

Monoamine oxidase-B inhibitors in the treatment of Alzheimers disease

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Abstract

The monoamine oxidase-B (MAO-B) inhibitor L-deprenyl (Selegiline) is effective in treating Parkinson's disease and possibly Alzheimer's disease, with a concomitant extension of life span. It has been suggested that the therapeutic efficacy of L-deprenyl may involve actions other than the inhibition of the enzyme MAO-B. This article reviews some novel actions of L-deprenyl and suggests that stimulation of nitric oxide (NO) production could be central to the action of the drug. L-Deprenyl induced rapid increases in NO production in brain tissue and cerebral blood vessels. In vitro or in vivo application of L-deprenyl produced vasodilatation. The drug also protected the vascular endothelium from the toxic effects of amyloid- β peptide. Because NO modulates activities including cerebral blood flow and memory, and reduced NO production has been observed in AD brain, stimulation of NO production by L-deprenyl could contribute to the enhancement of cognitive function in AD. MAO-B inhibitors are unique in that they exert protective effects on both vascular and neuronal tissue and thus warrant further consideration in the treatment of vascular and neurodegenerative diseases associated with aging. © 2000 Elsevier Science Inc. All rights reserved.

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1. Introduction

Even though significant advances have been made in delineating the molecular and cellular factors contributing to the etiology of Alzheimer's disease (AD), satisfactory approaches to ameliorate the symptoms or retard the degenerative course of the disease have not been developed. Currently acetylcholinesterase inhibitors are the only drugs approved for treatment of cognitive dysfunction in AD. But acetylcholine enhancing drugs can compensate for only part of the neuronal dysfunction in AD. The enhancement of cognition produced by acetylcholinesterase inhibitors are transient [14], and these drugs do not prevent the progressive loss of neurons in AD. The current emphasis is focused on delaying the disease, as delaying the onset by 5 years could reduce the number of cases by as much as 50%, thus relieving the stress on social and medical resources devoted to caring for patients with dementia.

Among the drugs now moving into clinical trials are several compounds that may modify the progression of AD.

These include anti-inflammatory agents, antioxidants, estrogen, antagonists of apolipoprotein E4, inhibitors of amyloid- β production and aggregation, and monoamine oxidase-B (MAO-B) inhibitors [22]. Evidence that inflammatory processes play a significant role in neuronal damage in AD is supported by the protective effect of nonsteroidal anti-inflammatory drugs (NSAIDs) [23]. But the long term use of NSAIDs is associated with undesirable side effects, and so novel anti-inflammatory agents devoid of these effects are currently being explored. A large number of studies have shown that estrogen has a protective effect on the development of Alzheimer's disease in postmenopausal women [34,36]. The compliance rates for estrogen are dismal due to concerns about increased risk for breast cancer and endometrial hyperplasia. Several other drugs targeting A β , TAU, and apo E4 are currently being explored and will have to await extensive clinical trials.

2. MAO-B inhibitors

MAO-B inhibitors might offer an alternative for AD therapy as they have a long history of clinical use and are considered safe and nontoxic. This article evaluates the

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current evidence indicating a role for MAO-B inhibitors in the treatment of AD and explores the concept that actions other than the inhibition of the enzyme MAO-B may contribute to the therapeutic efficacy of the drug. A significant portion of the clinical data and biological actions of MAO-B inhibitors is based on the effects of L-deprenyl. The actions of a limited number of other MAO-B inhibitors also will be discussed.

MAO exists in two forms, MAO-A and MAO-B, coded by two distinct gene loci [16,30], with different patterns of tissue distribution. MAO-A preferentially deaminates serotonin (5-HT) and is more sensitive to inhibition by clorgyline, whereas MAO-B deaminates preferentially β -phenylethylamine and is inhibited by drugs such as L-deprenyl. The optical isomer D-deprenyl is biologically less active than L-deprenyl. Clinically the most important monoamine that is elevated by L-deprenyl is dopamine, which is a substrate for both MAO-A and B. L-Deprenyl (selegiline) has been used as an effective adjuvant to L-DOPA in the treatment of Parkinson's disease. It has also been reported that L-deprenyl by itself can delay the onset of disability associated with early untreated Parkinson's disease [28]. L-Deprenyl also prevents MPTP-induced neurotoxicity and Parkinson-like symptoms in animals [12]. Chronic administration of low doses of L-deprenyl may cause some of its effects by nonselective inhibition of MAO-A. The antidepressant activity of L-deprenyl has been attributed to inhibition of MAO-A in addition to MAO-B.

