**International Journal of Medicine Research**
**ISSN: 2455-7404; Impact Factor: RJIF 5.42**
**www.medicinesjournal.com**
**Volume 1; Issue 4; September 2016; Page No. 44-49**

# Pharmacology of Rasagiline

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**Abstract**
Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting 1% to 2% of people older than 60 years. Treatment of Parkinson's disease (PD) consists of symptomatic treatments however neuroprotective strategies have remained elusive. Rasagiline (N-propargyl-1R-aminoindan) is a new, effective and selective monoamine oxidase-B inhibitor. Rasagiline was shown to have neuroprotective properties in various in vitro and in vivo models independently of MAO-B inhibition. Rasagiline inhibits MAO-B more effectively than selegiline and has the advantage of once daily dosing. However, in contrast to selegiline, rasagiline is not metabolized to amphetamine like products, which cause adverse side effects and neuronal cell death. Therefore, rasagiline, whose neuroprotective properties are basic by the production of neurotoxic metabolites, may have an advantage over selegiline in the treatment of Parkinson's disease (PD). Rasagiline also show the Protective effect in Aminoglycoside Ototoxicity.

**Keywords:** Rasagiline, Parkinson's disease (PD)

## Introduction: Rasagiline

Rasagiline (N-propargyl-1(R)-aminoindan) is an aromatic propargylamine and highly effective selective irreversible monoamine oxidase (MAO)-B inhibitor, indicated for the treatment of motor symptoms in both initial and developed for the treatment of Parkinson's disease. Like selegiline, the only selective MAO-B inhibitor currently in clinical use for the treatment of Parkinson's disease, rasagiline exerts symptomatic anti-Parkinsonian effect by blocking the oxidative metabolism of dopamine, thus prolonging its physiological action in control of movement (Bonneh-Barkay D *et al.*, 2005) [6]. Several preclinical studies have established that rasagiline exerted neuroprotective effects against various neurotoxins in both cell cultures and animal Parkinson's disease (PD) models and in a variety of non-Parkinson's disease (PD) related models (Weinreb O *et al*., 2015) [7]. Rasagiline also includes a propargyl ring within its molecule structure and like other propargylamines it has been shown to possess anti-apoptotic activity. In vitro rasagiline prevents pre-apoptotic swelling of mitochondria, caspase-3 activation, activation of nuclear PARP-1, translocation of GADPH and nucleasomal DNA fragmentation (Stefanova N *et al*., 2008) [8]. Considerable attention has been recently attracted by rasagiline [R(+)-N-propargyl-1- aminoindane], the most potent propargylamine, which, although structurally related to selegiline, is different in that it is not metabolized to amphetamine and metamphetamine. Phase III clinical studies have already reported significant efficacy of rasagiline for Parkinson's disease (PD) treatment, either as addition therapy to L-Dopa or as monotherapy in early Parkinson's disease (PD) (Blandini F *et al*., 2004) [9]. Rasagiline has recently been shown to reduce glutamate toxicity in cultured hippocampal neurons and to prolong survival of cultured, serum-deprived rat fetal mesencephalic cells (Huang W *et al*., 1999) [10]. Recent studies have shown that treatment with rasagiline protects against serum and nerve growth factor withdrawal induced death in PC-12 cells and increases the expression of glial cell line-derived neurotrophic factor in human dopamine- derived neuroblastoma cells through the activation of the nuclear transcription factor NF-nB (Huang W *et al*., 1999) [10]. In pharmacokinetic studies, it is evident that rasagiline can reach concentrations in the brain equal with its neuroprotective activity *in vitro* and *in vivo* (Youdim MB *et al*., 2007) [11]. Rasagiline is rapidly absorbed and achieves the peak plasma concentration within 30 min; however is has a low oral bioavailability (36%) with a very short elimination half-life (0.6–2 h). These bio pharmaceutic and pharmacokinetic characteristics and its ability in a chronic disease such as Parkinson's disease (PD) make rasagiline a suitable candidate for the development of a controlled release system. The use of decomposable and biocompatible microspheres for the controlled release of rasagiline could represent an attractive alternative to its oral administration. The system would not require its removal once the treatment is finished and controlled drug release from the micro particles will allow decreasing the number of administrations there by leading to a better patient obedience and possibly a reduction of adverse side effects (Fernandez M *et al*., 2011) [12]. Rasagiline undergoes almost complete biotransformationin the liver, and two main pathways are elaborate in the metabolism of rasagiline, which include N-dealkylation and orhydroxylation to yield 1-aminoindan (AI), 3-hydroxy-N-propargyl-1-aminoindan (3-OH-PAI) and 3-hydroxy-1-aminoindan (3-OH-AI). In vitro experiments show that both pathways are dependent on the cytochrome P450 (CYP) system, with CYP1A2 as the major isoenzyme involved in the rasagiline metabolism (Wang T *et al*., 2016) [13].

