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Brain Research Reviews 48 (2005) 379–387

BRAIN RESEARCH REVIEWS

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Review

Mechanism of neuroprotective action of the anti-Parkinson drug rasagiline and its derivatives

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Accepted 9 December 2004

Abstract

The mitochondria are directly involved in cell survival and death. Drugs that protect mitochondria viability and prevent apoptotic cascade mechanisms involved in mitochondrial permeability transition pore (MPTp) will be cytoprotective. Rasagiline (*N*-propargyl-1R-aminoindan) is a novel, highly potent irreversible monoamine oxidase (MAO) B inhibitor, anti-Parkinson drug. Unlike selegiline, rasagiline is not derived from amphetamine, is not metabolized to neurotoxic l-methamphetamine derivative, nor does it have sympathomimetic activity. Rasagiline is effective as monotherapy or adjunct to L-dopa for patients with early and late Parkinson's disease (PD), and adverse events do not occur with greater frequency in subjects receiving rasagiline than those on placebo. Controlled studies indicate that it might have a disease-modifying effect in PD that may be related to neuroprotection. Its S-isomer, TVP1022, is a relatively inactive MAO inhibitor. However, both drugs have similar neuroprotective activities in neuronal cell cultures in response to various neurotoxins and in vivo (global ischemia, neurotrauma, head injury, anoxia, etc.), indicating that MAO inhibition is not a pre-requisite for neuroprotection. Structure activity studies have shown that the neuroprotective activity is associated with the propargyl moiety of rasagiline, which protects mitochondrial viability and MPTp by activating Bcl-2 and protein kinase C (PKC), and down regulating pro-apoptotic FAS and Bax. Rasagiline and its derivatives also process amyloid precursor protein (APP) to the neuroprotective-neurotrophic soluble APP alpha (sAPPα) by PKC and MAP kinase-dependent activation of α-secretase. The neuroprotective activity of propargylamine has led us to develop novel bifunctional neuroprotective iron-chelating MAO-inhibiting drugs possessing propargyl moiety for the treatment of other neurodegenerative diseases.

Theme: Disorders of the nervous system
Topic: Parkinson's disease and other neurodegenerative diseases

Keywords: Parkinson's disease; Neuroprotection; Rasagiline; Propargylamine; Ladostigil; PKC; Bcl-2; Cell death; MAPK

Contents

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doi:10.1016/j.brainresrev.2004.12.027

1. Introduction

The selective monoamine oxidase (MAO) B inhibitor anti-Parkinson drug rasagiline [4,59,60,75] has neuroprotective activity against a variety of neurotoxins and serum-starved cell cultures [13,33,34,78], in animal models of head trauma [20] and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neurotoxicity model of Parkinson's disease (PD) [53] (Tables 1 and 2). The mechanism underlying the neuroprotection by rasagiline has been studied in dopaminergic neuroblastoma SH-SY5Y and PC12 cells in culture, in which apoptosis was induced by *N*-methyl (*R*) salsolinol, the peroxynitrite donor SIN-1, 6-hydroxydopamine, and serum or nerve growth factor (NGF) withdrawal [44]. Rasagiline and related propargylamines suppress the apoptotic cell death cascade initiated by the mitochondria; they prevent pro-apoptotic decline in mitochondrial membrane potential ($\Delta\Psi m$) due to permeability transition and the activation of apoptotic processes including activation of caspase 3, nuclear translocation of glyceraldehyde-3-phosphate dehydrogenase, and nucleosomal DNA fragmentation [74]. In addition, rasagiline increases the expression of anti-apoptotic Bcl-2 and Bcl-xL in SH-SY5Y cells [2]. Structure activity studies have indicated that the propargyl moiety is essential for the anti-apoptotic function of rasagiline [32] and aliphatic-[*N*-(2-heptyl)-*N*-propargylamine] propargylamines [35], since N-propargylamine itself has a similar neuroprotective activity with the same potency in neuronal cell cultures [64] (Fig. 1).