3. Other actions of MAO-B inhibitors

Several reported actions of MAO-B inhibitors, particularly L-deprenyl, suggest the possibility that properties other than the inhibition of MAO-B may play a significant role in the biological effects of these compounds. The efficacy of L-deprenyl in the treatment of Alzheimer's disease [6,35], as well as increased longevity and sexual performance [17,3], particularly support the contention that novel actions of MAO-B inhibitors may be involved.

The majority of studies have indicated a beneficial effect of L-deprenyl in Alzheimer's disease (AD) [17,29], whereas a few studies failed to note any improvement [9]. Several mechanisms have been proposed to account for the therapeutic effects of L-deprenyl in AD. The enhancement of central monoaminergic systems through inhibition of MAO-B is considered to be the prominent effect of L-deprenyl. MAO-B is the predominant form of MAO in human brain. In addition to loss of cholinergic neurons, there is a decrease in the levels of the monoamines dopamine, norepinephrine, and serotonin in the brains of AD patients compared with normal aging brain. [27]. MAO-B activity is significantly increased in the platelets and selected brain regions of AD patients [17]. MAO-B inhibitors may act by both reducing the formation of oxygen radicals

and by preventing the breakdown and thus elevating the levels of monoamines in the brains of AD patients.

It has been suggested that the efficacy of L-deprenyl may result from its conversion to stimulants L-amphetamine and L-methamphetamine. But D-deprenyl, which is converted to D-amphetamine, a more potent stimulant, shows less biological activity compared to L-deprenyl [25]. The amphetamine-like activity of L-deprenyl is further discounted by the efficacy of MAO-B inhibitors Lazabemide and Rasagiline [15,43], which are devoid of amphetamine metabolites. Other actions of L-deprenyl that may contribute to the neuroprotective property include the following: antagonism of NMDA receptors by elevated levels of N-acetylated polyamines [11], induction of antioxidant enzymes such as superoxide dismutase and catalase [19], and anti-apoptotic activity [10,41].

4. Nitric oxide

The role of nitric oxide as a major intracellular molecule mediating immunological, vascular, and neuronal actions has been clearly established. NO or a labile NO-containing compound is considered to be the endothelium-derived relaxing factor and maintains the vascular tone. Many of the cellular actions of NO involve the enzyme guanylate cyclase and production of the intracellular messenger cyclic GMP [5]. In addition to functioning as a neurotransmitter in the peripheral and central nervous system, NO plays a critical role in cerebral circulation. It is the major second messenger mediating the activation of glutamergic/NMDA pathway [31]. NO also has a role in the cellular basis of memory by facilitating long-term potentiation (LTP) [4,31]. NO also mediates some of the effects of glutamate/NMDA receptor pathway on neuronal functioning and synaptic plasticity [4].

A decrease in NO production in the CNS of both AD and Parkinson's disease patients has been reported [18]. This has been attributed to decreased levels of tetrahydrobiopterin (BH₄), an essential cofactor for the enzyme NO synthase [42]. Thus there seems to be a reduced synthesis of NO in neurodegenerative diseases, and enhanced production of NO would be beneficial in these conditions. Novel compounds to manipulate the NO activity in the brain are currently being explored in the treatment of neuropsychiatric conditions and the sequelae of traumatic brain injury.

5. L-Deprenyl and NO

We recently demonstrated that vascular damage induced by A β may be an early event in the pathology of AD, and this free radical-mediated damage was prevented by antioxidants [37,38]. Because L-deprenyl has been shown to have a protective effect against progression of neurodegenerative diseases, we investigated the action of this com-