## Neuroprotective and neurorestorative

Rasagiline exerts its primary effect in Parkinson's disease (PD) likely by MAO-Binhibition, resulting in a slower metabolism of endogenous andexogenous dopamine (DA), thus providing symptomatic benefits. In addition, rasagiline

has been shown in preclinical studies, to have broad neuroprotective/neurorestorativeactivities against a variety of neurotoxins in in vivo and neuronal cell cultures models of neurodegeneration, which may contribute to its possible disease-modifying activity (Bonneh-Barkay D *et al*., 2005) [6]. More importantly, rasagiline was found to possess an in vivo neurorestorative activity in substantia nigra pars compacta (SNpC) neurons, when given post-treatment with MPTP or the proteasome inhibitor, lactacystin (Weinreb O, *et al*., 2010) [16, 17]. In in vitro studies, the protective activity of rasagiline includes attenuation of cell death in partially differentiated rat pheochromocytoma PC-12 cells deprived of oxygen–glucose, serum and nerve growth factor (NGF), and neuroprotection against theendogenous neurotoxin N-methyl-(R)-salsolinol (N-M-(R)-Sal) 6-hydroxydopamine (6-OHDA),3-morpholinosydnonimine (SIN-1), ethanol and glutamate toxicity in human SH-SY5Y neuroblastoma cells (Weinreb O *et al*., 2010) [16, 17]. Structure–activity studies provide evidence that the N-propargyl moiety of rasagiline and selegiline promotes neuronal survival via similar neuroprotective/neurorescue pathways, thus enlightening the importance of this moiety for the novel activities of rasagiline (Bonneh-Barkay D *et al*., 2005) [6]. Indeed, we have shown that propargylamine significantly attenuated cell death induced by serum deprivation in neuronal cells. The potent MAO-B inhibitory activity of rasagiline, which resides in the interaction of its N-propargyl moiety with FAD cofactor of the enzyme is not a pre-requisite for its neuroprotective activity (Weinreb O *et al*., 2010) [16, 17]. Indeed, this is supported by both observations that the putative neuroprotective mechanism of rasagiline and selegiline was established in cell cultures that do not contain MAO-B and the finding that the (S)- isomer of rasagiline, TVP1022, which lacks of MAO-B inhibitory activity, exerts neuroprotective effects similar to those of rasagiline and selegiline (Amit T and Youdim MB, 2004) [18].

In addition, recent neuroprotective studies established that the major metabolite of rasagiline, 1-(R)-aminoindan possesses useful pharmacological effects in animal and cell culture models (Bonneh-Barkay D *et al*., 2005) [6]. Definitely, 1-(R)-aminoindan exerted neuroprotective properties against the Parkinsonian neurotoxin, 6-OHDA in PC-12 cells, prohibited cell death in a cytotoxic model of human neuroblastoma SK-N-SH cells in high density culture and comprised a significant neuroprotective effect against hydrogen peroxide induced damage in SH-SY5Y neuroblastoma cells and rat primary cortical neuron (Amit T and Youdim MB, 2004) [18].

