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A critical review of evidence for preclinical differences between rasagiline and selegiline

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ABSTRACT

Monoamine oxidase M (MAO-B) inhibitors are used in the symptomatic treatment of Parkinson's disease (PD) as they prolong the availability and activity of endogenous dopamine in the striatum by blocking its degradation. Two MAO-B inhibitors, rasagiline and selegiline, are currently licensed in Europe and North America. The differences between these agents at the clinical and preclinical level have been much debated. This review critically explores the evidence for preclinical differences between rasagiline and selegiline, and discusses the relevance of these differences for the treatment in PD.

Rasagiline is about 10 times more potent in the inhibition of MAO-B than selegiline in *ex vivo* studies. To achieve similar potency in the clinical setting the doses were adapted. At their selective MAO-B inhibitory dosages, rasagiline and selegiline do not produce the "cheese reaction" and do not cause a potentiation of the effects of L-DOPA combined with the decarboxylase inhibitor carbidopa on blood pressure or heart rate in conscious rats. However, in pithed rats, selegiline but not rasagiline increased noradrenaline and adrenaline release, and pulse rate, and potentiated dopamine pressor response at MAO-B selective dose. It is believed that this difference is the result of their different chemical structure that gives rise to different metabolites with distinct pharmacological properties. Whether this difference is relevant for the clinic in regard to the occurrence of cardiovascular adverse drug reactions is not known, because, it is not known at what concentrations L-amphetamine and L-methamphetamine exert a sympathomimetic effect *in vivo*, and whether such concentrations are achieved in the blood of PD patients.

Rasagiline is superior to selegiline in its potency to prevent spontaneous cell death seen in cell culture, and to reduce accelerated cell death following serum deprivation *in vitro*. In addition, rasagiline is more effective in regard to its ability to reverse changes in mitochondrial function that lead to apoptosis. Finally, in the lactacystin-treated mouse, rasagiline exerts a neurorestorative effect where selegiline has none. These effects were considered to be independent of the ability of both agents to inhibit MAO-B. It was concluded that these superior effects of rasagiline are attributable to additive effects of the parent active substance and its major metabolite, 1-R-aminoindan, and to possible neurotoxic effects of L-methamphetamine, one metabolite of selegiline. However, it is not known at what concentrations these compounds may exert any protective and neurotoxic effect, respectively, *in vivo*, and whether respective concentrations are achieved in the brain of PD patients.

Introduction

Rasagiline and selegiline (previously used name L-deprenyl) are potent and irreversible inhibitors of monoamine oxidase type B (MAO-B) [1]. MAO-B and the other iso-enzyme MAO-A occur both in the central nervous system (CNS) and in peripheral tissues [2]. These enzymes are integral proteins of the outer mitochondrial membrane that catalyze the oxidative deamination of neuroactive and vasoactive amines such as dopamine, noradrenaline and serotonin (5-HT), as well as amines such as tyramine which are absorbed from the diet or arise as the result of bacterial transformations according to the overall equation 1 shown below.

$$R - CH_2NH_2 + O_2 \rightarrow R - CHO + NH_3 + H_2O_2 \quad (1)$$

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The name MAO is not entirely appropriate, because the enzymes are also capable of deaminating long-chain diamines such as 1, 10-decamethylen diamine, compounds such as 2-n-pentylaminoacetamide, and even tertiary cyclic amines such as the Parkinsonism-inducing 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 1-methyl-β-carboline (harman) [3]. MAO-A predominantly deaminates 5-HT and noradrenaline and is inhibited by low (in the nanomolar range) concentrations of clorgyline, whereas MAO-B is not inhibited until micromolar concentrations of this inhibitor are used. MAO-B has a great affinity for benzylamine and for β-phenethylamine and is selectively inhibited by low concentrations of selegiline and rasagiline. In the rodent brain, as in other tissues, dopamine and tyramine are substrates for both forms of the enzyme, while dopamine in human brain has a somewhat higher affinity for MAO-B [3].

The original idea to use a MAO-inhibitor without the cheese effect and without liver toxicity for the treatment of off-phases in Parkinson's disease (PD) has been put forward to Merton Sandler and Moussa Youdim in November 1973 by one of us (PR). As a consequence PR proposed to use L-deprenyl to Moussa Youdim in October 1974. Indeed, Birkmayer et al. showed in a clinical trial that selegiline potentiates the efficacy of L-DOPA (L-3,4-dihydroxyphenylalanine, levodopa) in patients with PD [4]. The knowledge that dopamine is a preferred MAO-B substrate in humans [5] and the dominance of MAO-B (80%) as compared to MAO-A in the human extrapyramidal brain regions [5–7] led to further developments. Selegiline and rasagiline (Fig. 1) are currently licensed in Europe and North America for the symptomatic improvement of early PD and to reduce off-time in patients with more advanced PD and motor fluctuations related to L-DOPA [8]. These drugs have also been studied extensively for possible neuroprotective or disease-modifying actions.