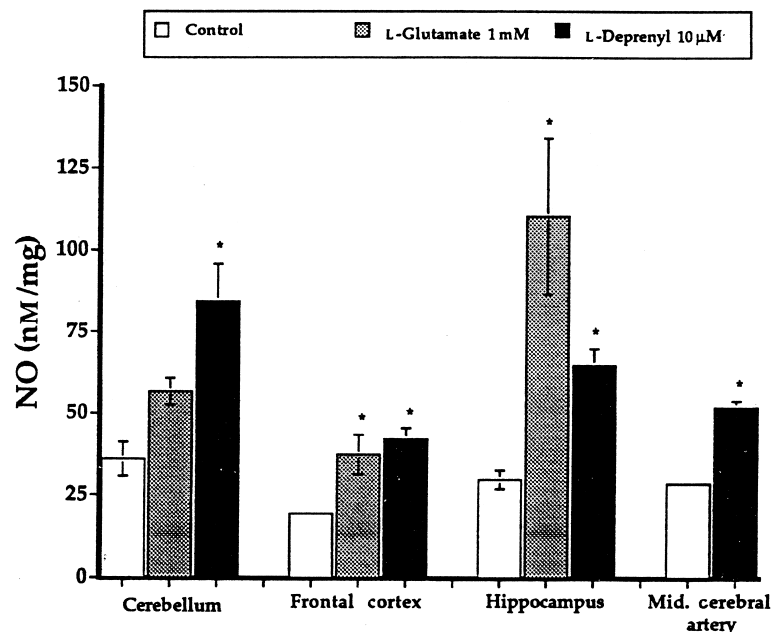


Fig. 1. Stimulation of NO production by 1 mM L-glutamate and 10 μ M L-deprenyl in freshly dissected bovine brain regions and mid-cerebral artery. Brain tissue or blood vessel segments were incubated for 30 min at 37°C alone or in presence of the various compounds. Asterisks indicate that the values are significantly different from controls ($P < 0.05$). Each data point represents mean \pm SEM from three or more different tissue samples.

pound on NO production, vasoactivity, and A β -induced vascular damage.

In several regions of the bovine brain and isolated middle cerebral artery, L-deprenyl stimulated the production of NO (Fig. 1). In all brain regions except the hippocampus, the enhancement of NO production by 10 μ M L-deprenyl was more than that produced by 100-fold higher concentration of the endogenous nitric oxide synthase (NOS) stimulant

L-glutamate. The induction of NO was rapid, with significant increases noted in one minute [39]. L-Deprenyl also produced rapid dilation of cerebral and peripheral blood vessels when treated in vitro or in vivo (Fig. 2) [39,40]. The endothelium-dependent relaxation by low doses of L-deprenyl was inhibited by the NOS inhibitor L-NAME. High concentrations of the drug also directly relaxed the vascular smooth muscle through NO-independent mechanism. Fig. 3

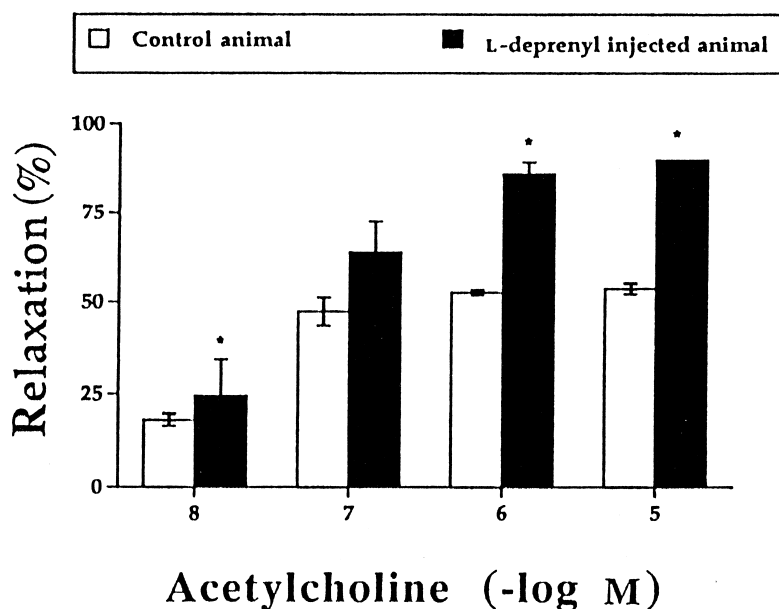


Fig. 2. In vivo vascular action of L-deprenyl. Aorta were isolated 1 h after treating rats with 10 mg of L-deprenyl. Enhancement of vasodilation by L-deprenyl is indicated by the increased response to the vasodilator acetylcholine.

