Rasagiline – a novel MAO B inhibitor in Parkinson's disease therapy

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Abstract: Parkinson's disease (PD) is a progressive neurodegenerative, dopamine deficiency disorder. The main therapeutic strategies for PD treatment relies on dopamine precursors (levodopa), inhibition of dopamine metabolism (monoamine oxidase [MAO] B and catechol-O-methyl transferase inhibitors), and dopamine receptor agonists. Recently, a novel selective and irreversible MAO B propargylamine inhibitor rasagiline (N-propargyl-1-R-aminoindan, Azilect®) was approved for PD therapy. In contrast to selegiline, the prototype of MAO B inhibitors, rasagiline is not metabolized to potentially toxic amphetamine metabolites. The oral bioavailability of rasagiline is 35%, it reaches T_{max} after 0.5–1 hours and its half-life is 1.5–3.5 hours. Rasagiline undergoes extensive hepatic metabolism primarily by cytochrome P450 type 1A2 (CYP1A2). Rasagiline is initiated at 1 mg once-daily dosage as monotherapy in early PD patients and at 0.5–1 mg once-daily as adjunctive to levodopa in advanced PD patients. Rasagiline treatment was not associated with "cheese effect" and up to 20 mg per day was well tolerated. In PD patients with hepatic impairment, rasagiline dosage should be carefully adjusted. Rasagiline should not be administered with other MAO inhibitors and co-administration with certain antidepressants and opioids should be avoided. Although further clinical evidence is needed on the neuroprotective effects of rasagiline in PD patients, this drug provides an additional tool for PD therapy.

Keywords: rasagiline, MAO B inhibition, therapy, safety, neuroprotection

Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder clinically characterized as tremor at rest, muscular rigidity, bradykinesia, and postural instability. Clinical symptoms of the disease appear after 60% of the dopaminergic neurons population in the substantia nigra pars compacta (SNpc) already degenerated. One to two per cent of the adult population over the age of 60 is clinically diagnosed with PD; however, the number of affected people is much higher because of the initial asymptomatic progression of the disease (Tabakman et al 2004). Recent pathological attempts to classify the pathophysiological processes responsible for PD suggest a 6- stage evaluation scale of progression in PD-related symptoms (Braak et al 2003). Stages 1–2 appear as lesions confined to the brain medulla oblongata, while PD-related clinical symptoms are absent. Stage 3 is defined as additional progression of the brain lesions towards midbrain, in particular in the SNpc monitored by PD-associated motor disorders. Stages 4–6 are characterized as further progression of the brain lesions towards the cortex with some changes in the sensory areas of the brain (Braak et al 2003). The therapeutic approaches available today are symptomatic: they address mainly stages 3–6, although even with treatment, the longevity of these PD patients is short and their quality of life is poor. Since PD is generally regarded as a dopamine deficiency disorder it is not surprising that most drugs available to treat PD attempt to correct dopamine deficiency. However, none of these agents retards the progressive

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neurodegeneration associated with PD. Therefore, there is a need for novel therapeutic approaches to ameliorate the pathophysiological process of the disease.

PD cellular pathological mechanisms

PD is generally considered to be idiopathic (of unknown origin) and the precise cellular and molecular pathological processes causing the disease are not fully understood. In a minor subset of PD patients several genetic alterations have been identified and related to the expression and/or aggregation of two major proteins such as α-synuclein and parkin involved in part in the disease process (Dawson and Dawson 2003). In other sporadic forms of PD, additional biochemical abnormalities such as nuclear translocation of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (Tatton et al 2003) and activation of proapoptotic proteins (eg, bax, caspases) (Hartmann et al 2000; Tatton 2000) have been identified. These genetic and biochemical changes are assumed to cause the apoptotic and/or necrotic cell death of the dopaminergic neurons of the SNpc by mitochondrial (Szeto 2006) and proteasomal dysfunctions (Dawson and Dawson 2003), as well as oxidative stress (Szeto 2006). Excitotoxicity (Rodriguez et al 1998), environmental toxins (Landrigan et al 2005), inflammation (McGeer and McGeer 2004), reduced levels of neurotrophins (Levy et al 2005), and changes in cerebral blood flow (Thanvi et al 2005) may also contribute to the development of PD. The complexity of pathological mechanisms is a significant obstacle in effective treatment of the disease.