**Neuroprotection by rasagiline in thiamine deficient rats**

Thiamine deficiency (TD) in rats is a model of chronic impairment of oxidative metabolismleading to neuronal loss. TD rats exhibit neuropathological, behavioral and cognitive abnormalities. Thiamine (vitamin B1) as pyrophosphate is an essential cofactor for the mitochondrial enzymes α-ketoglutarate dehydrogenase complex, transketolase and pyruvate dehydrogenase complex (Gibson *et al*., 1984; Butterworth *et al*., 1986; Giguère and Butterworth, 1987). Thiamine deficiency (TD) severely affects the activity of these enzymes, inhibiting the conversion of pyruvate into acetyl CoA and α-ketoglutarate into succinate (Bubber *et al*., 2004). The α-ketoglutarate dehydrogenase complex is a key and rate-controlling enzyme of the citric acid cycle and is reduced in neurodegenerative diseases (Gibson *et al*., 2005, 1999; Gibson and Zhang, 2002).

Inactivation of this enzyme by factors elevated in oxidative stress such as $H_2O_2$ and peroxynitrite supports its role in degenerative processes. The neurological disorder most clearly associated with TD in humans is the Wernicke–Korsakoff syndrome (WKS). It is a behaviorally and pathologically heterogenous disorder most commonly observed in malnourished, chronic alcoholics. Patients display deficits in neuropsychological tests ranging in severity from spared cognitive ability to amnesia with mild to moderate cognitive deficits to dementia. Thinning of the cortex and loss of white matter are often seen and are attributed to heavy alcohol consumption. Lesions in the medial thalamus and mammillary bodies are also common and are attributed to TD. These diencephalic lesions damage nuclei and tracts of memory systems causing the amnesia in WKS (Langlais and Savage, 1995). The most common animal model of TD and WKS is the nonsurgical rodent model termed pyrithiamine-induced TD (Troncoso *et al*., 1981). In this model, rats are free-fed thiamine deficient chow and given daily injections of pyrithiamine hydrobromide. Pyrithiamine inhibits thiamine metabolism as well as its blood–brain transport (Rindi *et al*., 2003) resulting in a sequence of neurological disturbances, such as ataxia and inhibition of the righting reflex, which are alleviated only when thiamine is restored (Pitkin and Savage, 2001). The range of chronic brain lesions is very similar to those of WKS (Langlais *et al*., 1996).

Rasagiline, N-propargyl-1-(R) aminoindanmesylate is used for the symptomatic treatment of Parkinson's disease. Its predecessor is selegilinewhich shares with it thepropargylamine structure. Both rasagiline and selegiline are selective MAO-B inhibitors, thus providing the rationale for their use in Parkinson's disease (Finberg *et al*., 1999). Rasagiline is metabolized to aminoindan (Chen and Swope, 2005), which has demonstrated neuroprotective activity (Bar Am *et al*., 2004) while selegiline is metabolized to neurotoxic L-methamphetamine (Abu-Raya *et al*., 2002; Reynolds *et al*., 1978). Selegiline was investigated as a disease-modifying agent in several models of evoked neuropathy including thiamine deficient rats (Todd and Butterworth, 1998) and showed varying levels of neuroprotection (Seniuk *et al*., 1994; Tatton *et al*., 1994; Semkova *et al*., 1996; Mytilineou *et al*., 1997) [31, 29]. In long-term disease modification of Parkinson's disease, beneficial effects were demonstrated (Stocchi and Olanow, 2003; Fernandez and Chen, 2007). However the mechanism has not been resolved.

Rasagiline has been evaluated as a neuroprotective agent in several whole animal rodent models. In permanent focal ischemia in the rat, it decreased infarct size and restored motor function (Speiser *et al*., 1999, 2007). It restored cognitive function in post-natal anoxia lesioned rats, as well as in adult and senescent hypoxia lesioned rats (Speiser *et al*., 1998a,b). In spontaneously hypertensive rats (SHR), it prevented spontaneous hypothalamic cell death (Eliash *et al*., 2005). In strokeproneSHR, it increased survival and delayed or prevented the incidence of stroke (Eliash *et al*., 2001). In closed head injury in mice, it restored motor and cognitive function (Huang *et al*., 1999) [10] as well as in a transgenic model of multiple system atrophy (Stefanova *et al*., 2008) [8].