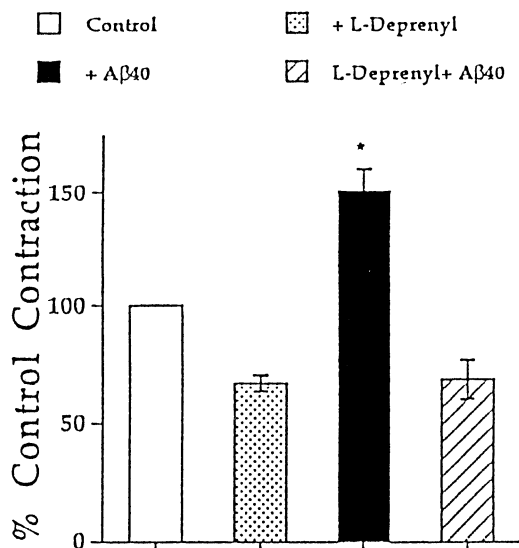


Fig. 3. Attenuation of amyloid β -induced endothelial dysfunction in bovine mid-cerebral artery. L-Deprenyl significantly blunted the enhanced vasoconstriction induced by A β . Values are expressed as percentage of vasoconstriction by 5-HT under control conditions. Each data point represents the mean \pm SEM from four or more experiments.

illustrates the ability of L-deprenyl to attenuate vascular damage produced by the Alzheimer protein amyloid- β . Similar actions of several other MAO-B inhibitors were also noted in our laboratory. Fig. 4 demonstrates the stimulation

of NO by L-deprenyl and various vascular and neuronal action of NO involved in cytoprotection.

6. Discussion

The protective effect of L-deprenyl in Parkinson's disease and Alzheimer's disease as well as enhanced longevity and improved sexual performance cannot be accounted for by the inhibition of the enzyme MAO-B alone. Even though other biological actions of MAO-B inhibitors are actively being explored, our finding that L-deprenyl may enhance NO-mediated mechanisms in vascular and neural tissue (Fig. 4) may partly account for the therapeutic efficacy of the drug and suggests novel applications. Putative cellular targets of NO as well as its potential physiologic roles in morphogenesis and synaptic plasticity need to be considered while using MAO-B inhibitors.

NO also has a cytotoxic role in host defense mechanisms and degenerative conditions. The radical nature of NO alone is not sufficient to explain its cytotoxicity. NO reacts with the oxygen radical superoxide to produce toxic peroxynitrite, a powerful oxidant that further decomposes to hydroxyl radicals. Hydroxyl radicals are highly reactive and biologically destructive. The possibility that neurodegenerative disorders may reflect a NO/superoxide imbalance has potential therapeutic implications. A relative excess of NO over O₂ is protective to the tissue [32]. MAO-B inhibitors

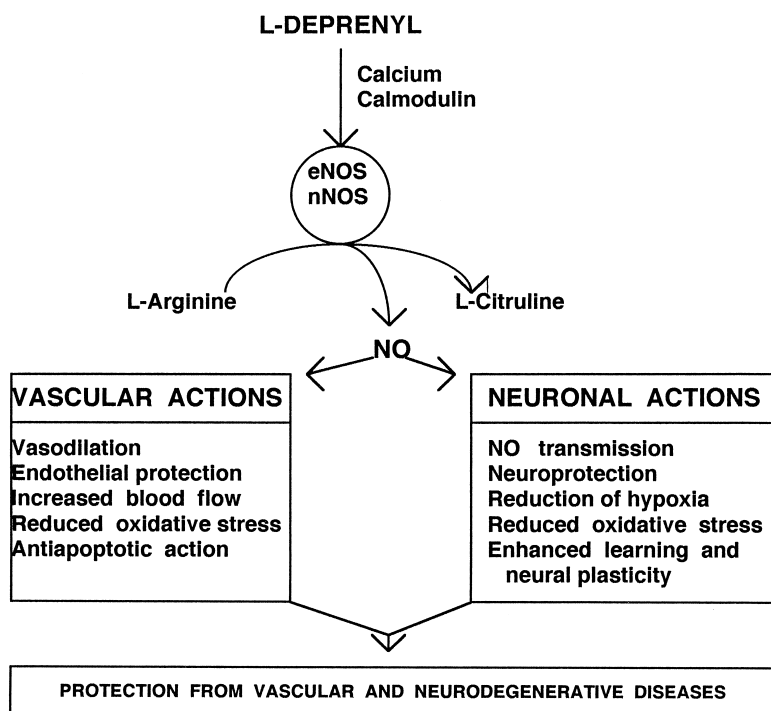


Fig. 4. Schematic representation of the stimulation of NO production by L-deprenyl and protection from degenerative diseases through vascular and neuronal actions. L-Deprenyl may activate endothelial (eNOS) or neuronal (nNOS) nitric oxide synthase through calcium/calmodulin mediated effects. Subsequently, NO exerts a number of vascular and neuronal actions as shown. These NO-mediated actions along with MAO-B inhibition and other reported properties of the compound accords protection from vascular and neurodegenerative diseases.

may shift the equilibrium in favor of NO, thus diminishing the oxidative stress. These compounds may also rectify the reported deficiency of NO in AD by stimulating the production of NO.