PD therapeutic strategies

The first strategy for PD treatment relies on the use of dopamine precursors, such as levodopa (L-dopa) which is able to cross the blood–brain barrier (BBB) and is the most accepted and a powerful symptomatic drug available today for the treatment of PD. It increases the amount of dopamine in SNpc, thus compensating for the loss of dopaminergic neurons (Figure 1, step 1). Most PD patients respond to L-dopa monotherapy. Nevertheless, the chronic treatment with L-dopa has several significant limitations and side-effects which include motor fluctuations, dyskinesias, and neuropsychiatric problems due to the increased dopaminergic activity of all five dopaminergic pathways in the brain, as well as up and down regulations of dopaminergic receptors (Olanow and Jankovic 2005). After 3–5 years of L-dopa therapy, patients may exhibit an "on-off" phenomenon characterized by marked fluctuations in patient response to L-dopa. Such a person may be symptom free ("on" effect) and abruptly experience marked hypokinesia ("off" effect). The "on-off" phenomenon may be in part resolved by a novel pharmacokinetic approach. Taking into account that L-dopa has a narrow absorption window, an expandable gastroretentive dosage form of L-dopa delivery enables a signifi cant extension of the absorption phase, thus providing more consistent blood levels of the drug (Klausner et al 2003; Hoffman et al 2004). Unfortunately, in the latest stages of the disease, when the number of surviving dopaminergic neurons in the patients is extremely low, this therapeutic strategy is not effective.

The second strategy for PD treatment is based on dopamine agonists that compensate for the lack of endogenous neurotransmitter by activating postsynaptic dopamine receptors (Figure 1, step 2). Several dopamine agonists such as bromocriptine and cabergoline are widely used for symptomatic monotherapy of PD. Recently developed pramipexole and ropinirole are effective in treating symptoms of PD and data suggest that they also exert neuroprotective effects (Radad et al 2005).

The third strategy for PD treatment uses inhibitors of dopamine-metabolizing enzymes: catechol-O-methyl transferase (COMT) and monoamnine oxidase B (MAO B) (Figure 3, step 3). Using this therapeutic approach the endogenous content of dopamine is increased, causing the reduction of PD symptoms. COMT inhibitors such as tolcapone and entacapone are not effective as monotherapy, but provide symptomatic relief when added to L-dopa treatment (Leegwater-Kim and Waters 2006). Selegiline (deprenyl), however, is the most common inhibitor of MAO B used as monotherapy. Recently, neurologists have preferred to initiate selegiline monotherapy on patients in the early stage of PD, therefore postponing L-dopa treatment for a later stage, to avoid the side-effects associated with L-dopa (Olanow and Jankovic 2005).