Mechanism-oriented studies have also been performed in various cell cultures (Abu-Raya *et al*., 1999; Maruyama *et al*., 2001a, 2002a; Yi *et al*., 2006). Rasagiline and related propargylaminessuppressed the apoptotic cell death cascade initiated at the mitochondria (Akao *et al*., 2002a). The proapoptoticdecline in mitochondrial membrane potential was prevented and the following apoptotic processes were inhibited: activation of caspase-3; nuclear translocation of glyceraldehyde-3- phosphate dehydrogenase; and nucleosomal DNA fragmentation (Maruyama *et al*., 2001a,b; 2002b; Youdim and Weinstock, 2002) [14]. In addition, rasagiline increased the expression of antiapoptotic Bcl-2 and Bcl-XL in SH-SY5Y cells (Akao *et al*., 2002b). Increasing experimental evidence implicates the propargylamine group in neuroprotection (Youdim *et al*., 2005; Weinreb *et al*., 2005).

The neuroprotective effects of propargylamine MAO-B inhibitors in the whole animal using TD as a model of chronically impaired oxidative metabolism correlating pathology and function. In pyrithiamine-induced TD, advancing age increases the vulnerability to the acute and chronic effects (Pitkin and Savage, 2001, 2004). Therefore the drugs' neuroprotective effects were studied in both middle-aged and young rats was limited to 17 days which was the cut-off time.

Rasagiline has been shown to have neuroprotective properties against Aβ1-42-induced neurotoxicity (Yogev-Falach *et al*., 2003). In TD, altered metabolism of amyloid precursor protein and nuclear translocation of carboxy-terminal fragments have been demonstrated in the vulnerable thalamus but not in the cortex which is more resistant to TD-induced neurodegeneration (Karuppagounder *et al*., 2008). Mitochondrial induction of apoptosis has been associated with neurodegeneration. The mitochondrial membrane potential provides a sensitive measure of mitochondrial function (Huang *et al*., 2004) [10]. In apoptosis, a neurotoxic challenge promotes the opening of the mitochondrial permeability transition pore (MPTp) complex causing a decline in mitochondrial membrane potential (ΔΨm) followed by rupture of the mitochondrial outer membrane and subsequent release of proapoptotic catalysts, such as caspase 3, glyceraldehyde-3- phosphate dehydrogenase (GAPDH), mitochondrial cytochrome C, and poly(ADP-ribose) polymerase (Susin *et al*., 1999; Akao *et al*., 2002a ). In isolated cell lines, TD was found to promote cytochrome C release related to mitochondrial membrane potential (Huang *et al*., 2003) [10]. Rasagiline has been found to bind directly to MPTp, which stabilizes ΔΨm, thereby preventing activation of these pro-apoptotic factors (Akaoet
al., 2002a; Yogev-Falach *et al*., 2003). Multifactorial mechanisms appear to be involved in the neuroprotective effects of rasagiline (Mandel *et al*., 2005).

These mechanisms have been studied in many in vitro studies and include up-regulation of cellular antioantiapoptotic factors (Mandel *et al*., 2005). It has also been found to deactivate GAPDH, which is overexpressed during apoptosis; and to induce activation of the prosurvival protein kinase C pathway (Youdim *et al*., 2003). The Bcl-2 family of proteins is involved in apoptotic cell death pathways. Bcl-2 and Bcl-XL proteins are antiapoptotic, whereas Bax and Bad promote apoptosis. Rasagiline has been found to induce expression of the antiapoptotic proteins Bcl-2 and Bcl- XL (Akao *et al*., 2002b) and to down-regulate the proapoptotic proteins, Bax and Bad (Maruyama *et al*., 2001a; Weinreb *et al*., 2004). Further study is necessary in order to evaluate which or
a combination of which of these in vitro neuroprotective mechanisms is relevant in this whole animal model of neurodegeneration.