L-Deprenyl is one of the compounds that is capable of delaying functional deterioration in neurodegenerative diseases [29]. The renewed interest in MAO-B inhibitors is based on the possibility that they could be prototypic agents with neuroprotective property and also enhance longevity [41,3]. The current view is that endothelial dysfunction underlies many aspects of vascular disease, beginning with the initiation and progression of the pathological process. Endothelial dysfunction and hypertension contribute to the impairment of cognitive function in old age [33]. NO plays a critical role in cerebral circulation. Impaired nitric oxide-mediated vasodilation may contribute to cerebral ischemia in several pathological conditions [8,21]. Several reports have shown a consistent relationship between neurodegeneration and vascular pathology contributed mainly due to endothelial dysfunction. A variety of vascular diseases such as hypertension, atherosclerosis, coronary artery disease, vasospasm, stroke, and cerebral ischemia [7,13,24] often precede or accompany the onset of AD. It has been previously reported that mid-life systolic blood pressure is a significant predictor of reduced cognitive function in later life and antihypertensive agents have been reported to produce some improvement in AD symptoms [20]. By stimulating NO production, L-deprenyl will ameliorate endothelial dysfunction associated with aging, menopause, and cardiovascular disease and AD. The blood–brain barrier is composed of endothelial cells, and by protecting the endothelium, L-deprenyl would also preserve the integrity of the blood–brain barrier. Through NO-mediated vasodilation, MAO-B inhibitors could improve the reduction in cerebral blood flow observed in AD and PD [26] and enhance cognitive function by facilitating neuronal activity.

Deposition of A β and other cytotoxic macromolecules have been implicated as mediators of oxidative and inflammatory damage to the neurons in the brains of AD patients. Recently we demonstrated that low levels of soluble A β produces rapid endothelial dysfunction through the production of oxygen radicals and also induces an inflammatory reaction [36].

The A β -induced vascular dysfunction could be an early event relative to the development of neurodegenerative diseases. The prevention of A β toxicity to endothelial cells by L-deprenyl represents another mechanism whereby MAO-B inhibitors may provide cytoprotection against the progression of neurodegenerative diseases.

The role of oxidative stress in degenerative diseases may account for the cumulative damage associated with the delayed onset and protracted course of these conditions.

Free radical generation by A β or other noxious stimuli could contribute to an imbalance between the production of nitric oxide and oxygen radicals and precipitate an oxidative stress [32]. The rapid stimulation of NO production in brain

tissue and blood vessels by MAO-B inhibitors indicates the activation of the constitutive form of NO synthase, which could alleviate the oxidative stress and prevent degenerative changes also by ensuring adequate tissue perfusion. The facilitation of LTP and synaptic plasticity by NO might enhance cognitive function. The vasodilatory actions of NO and cyclic GMP would enhance cerebral blood flow, increase tissue perfusion, and ameliorate ischemic damage to surrounding neurons.

Selegiline readily crosses the blood brain-barrier, has minimal adverse effects in the elderly, and can be administered orally or transdermally [2]. A tyramine-free diet is not required for doses up to 10 mg per day. But patients should be warned about the possibility of hypertensive crisis. The major side effect of L-deprenyl is orthostatic hypotension.

L-Deprenyl is contraindicated in patients taking selective serotonin reuptake inhibitors, tricyclic antidepressants, meperidine, or receiving general anesthesia. because of a risk of severe central nervous system toxicity. The new generation of MAO-B inhibitors such as Lazabamide and Rasagiline are devoid of amphetamine-like stimulant effect of L-deprenyl. But they have not yet been approved for clinical use. In view of the vasculoprotective actions of L-deprenyl, it may have a role in the treatment of vascular dementia.