Several emerging therapeutic approaches are on the horizon to attenuates symptoms and/or neurodegeneration associated with PD with the hope of avoiding the motor complications seen with dopaminergic therapies: i) adenosine receptor type A2A antagonist (such as istradefylline) (Wu and Frucht 2005); ii) glutamate AMPA receptor antagonist (such as talampanel) (Wu and Frucht 2005); iii) opioid-like neuropeptide mociceptin/orphanin FQ (N/OFQ)/receptor NOP antagonist (Marti et al 2005). These and other therapies currently under investigation represent a new phase of treatment strategies for PD.
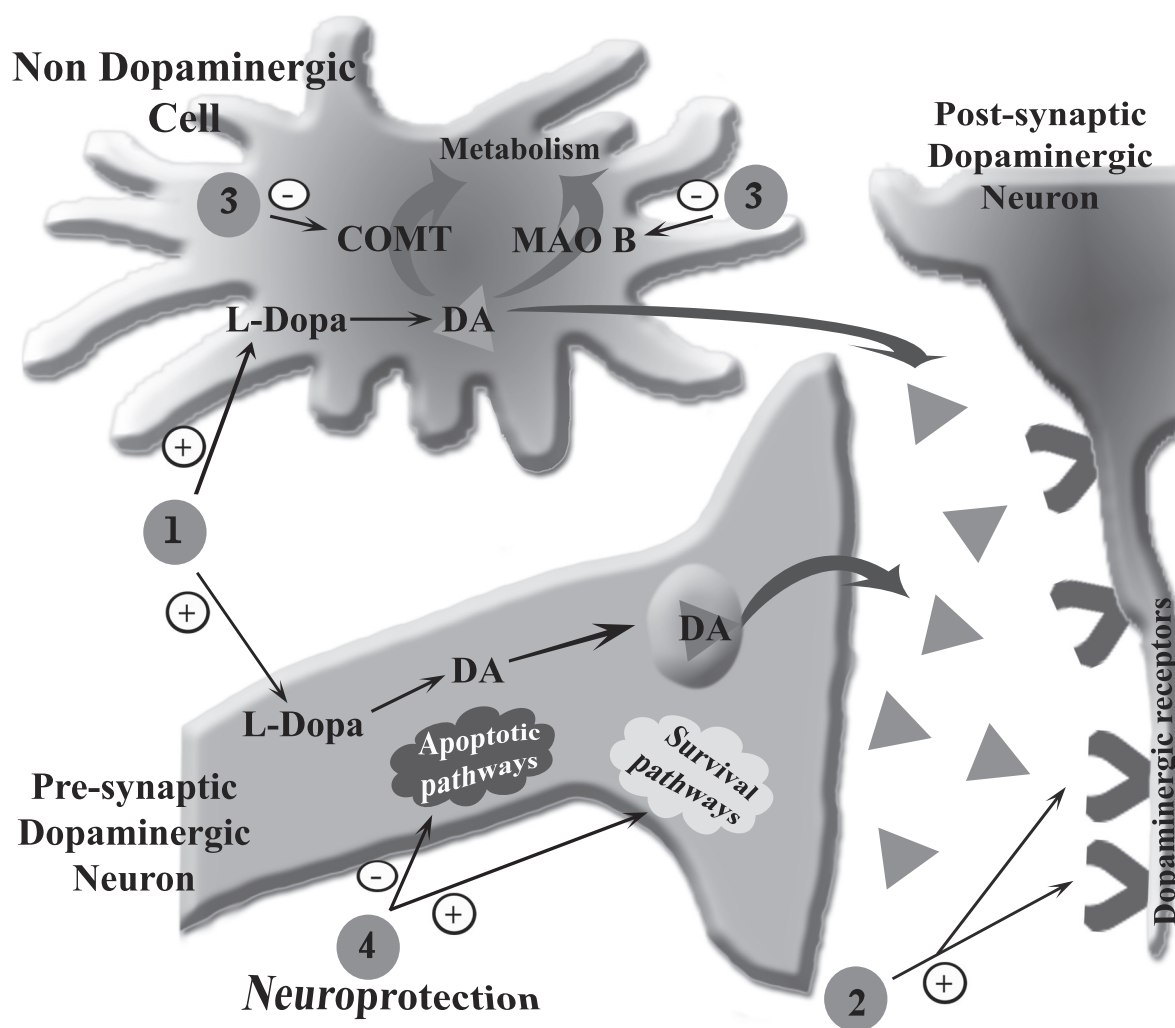
Figure 1 Schematic of the major dopaminergic therapeutic strategies for Parkinson's treatment. Step 1, dopamine precursor L-dopa; Step 2, dopamine receptor agonists; Step 3, dopamine metabolizing enzymes (COMT and MAO B) inhibitors; Step 4, neuroprotective compounds. +, increase in the synaptic dopamine or stimulation of dopamine receptors and survival pathways; −, inhibition of dopamine metabolizing enzymes or apoptotic pathways; ▲, dopamine neurotransmitter; V, dopamine receptors; DA, dopamine; MAO B, monoamine oxidase type B; COMT, cathechol-O-methyl transferase.