**Neuroprotective effect of rasagiline against closed head injury in the mouse**

Traumatic brain injury induces determined neurological deficits which include motor and memory injuries (Smith *et al*., 1991; Hamm *et al*., 1996). Cerebral oedema is an additional acute complication of brain injury and results from excess accumulation of water in the intra and extracellular space (Lobato *et al*., 1988). The mechanisms underlying the production of these deficits are still unclear, but a role for glutamate excitotoxicity has been suggested (Shohami *et al*., 1995) [25]. Reactive oxygen radicals are also triggered by the injury and could contribute to its pathophysiology (Smith *et al*., 1994). These radicals can be produced from oxidation of catecholamines and from an increase in free iron. The latter could occur from extravasated haemoglobin through rupture of cerebral Similar mechanisms are involved in the brain damage resulting from ischemia. The selective monoamine oxidase- B inhibitor, selegiline, has been shown to improve neuronal survival in gerbils following transient global ischaemia (Lahtinen *et al*., 1997), and in rats subjected tounilateral hypoxia ischaemia. Selegiline also rescued immature rat axotomised facial neurons from death (Ansari *et al*., 1993). Its action has been recognizedto a reduction in the formation of free radicals by stimulating catalase and superoxide dismutase an increase in theexpression of nerve growth factor (Semkova *et al*., 1996) [29], and a reduction of apoptosis. Selegilineis metabolised to amphetamine and methamphetamine by liver enzymes (Heinonen *et al*., 1994). These metabolites
lack the neuroprotective effect of the parent drug and may even cause cell damage in some preparations (Oh *et al*., 1994). This could interfere with the potential positiveeffects of selegiline in vivo, particularly after oral administration.

Rasagiline(TVP1012; *N*-propargyl-1*R*-aminoindan) is an irreversible monoamine oxidase inhibitor with selectivity towards the B form similar to that ofselegiline. Unlike selegiline, rasagiline is not metabolised to amphetamine and methamphetamine, and thus should be devoid of the undesirable effects of these substances. Rasagiline has recently been shown to reduce glutamate toxicity in cultured hippocampal neurons and to prolong survival of cultured, serum deprived rat fetal mesencephalic cells. Chronic prophylactic treatment of the nursing rats with rasagiline also reduced memory impairments in their offspring in adulthood, resulting from prolonged hypoxia during the neonatal period (Speizer *et al*., 1998). The aim of the current study was to see whether rasagiline could protect mice against the brain oedema, impairments in motor function and memory that occur after closed head injury. In order to establish whether or not any neuroprotective effects of the drug resulted from inhibition of monoamine oxidase-B, we compared its effects with those of its enantiomer, *N*-propargyl-1*S*aminoindan, TVP1022. This compound is at least 100 fold less active as an inhibitor of this enzyme in rat brain. A reduction in cholinergic indices occurs after brain trauma (Leonard *et al*.,

1994), which may be responsible for the motor and memory deficits. Therefore, we also determined whether any neuroprotective effects of rasagiline or its enantiomer were associated with prevention of the loss in cholinergic activity by testing their exposure to blockade by scopolamine.