The D,L-racemic mixture of deprenyl was developed in Hungary by Knoll in 1964 as a novel MAO-inhibitor antidepressant [9]. However, the MAO-B-inhibitory efficacy of the D-isomer is only 1/150 that of the D-isomer [10]. More importantly, the D-isomer is metabolised to D-amphetamine and D-methamphetamine [11], which have ten times the amphetamine potency of the corresponding L-isomers [12]. For these reasons L-deprenyl became the clinically useful form for the treatment of patients with PD, and the designation L-deprenyl, together with R(-)-deprenyl, predominates in the literature. Present usage uses the generic name selegiline.

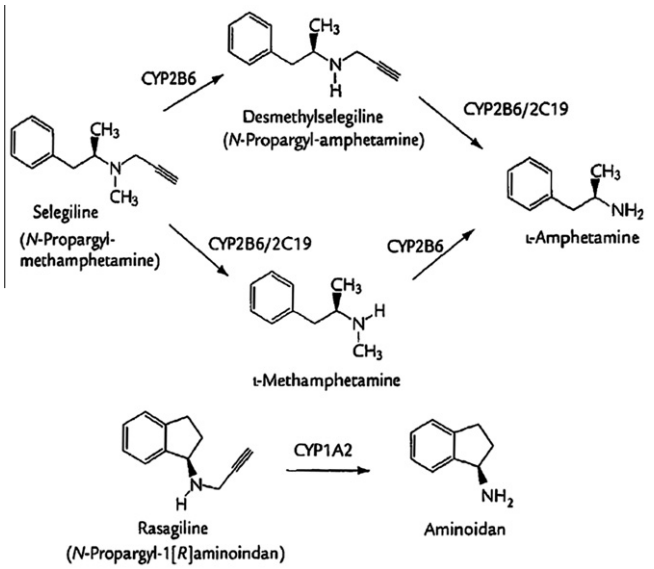

Fig. 1. Chemical structures of rasagiline (N-propargyl-1-(R)-aminoindan) and selegiline ((R)-(-)-N,2-dimethyl-N-2-propynylphenethylamine) and their metabolites. Reproduced from Müller and Reichmann 2012 [56].

Rasagiline (previously used name TVP1012), the R-isomer of the selective MAO-B inhibitor AGN1135 [1]was developed because it is not metabolised to amphetamine-like substances but to 1-aminoindan (Fig. 1) which does not function as a MAO-B inhibitor. Because of its ability to stimulate functions normally controlled by the sympathetic nervous system, amphetamine has long been recognized as a "sympathomimetic amine" [13]. Both amphetamine and methamphetamine interact with the noradrenaline transporter and storage vesicle mechanisms in the sympathetic nervous system to cause a release of noradrenaline that is independent of nerve activity [13]: In practice this means that amphetamines cause an increase in blood pressure and pulse rate in both animals and humans. In addition to its sympathomimetic effect, methamphetamine has been shown to be neurotoxic *in vivo* [14].

The differences between rasagiline and selegiline at the clinical and preclinical level have been much debated [15–17]. From an evidenced-based perspective, it is difficult to compare the clinical and preclinical effects of both agents because there are only few head-to-head studies. This review critically explores the evidence for preclinical differences between rasagiline and selegiline, and discusses the relevance of these differences for the treatment in PD. Preclinical studies refer to *in vitro* and animal studies before proceeding to human subjects and research studies to reveal the pharmacodynamic effects underlying the clinical effects.

Differences in pharmacodynamics related to MAO-B inhibition?

Selective inhibition of MAO-B

MAO-A and -B inhibitory activities of rasagiline have been compared to those of selegiline in various tissues (e.g. brain, intestine and liver) of mice, rats, cats and monkeys both *in vitro* and *in vivo* [15]. Depending on their concentrations, both agents inhibit the two MAO isoenzymes *in vitro*: rasagiline and selegiline were shown to possess highly potent selective irreversible inhibitory activity of MAO-B *in vitro* with equal IC_{50} values (4 nM); the degree of selectivity of rasagiline for inhibition of MAO-B, compared to MAO-A was similar to that of selegiline [18]. However, *ex vivo* studies have demonstrated that rasagiline is significantly more potent than selegiline in regard to the inhibition of brain MAO-B activity in chronically (21 days) orally treated rats [18]: The doses that selegiline required to reach a clinically relevant degree of MAO-B inhibition in the brain (i.e. ~80%) were about ten times those required for rasagiline to produce the same effect: For this reason, the dosages are adapted appropriately (approved daily dose 1 and 5–10 mg for rasagiline and selegiline, respectively).

Effects induced by MAO inhibition

The MAO-B inhibitory properties of rasagiline and selegiline are attributed to irreversible covalent binding of their propargyl moiety to the flavin adenine dinucleotide (FAD) moiety of the enzyme located in the outer mitochondrial membrane. By binding to the FAD moiety, these MAO-B inhibitors inactivate the enzyme. Therefore the recovery of MAO-B activity after *in vivo* inhibition by rasagiline and selegiline is related to the *de novo* synthesis of the enzyme protein. The 1:1 interaction of the propargyl moiety with MAO-B has been used to determine the molecular turnover of the enzyme in the oestrous cycle and its regulation by steroids in the adrenal gland and brain [19]. Indeed, a comparison of the turnover of rat striatal MAO-B inhibition by rasagiline and selegiline showed remarkable similarities [18,20].