a variety of toxic insults in vivo and in vitro, and mechanisms may include stabilization of mitochondrial membrane potentials, induction of neurotrophic factors and upregulation of antiapoptotic factors. The S-isomer of ladostigil inhibits cholinesterase but not MAO while still exerting neuroprotective effects in vitro (5).

Although much of the literature on neuroprotective actions of MAO inhibitors has focused on MAO-B inhibitors, selective inhibitors of MAO-A have also been reported to be potential neuroprotective and/or neurorescue agents. Moclobemide, a reversible inhibitor of MAO-A (RIMA), has been reported to have anti-Parkinson activity and neuroprotective effects in a cerebral ischemia model, and these effects appear to be independent of inhibition of MAO-A (5). This RIMA has also been reported to facilitate differentiation of stem cells into functional neurons (25)

and to reduce anoxia- and glutamate-induced neuronal damage in cerebral cortex cultures (26). Clorgyline, a selective irreversible MAO-A inhibitor, has been reported to be protective against apoptosis induced by serum starvation (27) and against damage caused by the mitochondrial toxin malonate (28). It is interesting that, like l-deprenyl and rasagiline, clorgyline contains a N-propargyl group and that a number of N-propargyl aliphatic amines have been reported to possess excellent neuroprotective properties (29).

The irreversible, non-selective (inhibits both MAO-A and MAO-B) inhibitor tranylcypromine has been reported to cause an increase in mRNA for brain-derived neurotrophic factor (BDNF) and cyclic AMP response element binding (CREB) protein in rat hippocampus, actions which could lead to neurogenesis (30). It is interesting that several other MAO inhibitors, including l-deprenyl, phenelzine, rasagiline and ladostigil, have been reported to upregulate BDNF and other neurotrophic factors (6 for review).

Phenelzine (phenylethyldihydrazine, PLZ) is an irreversible, nonselective MAO inhibitor which has been used for many years as an antidepressant, but is also effective in treating panic disorder and social anxiety disorder. Although it is an MAO inhibitor, it is a multifaceted drug that also inhibits GABA transaminase (GABA-T) and produces marked increases in brain levels of GABA (31,32), decreases K⁺-induced glutamate overflow in prefrontal cortex in rats (33), sequesters reactive aldehydes (34), inhibits primary amine oxidase and can counteract the reduction of glutamate uptake in astrocytes produced by the reactive aldehyde, formaldehyde (35). All of these effects may contribute to its demonstrated neuroprotective actions in animal models such as the global ischemia model in gerbils (34). Interestingly, PLZ has also been reported to reduce some of the motor and behavioral symptoms in the EAE mouse model of multiple sclerosis (36). PLZ is an interesting drug in that it is a substrate and an inhibitor of MAO. A resultant metabolite, phenylethylidenedihydrazine (PEH), is a weak inhibitor of MAO but also inhibits GABA-T and primary amine oxidase and sequesters reactive aldehydes, almost certainly contributing to the neuroprotective actions of the parent drug (37).

Primary amine oxidase (PrAO), formerly called semicarbazide-sensitive amine oxidase (SSAO), is an

enzyme utilizing copper and quinine as cofactors. It catalyzes the oxidation of some primary amines to produce the corresponding aldehyde, hydrogen peroxide and ammonia. Metabolism of methylamine and aminoacetone results in production of the reactive aldehyde metabolites formaldehyde and methylglyoxal, respectively. These aldehydes have been demonstrated to induce β -amyloid β -sheet formation and subsequent fibrillogenesis in vitro (38,39), indicating a possible involvement in the etiology of AD. Increased serum PrAO activity has been reported in complications of diabetes and in congestive heart failure, atherosclerosis, multiple cerebral infarctions and AD (38,39). Co-localization of a strong expression of PrAO with β -amyloid deposits on blood vessels in post-mortem brain samples from patients with AD has been reported (40). It is of interest that PLZ and PEH are relatively potent inhibitors of this enzyme (41,42) and are also capable of sequestering the resultant reactive aldehydes. A number of specific PrAO-inhibitors have been synthesized, and it will be of interest to see their clinical utilization in the future.

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Acknowledgments

The authors are grateful for funding provided by the Canadian Institutes of Health Research (CIHR), the University of Alberta, Alberta Health Services, and the QE II studentship program and to Ashley Radomski for typing this manuscript.

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