**Characterization of the neuroprotective activityof rasagiline in cerebellar granule cells**

Marked differences were seen in the ability of the propargylamine derivative rasagiline to protect cerebellar granule cells from the different toxic insults used in this study, all of which have been shown to induce neuronal death by apoptosis. The drug was very effective in protecting against cell death induced by BSO and glutamate, showed significant but moderate effectiveness against Ara-C, but failed to show any neuroprotective activity against cell death induced by change from highto physiological potassium concentration or serum deprivation. Our findings with rasagiline are similar to those showing that both selegiline and the aliphatic MAO-B inhibitor R-2-heptyl-N-methylpropargylamine prevented Ara-C induced apoptosis but could not prevent apoptosis induced by transferring the cells from high to physiological potassium levels (Paterson *et al*., 1998). These differences in neuroprotective effectiveness could be related to the different intracellular signalling pathways activated by the various challenges. Mature cerebellar granule cells grown in high potassium medium and then exposed to physiological potassium concentration degenerate and die by apoptosis which is dependent on RNA and protein synthesis (Galli *et al*., 1995; Nardi *et al*., 1997) [35, 36]. The high potassium medium induces an increase in intracellular calcium concentration which induces transcription of neurotrophins (Favaron *et al*., 1993) [37]. Transfer of neurons to low potassium–low serum medium (Harris *et al*., 2002; Iacovelli *et al*., 2002), as well as addition of high concentration glutamate (Kawasaki *et al*., 1997; Chen *et al*., 2003), and Ara C (Paterson *et al*., 1998) have been found to activate the JNK signalling pathway. However a major difference between the stimuli is that low K induced apoptosis does not depend on an initial loss in mitochondrial function (Paterson *et al*., 1998), whereas glutamate (Bobba *et al*., 1999) and Ara-C induced apoptosis (Paterson *et al*., 1998; Zhang *et al*., 1999) do. Another difference between these challenges is that transfer to low potassium medium is associated with a loss of MAPK activity, and especially of PI3-kinase activity, which is a recognised pro-survival factor (Harris *et al*., 2002). In addition, Ara-C treatment induces enrichment of GAPDH in the nuclear fraction while physiological potassium concentration induces expression of GAPDH not only in the nuclear fraction but also in the mitochondrial fraction (Ishitani *et al*., 1998). These differences between cell death induced by Ara-C or glutamate and that caused by transfer from high to physiological potassium concentration may account for the variation in the neuroprotective effectof rasagiline and other propargylamines between these different neurotoxic challenges. Rasagiline failed to protect cerebellar granule cells from cell death induced by serum deprivation, which is not associated with the activation of JNK and p38 (Gunn-Moore and Tavare, 1998). Neurotrophins such as BDNF activate a variety of intracellular signalling pathways, not all of which have been characterized. The major receptor activated by BDNF in cerebellar granule cells is the TrkBneurotrophin receptor, which initiates a multitude of intracellular phosphorylation reactions (Goggi *et al*., 2003). The multiplicity of pathways activated by BDNF probably explains its ability to exert neuroprotective effect against a variety of stressors, as seen in the present study. The neuroprotective effect of rasagiline was apparent even when it was added 20 min after glutamate. A similar observation was made by Maruyama *et al*. (2002) in SHSY-5Y cells exposed to N-methyl(R)-salsolinol. Such a rapid protective effect is in support of the finding that rasagiline inhibits the opening of the mitochondrial permeability transition pore in SH-SY5Y cells and in isolated mitochondria, and prevents the accumulation of GAPDH in the nucleus induced by N-methyl(R)-salsolinol (Maruyama *et al*., 2001, 2002). In previous studies it was found that glutamate induces cell death after a short time period. Twenty minutes after glutamate addition there is an increase in trypan blue staining (Ankarcrona *et al*., 1995), within a fewminutes free radicals like superoxide are produced (Atlante *et al*., 1997), after 20 min there is an increase in intracellular calcium concentrations and after 30 min there is a change in the DNA binding complexes of the transcription factor YY1 in cerebellar granule cells (Korhonen *et al*., 1997). These findings suggest that rasagiline is able to protect the cells even though they are already in a state of oxidative stress and activated intracellular signals.