Rasagiline, a novel MAO B inhibitor for PD therapy

In January 2005 the propargylamine-based, irreversible MAO B inhibitor rasagiline (Azilect®, Teva Pharmaceutical Industries Ltd., Israel) was first approved in Israel for the treatment of idiopathic PD as monotherapy or as adjunct therapy with L-dopa in patients with end-of-dose fl uctuations. In February 2005 it was approved by the European Agency for the Evaluation of Medicinal Products (EMEA) for the same indication, and later on, in May 2006, rasagiline was approved by the US Federal Drug Administration (FDA). From mid 1970, selegiline (deprenyl), a selective and irreversible propargylamine drug, was the main selective MAO B inhibitor used in the clinic. Rasagiline is also a selective and irreversible propargylamine, with a slight chemical difference in the side chain structure (Tabakman et al 2004). Rasagiline, in contrast to selegiline, is not metabolized to potentially toxic amphetamines and its major metabolite 1-R-aminoindan has demonstrated therapeutic effects in neuronal cultures (Abu-Raya et al 2002) and animal models of PD (Speiser et al 1998).

Rasagiline – pharmacokinetic characteristics

Rasagiline is well absorbed after oral administration (Thebault et al 2004) and readily crosses the BBB. The bioavailability of rasagiline is about 35% (Chen and Ly 2006) and it exerts linear absorption at doses of 1–10 mg/day (FDA 2006). Maximal plasma concentration (C_{max}) obtained after 1 mg and 2 mg oral dose is 2.5 ng/mL and 4.9 ng/mL,

respectively. The time to reach maximal concentration (T_{max}) is 0.5–1 hours and is unaffected by food intake (Parkinson Study Group 2005; Chen and Ly 2006; FDA 2006). High-fat meal decreases the area under the curve (AUC) of rasagiline by 20%, which is considered clinically insignifi cant; therefore, rasagiline can be administered independently of food intake (Chen and Ly 2006; FDA 2006). The volume of distribution (Vd) of rasagiline varies between 87 to 243 L (Chen and Ly 2006; FDA 2006), according to different reports. Plasma albumin binding is considered to be 60%–70% (Chen and Ly 2006), although a higher plasma protein binding value was reported (FDA 2006). The half-life of rasagiline is 1.5–3.5 h and may be dose-dependent (Chen and Ly 2006; FDA 2006). It is interesting to note that there is no linear pharmacokinetic-pharmacodynamic (PK-PD) correlation that can be explained by the prolonged irreversible inhibition of MAO B up to 40 days (pharmacodynamic t½). PK profi le of rasagiline is similar in men and women. Rasagiline undergoes extensive hepatic metabolism and almost complete biotransformation in the liver, primarily by cytochrome P450 1A2 (CYP 1A2) to form 1-R-aminoindane (major metabolite), 3-hydroxy-N-propargyl-1-aminoindan, and 3-hydroxy-aminoindan. The major metabolite 1-R-aminoindan has a T_{max} of about 2 hours (Stern et al 2004). Oral clearance of the drug is 94.3 L/hour, and since the liver blood flow is about 90 L/hour, this finding implies that extra-hepatic processes are not involved in elimination of rasagiline.

Rasagiline therapy in PD patients as evident from clinical trials

The recommended dose of rasagiline in treatment of PD is 1 mg once daily as monotherapy or 0.5 mg once daily as adjunctive to L-dopa. If satisfactory clinical response is not achieved, the dose may be increased to 1 mg administered once daily. The effectiveness of rasagiline was concluded from several clinical trials as monotherapy in early PD or as adjunct therapy with L-dopa in advanced PD. Rasagiline monotherapy efficacy was demonstrated by the accepted Unified Parkinson Disease Rating Scale (UPDRS) scores compared with placebo (Table 1). Signifi cant benefi ts were observed in the reduction in "off" time of L-dopa treated patients, improvement in motor activity (rigidity and tremor) comparable to the efficacy of selegiline and lazabemide, a 2-aminoethyl carboxamide derivative which is an antioxidant with reversible, and a highly selective MAO B inhibition property. Evaluation of lazabemide discontinued in phase III clinical trials (Parkinson Study Group 2002). Upon treatment with rasagiline in combination with L-dopa, a decrease in

L-dopa dosage may be expected. Indeed in the clinical trials performed, up to 16% of patients received a 13% reduced dosage of L-dopa (FDA 2006).

In a subanalysis of delayed-start TEMPO study, quality of life (QOL) was measured by Parkinson's Disease Quality of Life questionnaire (PDQUALIF) at 0, 14, 26, and 52 weeks. Rasagiline treatment improved QOL scores in PD patients compared with placebo after 6 months of initial TEMPO study. But no difference in QOL scores was observed after 12 months, when all the patients had received rasagiline for at least 26 weeks (Biglan et al 2006).