Multiple factors contribute to the pathology of AD, and the disease process may involve several cellular and molecular aberrations. So it is a rather simplistic therapeutic approach to use only drugs such as acetylcholinesterase inhibitors that will impact a single neurotransmitter system. The challenge is to identify compounds that not only will enhance cognitive function but also will prevent, retard, or halt the progression of AD. In this regard, compounds such as MAO-B inhibitors, which possess multiple biochemical actions and have protective effects on both vascular and neuronal tissue, need further consideration in the treatment and prevention of neurodegenerative diseases.

References

- [1] Adolfsson R, Gottfries CG, Olrelund L. Increased activity of brain and platelet MAO-B in dementia of Alzheimer type. *Life Sci* 1980; 27:1029–34.
- [2] Barrett JS, Hochadel TJ, Morales RJ, et al. Pharmacokinetics and safety of a selegiline transdermal system relative to single dose oral administration in the elderly. *Am J Therapeut* 1996;3:688–98.
- [3] Birkmayer WJ, Knoll P, Riederer P. Increased life expectancy resulting from the addition of L-deprenyl to madopar treatment in Parkinson's disease: a long term study. *J Neur Transm* 1985;64:113–27.
- [4] Bliss TVP, Collingridge GL. A synaptic model of long term potentiation in the hippocampus. *Nature* 1993;361:31–9
- [5] Bredt DS, Snyder SH. Nitric oxide, a novel neuronal messenger. *Neuron* 1992;8:3–11.
- [6] Burke WJ, Roccaforte WH, Wengel SP, et al. L-Deprenyl in the treatment of mild dementia of the Alzheimer type: results of a 15 month trial. *J Am Geriatr Soc* 1993;41:1219–25.