A significant percentage of Parkinsonian subjects develops dementia and 30–40% of Alzheimer type dementia is Lewy body (LB) disease with extrapyramidal syndrome. Recent studies have shown that such patients respond to L-dopa for their extra pyramidal and to cholinesterase (ChE) inhibitors (rivastigmine and galantamine) for the dementia symptoms, respectively [12]. Furthermore, a body of evidence has been provided that a significant number of such patients suffer from depressive illness, which might be a prerequisite to the neurological symptoms. To obviate the problems of giving several drugs, we have developed several bifunctional drugs with the carbamate ChE inhibitory moiety of rivastigmine in the aminoindan structure of rasagiline or selegiline [58]. The purpose was to preserve the neuroprotective and MAO inhibitory activities of rasagiline and also to inhibit acetyl ChE, to increase dopaminergic and cholinergic transmission, respectively [66]. The R-enantiomer of these compounds ladostigil (TV3326, [(*N*-propargyl-(3R)aminoindan-5-yl)-ethyl methyl carbamate]) inhibits AChE and butyrylcholinesterase (BuChE) for a longer time than rivastigime. The introduction of carbamate moiety in this compound resulted in the possession of brain selective type A and B MAO inhibitor activity, with little inhibition of liver and small intestine enzymes [65]. In addition, ladostigil improves memory impairments in scopolamine-treated rats. Interestingly, its S-isomer TV3279, which is also a ChE inhibitor but devoid of MAO inhibitory activity, exerts a similar action in the scopolamine impairment test [65,66]. In this respect, it is similar to the S-isomer of rasagiline, TVP-1022. Its lack of peripheral MAO inhibition results in a modest potentiation of the cardiovascular effect of tyramine, a limited side effect of older generation of non-selective MAO inhibitors [68]. Being a non-selective MAO inhibitor, ladostigil increases brain levels of dopamine, noradrenaline, and serotonin which is responsible for its antidepressant activity, similar to MAO inhibitors and amytriptaline in forced swim test [67]. Both ladostigil and its S-optical isomer TV3279 retain the neuroprotective activities of rasagiline in partially differentiated PC-12 cells deprived of serum and NGF and in in vivo model of PD [65,76]. Treatment with ladostigil and the optical S-isomers TVP1022 and TV3279 is neuroprotective against closed head injury in the mouse and accelerates the recovery of spatial memory [20,66,75]. This action is not related to the MAO B inhibitory activity of rasagiline and ladostigil, since their respective S-isomers, TVP1022 and TV3279, which are devoid of MAO inhibitory activities, have similar neuroprotective activities.

In addition, we have recently shown that rasagiline, as well as its anti-Alzheimer drug derivatives, ladostigil and TV3279 induce the release of the non-amyloidogenic neuroprotective-neurotrophic α-secretase-derived form of soluble amyloid precursor protein (APP) alpha (sAPPα) from SH-SY5Y neuroblastoma and PC12 cells by mitogen-activated protein kinase (MAPK)- and protein kinase C (PKC)-dependent mechanisms [71,72] (Fig. 2).

Table 1
In vivo neuroprotective activity of rasagiline in models of Neurodegenerative diseases [73]

1. MPTP models of Parkinson's diseases
2. Global ischemia
3. Neurotrauma model of head injury
4. Amyotropic lateral sclerosis
5. EAE model of multiple sclerosis
6. Heart ischemia
7. 6-Hydroxydopamine

Table 2
In vitro neuroprotective activity of rasagiline in neuronal cell cultures [73]

Neurotoxic agents	Cell type	
	PC-12	SH-SY5Y neuroblastoma
Glutamate	+	+
SIN-1	ND	+
NM-(*R*)-Salsolinol	ND	+
6-Hydroxydopamine	ND	+
Serum and NGF deprivation	+	ND
Glucose and oxygen deprivation	+	ND
Aβ amyloid aggregate	+	+
α-Synuclein-Fe aggregate	+	+
TNF-α	+	+