Clinical risk management of rasagiline therapy

Rasagiline was well tolerated in volunteers and PD patients, with treatment discontinuation rates similar to placebo (Table 1). A subanalysis of TEMPO and PRESTO clinical trials revealed that no cognitive and behavioral adverse events in either rasagiline 1 mg or placebo groups exceeded 10%, and the differences between rasagiline and placebo never exceeded 3%. This safety profile was achieved along with improved PD symptoms and better control of motor fluctuations (Elmer et al 2006). Most adverse effects were defined as "uncomfortable" rather than "serious". Rasagiline was well tolerated at doses up to 20 mg/day and no cases of overdose have been reported. The most common adverse effects seen in volunteers included headache, insomnia, xerostomia, abdominal discomfort, nausea, and diarrhea. Other adverse effects observed in clinical trials, although not different from placebo, included postural hypotension, dyskinesias, arthralgia, weight loss, anorexia, depression, vomiting, balance difficulty, and hallucinations (Chen and Ly 2006). The long-term safety profile of rasagiline is similar to that of short-term treatment (FDA 2006).

As a theoretical risk of hypertensive crisis exists with all MAO inhibitors, restriction in dietary tyramine (eg, cheese and wine) and sympatomimetic amines (eg, phenylephrine) is recommended in patients treated with rasagiline. Patients should be advised about symptoms and signs of hypertensive crisis that include severe headache, nausea and vomiting, blurred vision, chest pain, difficulty in thinking, stupor, coma, and seizures. However, the clinical trials indicated that rasagiline, like selegiline, is not associated with "cheese effect" at clinically relevant MAO B inhibition dosages. Specifi cally, oral challenge with 75 mg (Parkinson Study Group 2002) or 50 mg (Parkinson Study Group 2005) tyramine did not significantly change blood pressure or heart rate of rasagiline-treated patients (Biglan et al 2006).

Table I Clinical trials to evaluate rasagiline efficacy, safety, and side-effects

Study	Design	Treatment	Results	Conclusions	References
Double-blind study of rasagiline adjunctive to L-dopa therapy	Phase II, 12 weeks; 70 PD patients with advanced PD on L-dopa therapy	Doses: 0.5 mg, 1 mg, 2 mg, or placebo	No differences in incidence of side-effects. No signifi cant changes in blood pressure and heart rate in any group. Despite good clinical response, no statistical difference in UPDRS scores between the drug and placebo groups	Rasagiline is well tolerated	Rabey et al 2000
Double-blind, randomized, trial of rasagiline as monotherapy in early PD	Phase II, 10 weeks; 56 early stage, untreated PD patients	Doses: 1 mg, 2 mg, 4 mg, or placebo	No differences in incidence of side effects between the drug and placebo groups. 10% mean improvement in UPDRS scores in rasagiline 2 mg group vs 2.8% improvement in the placebo group ($p < 0.05$)	Rasagiline is well tolerated and effective	Stern et al 2004
TEMPO - double-blind, randomized, placebo-controlled clinical trial of rasagiline as monotherapy in early PD	26 weeks; 404 untreated patients with early PD	Doses: 1 mg, 2 mg, or placebo	UPDRS improvement: 4.2 units (1 mg vs placebo), 3.56 units (2 mg vs. placebo ($p < 0.001$ for both)	Signifi cant benefi ts observed on UDPRS motor, ADL, and mental subscales. The symptomatic benefi t of rasagiline is comparable with that seen with selegiline and labezamide. No signifi cant differences in adverse events between the placebo and rasagiline groups	Parkinson study group 2002
TEMPO delayed start double-blind, parallel-group, randomized trial of rasagiline as monotherapy in early PD	52 weeks; 371 patients from TEMPO 6-month study. Rasagiline group: 1 or 2 mg for 52 weeks, vs initial placebo group switched to rasagiline after 26 weeks	Doses: 1 mg and 2 mg (early start) or 2 mg (delayed start)	UPDRS improvement: 1.45 units for 2 mg, 1.93 units for 1 mg/day, and 3.75 units for the delayed start group ($p = 0.05$), rasagiline 1 mg vs 2 mg ($p = 0.018$)	Patients treated with 1 and 2 mg for 12 months showed less functional decline than those delayed treated for 6 months. The randomized delayed-start design used in this study was intended to separate an immediate symptomatic effect from an effect on disease progression	Parkinson Study Group 2004
LARGO double-blind, parallel-group, randomized, placebo controlled study of rasagiline adjunctive to L-dopa therapy.	18 weeks; 687 patients with advanced PD on L-dopa treatment with motor fl uctuations	Doses: rasagiline 1 mg/ L-dopa; entacapone 200 mg/L-dopa; placebo/L-dopa	Patients treated with rasagiline or entacapone showed 0.8 h (25%) less "off" time/day ($p = 0.0001$ for both) compared to placebo; no signifi cant difference between rasagiline and entacapone was measured	The "on" time, the CGI and gait freezing were signifi cantly improved. No signifi cant differences in adverse effects between the parallel groups	Rascol et al 2005
PRESTO double-blind, parallel-group, randomized, placebo controlled study of rasagiline adjunctive to L-dopa therapy	26 weeks; 472 patients with advanced PD on L-dopa treatment with motor fl uctuations	Doses: rasagiline 0.5 mg/L-dopa; rasagiline 1 mg/L-dopa; placebo/ L-dopa	Rasagiline 0.5 mg had 0.5 h (20%) less "off" time/day ($p = 0.02$) and 1 mg group had 0.94 h (25%) less "off" time/day ($p < 0.001$) vs placebo	CGI, UPDRS ADL scores were improved. No differences in adverse effects for rasagiline vs placebo were observed	Parkinson Study Group 2005