Certain derivatives of rasagiline were shown to protect cerebellar granule cells from glutamate-induced excitotoxicity. The optical enantiomer of rasagiline, TV-1022, which is more than 1000 fold less potent as a MAO-B inhibitor (Youdim *et al*., 2001b) was lessefficacious than rasagiline but showed significant neuroprotective activity at 10 mM. This is in accordance with previous findings that TV-1022 showed neuroprotective activity in serum and NGF deprived PC-12, in which it was found to inhibit the loss of mitochondrial potential (Youdim *et al*., 1999, 2001a), and is effective in in vivo models of neuroprotection (see Section 1). In our study, aminoindan (the primary metabolite of rasagiline) was devoid of protective effect against glutamate-induced neurotoxicity, and was previously also claimed by others to be devoid of neuroprotective effect in SH-SY5Y cells (Youdim *et al*., 2003). Recently, however, this compound was shown to have significant protective effect in NGF-differentiated PC-12 cells induced to apoptotic death by serum and NGF withdrawal (Bar-Am *et al*., 2004). The variable neuroprotective property of TV-136 in cell lines underlines the importance of examining neuroprotection in primary neuronal cultures. The very much lower neuroprotective effect of TV-3101, which differs from rasagiline only in that it possesses a double instead of a triple bond in the aliphatic part of the molecule, is further proof of the major role of the propargylamine group in causing neuroprotection. Recently, propargylamine itself has been reported to possess neuroprotective effect (Youdim*et al*., 2003) and a propargylamine non-MAO inhibitor compound (CGP-3466; N-methyl-N-propargyl-10-amino- methyl-dibenzo [b, f]oxepin) has been developed as a neuroprotectant

(Waldmeier *et al*., 2000). Clorgyline, however, was not neuroprotective in fetal rat mesencephalic neurons (Finberg *et al*., 1998), and in the present study, the 6-fluoro derivative of rasagiline (TV-114) was also considerably less active than the parent compound, so that obvious restrictions exist for neuroprotective activity in the rasagiline series. Other neuroprotective propargylamine compounds include the aliphatic compound R-2-hepyl-N-methylpropargylamine (Paterson *et al*., 1998) and the dual MAO- and cholinesteraseinhibitorTV-3326 (Youdim *et al*., 2001a). A number ofMAO- and nonMAO-inhibitor propargylamines havetherefore been found effective as neuroprotectants. The precise structure–activity relationship for neuroprotective effect of propargylamines awaits determination of the active site. Carlile *et al*. (2000) have proposed that selegiline binds to a site on the GAPDH molecule, and if this is the major neuroprotective pathway, then elucidation of the three-dimensional determinants of propargylamineneuroprotective compounds is possible. Interestingly, rasagiline was found to exert morphological changes in the astrocyes in cultures of cerebellar granule cells grown in physiological potassium concentrations. Previous studies show that selegiline induces an

activation of astrocytes and increases the expression of growth factors like bFGF (Biagini *et al*., 1994), NGF (Semkova *et al*., 1996) [29] and CNTF (Seniuk *et al*., 1994), which can increase the survival of the neurons. These findings suggest that the neuroprotective activity of rasagiline may be exerted via an indirect action through the astrocytes as well as a direct action on the neurons,

since in the conditions in which we studied glutamateinducedcell death, glial cell development was minimal. Although there are studies showing that selegilineinduces neurite outgrowth in dopaminergic neurons from the spinal ventral horn (Iwasaki *et al*., 1994; Kontkanen and Castren, 1999) rasagiline failed to affect synaptic bouton density in the cerebellar granule neuron preparation, and so rasagiline may exert a glialdependentas well as a non glial-dependent neuroprotective effect. In conclusion, rasagiline possesses neuroprotective effect in cerebellar granule cells following various insults. This finding reinforces preliminary findings of a neuroprotective effect against glutamate toxicity in primary culture of hippocampal neurons (Finberg *et al*., 1999) and provides further evidence that the neuroprotective effect of rasagiline is exerted against neurons of several types and not only those which produce dopamine or other catecholamines such as fetal mesencephalic neurons (Finberg *et al*., 1998; Goggi *et al*., 2000). Our findings are in support of others showing

thatrasagiline acts to prevent loss of mitochondrial potential, and is neuroprotective against apoptosis induced by JNK pathway activation. In addition it may induce glial changes that influence the survival of the neurons.

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