- [7] Esiri MM, Nagy Z, Smith MZ, Barneston L, Smith AD. Cerebrovascular disease and threshold for dementia in the early stages of Alzheimer's disease. *Lancet* 1999;354:919–20.
- [8] Faraci FM, Brian JE. Nitric oxide and cerebral circulation. *Stroke* 1994;25:692–703.
- [9] Freedman M, Rewilak D, Xerri T, et al. L-Deprenyl in Alzheimer's disease. Cognitive and behavioral effects. *Neurology* 1998;50:660–8.
- [10] Gelowitz DL, Patterson AI. neuronal sparing and behavioral effects of the antiapoptotic drug (-) deprenyl following kainic acid administration. *Pharmacol Biochem Behav* 1999;62:255–62.
- [11] Gerlach M, Reiderer P, Youdim MBH. The molecular pharmacology of L-deprenyl. *Eur J Pharmacol* 1992;226:97–108.
- [12] Heikkila RE, Hess A, Duvoisin RC. Dopaminergic neurotoxicity of MPTP in mice. *Science* 1984;224:1451–3.
- [13] Hoffman A, Ott A, Breteler MM, et al. Atherosclerosis, apolipoprotein e, and prevalence of dementia and Alzheimer's disease in the Rotterdam study. *Lancet* 1997;349:151–4.
- [14] Howell GJ. Use of tacrine Hcl (Cognex) in clinical practice. *Acta Neurol Scand (Suppl)* 1996;16S:123–7.
- [15] Huang W, Chen Y, Shohami E, Weinstock. Neuroprotective effect of rasaligine, a selective monoamine oxidase-B inhibitor, against closed head injury in mouse. *Eur J Pharmacol* 1999;366:127–35.
- [16] Knoll J, Magyar K. Some puzzling pharmacological effects of monoamine oxidase inhibitors. *Adv Biochem Psychopharmacol* 1972;5:3939–408.
- [17] Knoll J, Dallo J, Yen TT. Striatal dopamine, sexual activity and life span longevity of rats treated with L-deprenyl. *Life Sci.* 1989;45:525–31.
- [18] Kuiper MA, Visser JJ, Bergmans PLM, Scheltens P, Wolters EC. Decreased cerebral fluid nitrate levels in Parkinson's disease, Alzheimer's disease and multiple system atrophy patients. *J Neurol Sci* 1994;121:46–9.
- [19] Kushleika J, Checkoway H, Woods JS, et al. Selegiline and lymphocyte superoxide dismutase activities in Parkinson's disease *Ann Neurol* 1996;39:378–81.
- [20] Launer LJ, Masaki K, Petrouitch H, et al. The association between mid-life blood pressure levels and late-life cognitive function. *J Am Med Assoc* 1995;274:1846–51.
- [21] Leys D, Henon H, Pasquier F. Alterations of blood-brain barrier and glial cells in white matter lesions in cerebrovascular and Alzheimer's disease patients. *Stroke* 1997;28:874–6.
- [22] Marx J. Searching for drugs that combat Alzheimer's. *Science* 1996;273:50–3.
- [23] McGeer PI, Scholtzer M, McGeer EG. Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: a review of 17 epidemiologic studies. *Neurology* 1996;47:425–32.
- [24] Moody DM, Brown WR, Challa VR, Ghazi-Birry HS, Reboussin DM. Cerebral microvascular alterations in aging, leukoaraiosis, and Alzheimer's disease. *Ann NY Acad Sci* 1997;826:103–16.
- [25] Nickel R, Schultze G, Szelenyi I. Effect of enantiomers of deprenyl (Selegiline) and amphetamine on physical abuse liability and cortical electrical activity in rats. *Neuropharmacology* 1990;29:983–92.
- [26] Oishi MN, Mochizuki Y, Hara M, et al. Effects of i.v. L-dopa on P300 and regional cerebral blood flow in Parkinsonism. *Intern J Neurosci* 1996;85:147–54.
- [27] Olfsson J, Gottfries CG, Roos BE. Changes in brain catecholamines in patients with dementia of Alzheimer type. *Br J Psychiatr* 1979;134:216–23.
- [28] Parkinson study group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 1993;328:176–83.
- [29] Sano M, Ernesto C, Thomas RG, et al. A controlled trial of Selegiline, alpha tocopherol or both as treatment for Alzheimer's disease. *N Engl J Med* 1997;336:1216–22.
- [30] Shih JC. Molecular basis of human MAO-A and MAO-B. *Neuropsychopharmacology* 1991;4:1–7.
- [31] Southam E, Garthwaite J. Nitric oxide cyclic GMP signalling pathway in rat brain. *Neuropharmacology* 1993;32:1267–77.
- [32] Stamler JS. Alzheimer's disease: a radical vascular connection. *Nature* 1996;380:108–11.
- [33] Starr JM, Whalley J, Inch S, Shering A. Blood pressure and cognitive function in healthy old people. *J Am Geriatr Soc* 1993;41:753–6.
- [34] Tang M-X, Jacobs D, Stern Y, Marder K, Schofield P, et al. Effect of estrogen during menopause on risk and age at onset of Alzheimer's disease. *Lancet* 1996;348:429–32.
- [35] Tariot PN, Cohen RM, Sutherland T, et al. L-Deprenyl in Alzheimer's disease preliminary evidence for behavioral change with MAO-B inhibition. *Arch Gen Psychiatr* 1987;44:427–33.
- [36] Thomas T, Rhodin JAG, Sutton ET, et al. Estrogen protects peripheral and cerebral blood vessels from toxicity of Alzheimer peptide amyloid β and inflammatory reaction. *J Submicroscop Cytol Pathol* 2000;1:32–41.
- [37] Thomas T, Thomas G, McLendon C, et al. β -amyloid-mediated vasoactivity and endothelial dysfunction. *Nature* 1996;380:168–71.
- [38] Thomas T, Sutton ET, McLendon C, Thomas G. Cerebrovascular endothelial dysfunction mediated by β -amyloid. *Neuroreport* 1997;8:1387–91.
- [39] Thomas T, McLendon C, Thomas G. L-Deprenyl: nitric oxide production and dilation of cerebral blood vessels. *Neuroreport*. 1998;9:2595–2600.
- [40] Thomas T, McLendon C, Thomas G. L-Deprenyl protects vascular endothelium from amyloid- β toxicity and stimulates production of nitric oxide. In: Iqbal K, Swaab DF, Winbald B, Wisniewski HM, editors. *Alzheimer's disease and related disorders*. John Wiley and Sons Ltd, 1999. p. 493–500.
- [41] Wakako M, Makoto N. Neuroprotection by (-) deprenyl and related compounds. *Mech Ageing Dev.* 1999;111:189–200.
- [42] Werner-Felmayer G, Werner ER, et al. Pteridine biosynthesis in human endothelial cells: impact on nitric oxide-mediated formation of cyclic GMP. *J Biol Chem* 1993;268:1842–6.
- [43] Yu PH, Davis BA, Durden DA, et al. Neurochemical and neuroprotective effects of some aliphatic propargylamines: new selective non-amphetamine-like MAO-B inhibitors. *J Neurochem* 1994;697–704.