Abbreviations: ADL, advanced daily living; CGI, clinical global impression; PD, Parkinson's disease; UPDRS, Unified Parkinson Disease Rating Scale.

In patients with mild hepatic impairment the AUC of rasagiline increases by 80% and C_{max} increases by 38% (Chen and Ly 2006). Therefore, the dose of rasagiline recommended in patients with mild hepatic impairment is 0.5 mg/day (FDA 2006). In moderate hepatic impairment the AUC increases by 568% and C_{max} by 83%; therefore, therapy with rasagiline is not recommended in patients with moderate or severe hepatic impairment. Less than 1% of rasagiline is excreted unchanged in urine; therefore no dose adjustment is required in patients with renal insuffi ciency.

Rasagiline should not be administered along with other MAO inhibitors. Ciprofloxacin, a CYP1A2 inhibitor, at 500 mg twice daily dose increased rasagiline AUC by 83%. Therefore, the dose of rasagiline should be reduced by 50% in patients receiving ciprofloxacin or other CYP1A2 inhibitors like cimetidine and fluvoxamine (Chen and Ly 2006). Omeprazole, a CYP1A2 inducer, may reduce AUC of rasagiline; therefore, an increased dosage may be required to achieve the same clinical effi cacy.

In vitro studies indicated that rasagiline at a very high concentration (160 times higher than C_{max}) did not inhibit CYP 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, 3A4 (Chen and Ly 2006; FDA 2006). Therefore, we can predict that polypharmacy with rasagiline and other drugs which are substrates of the above CYPs will not result in metabolic drug-drug interactions although we cannot exclude other pharmacokinetic and/or pharmacodynamic interactions.

MAO inhibitors co-administered with antidepressants have been associated with serotonin syndrome which is a medical emergency clinically manifested by anxiety, mental status changes, hypertension, diarrhea, hyperrefl exia, myoclonus, loss of consciousness and death. In LARGO, TEMPO, and PRESTO clinical trials several patients were treated with antidepressants, including amitriptyline ≤50 mg/daily, trazodone ≤100 mg/daily, citalopram ≤20 mg/daily, sertraline ≤100 mg/daily, and paroxetine ≤30 mg/daily. Fluoxetine and fluvoxamine were not allowed. Although there are insufficient data to determine safety upon its co-administration with serotonin selective reuptake inhibitors, there have been no reports connecting serotonin syndrome to rasagiline.

We would like to stress that co-administration of an opioid receptor agonist meperidine (pethidine) with rasagiline is contraindicated due to possible serotonin syndrome. At least 14 days should elapse between discontinuation of rasagiline and initiation of meperidine treatment. Moreover, interaction is theoretically expected with tramadol, methadone, and propoxyphene as these opioid receptor agonists

have been shown to inhibit reuptake of serotonin in vitro (Gillman 2005).

Relevance of rasagiline – neuroprotective effects for PD treatment

Today's interest in PD therapy is in the development of drugs with multiple beneficial effects. In addition to the compensation of the reduction of dopamine in SNpc the drug to be developed is required to ameliorate the progression of dopaminergic neuron degeneration, ie, to induce neuroprotection of the degenerating neuron. Over the last decade a large body of evidence indicates that selegiline and rasagiline are neuroprotective in a variety of pharmacological models in vitro and in vivo (Abu-Raya et al 2000; Tabakman et al 2004). For example, selegiline and rasagiline (10 mg/kg body weight) markedly attenuated the neurotoxic effect of 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) in a non-human primate PD model at a behavioral, histological, and biochemical level in parallel to significant inhibition of MAOs activity (Kupsch et al 2001). Paradoxally, the anti-apoptotic and prosurvival properties of rasagiline appear to be independent of MAO B inhibition (Figure 1, step 5) but mediated by the propargyl moety (as reviewed Tabakman et al 2004). The pharmacological mechanism of rasagiline-mediated neuroprotection was studied in neuronal cell cultures using different types of oxidative and trophic withdrawal stress models. The antiapoptotic effects of rasagiline are proposed to be mediated by activation of antiapoptotic proteins as a result of drug binding to the fl avin adenine dinucleotide (FAD) binding site in GAPDH and other anti-apoptotic proteins resulting in neuroprotection (Tabakman et al 2004). Based on the proof of concept of neuroprotective effects of rasagiline in in vitro and in vivo pharmacological models, the potential neuroprotective effect of rasagiline was also considered in the clinical trials.

The delayed start TEMPO study is the first attempt to examine the neuroprotective effects of rasagiline in the framework of a double-blind, randomized, placebo-controlled clinical trial (Parkinson Study Group 2004). During the randomization of the patients two groups were created, one which received the drug during the whole period and another one that started the treatment at the middle of the study in order to separate between immediate symptomatic effects of the drug from a delayed, disease-modifying contribution (neuroprotection). In this clinical trial design, in the second part of the study the placebo-controlled group received

rasagiline; therefore at the end of the trial the symptomatic effects are presumably equalized between the two groups. The results revealed improvement in motor performance in patients that received rasagiline during the whole trial period compared with patients treated with rasagiline only during late phase. This finding may indicate a neuroprotective effect of rasagiline in the patients, but this aspect needs further exploration (Parkinson Study Group 2004).

Future directions

Current treatments of PD deal well with the symptomatic clinical presentation. The available therapeutic strategies mainly elevate the reduced levels of dopamine by utilizing different pharmacological mechanisms as schematically presented in Figure 1. However, none of the available therapeutic options can slow the progression of the disease. Unmet needs create opportunities for developing and evaluating neuroprotective agents. In theory, these drugs will modify the course of the disease by preventing or delaying the death of dopaminergic neurons and, moreover, other types of neuronal cells, thus being beneficial in the first stages of PD (Bonuccelli and Del Dotto 2006). MAO B inhibitors, such as selegiline and to a greater extent rasagiline, have been shown to have disease-modifying potential (Stocchi 2006). The neuroprotective effect of selegiline is compromised by its many amphetamine neurotoxic metabolites, and introduction of rasagiline circumvents this problem. It is important to remember that the neuroprotective mechanism of rasagiline and other propargylamines derivatives in different neuronal models appear to be independent of MAO B inhibition. Therefore, it is essential to further elucidate the pharmacological mechanism of action of propargylamines in order to get a better insight into the neuroprotective pathways and to apply them for new pharmacological targets for the development of novel anti-PD drugs. It is tempting to speculate that in future the novel drugs to be developed for PD treatment will be multi functional by correcting both the lack of dopamine as well as providing neuroprotection to the degenerating neurons (Wu and Frucht 2005). To optimize fully their therapeutic efficacy it would be important to identify the proper mode of administration (pharmaceutical compounding) that takes into account their pharmacokinetic properties (Hoffman and Stepensky 1999).

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