British Journal of Pharmacology (2004) 143, 371–378
www.nature.com/bjp

Cardiovascular activity of rasagiline, a selective and potent inhibitor of mitochondrial monoamine oxidase B: comparison with selegiline

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1 Selegiline is used for treating Parkinson's disease. Despite its efficacy, the clinical use of selegiline in combination with L-dihydroxphenylalanine in Parkinsonian patients is hampered by cardiovascular complications, such as hypotension. This study was designed to compare in rats the cardiovascular effects of selegiline and rasagiline, their metabolites L-methamphetamine and aminoindan (TVP-136), respectively, and the second rasagiline metabolite non-monoamine oxidase (MAO) inhibitor TVP-1022 (*N*-propargyl-1*S*(−)aminoindan).

2 Intravenous (i.v.) administration of selegiline and rasagiline (1 mg kg^{-1}) to anaesthetized rats (thiobutabarbital, 100 mg kg^{-1}, i.p.) did not affect mean arterial pressure (MAP), carotid blood flow (CBF) or carotid vascular resistance (CVR). Selegiline (10 mg kg^{-1}, i.v.) decreased MAP, CBF and increased CVR. In contrast, rasagiline (10 mg kg^{-1}, i.v.) caused a small transient decrease in MAP, while CBF and CVR were unchanged.

3 L-methamphetamine (1 mg kg^{-1}, i.v.) administration provoked a dramatic and long-lasting depressor response, decreased CBF and increased CVR. In contrast, injection of aminoindan or TVP-1022 at a similar dose produced gradual nonsignificant decreases in MAP and CBF.

4 Chronic oral treatment (21 days) of awake rats with selegiline at 10 mg kg^{-1} decreased systolic blood pressure (SBP), diastolic blood pressure (DBP), and MAP, whereas heart rate was unaffected. Since the effective MAO-B inhibitory and clinical dose of rasagiline is about one-tenth that of selegiline, administration of 1 mg kg^{-1} day^{-1} rasagiline resulted in moderate decreases in SBP, DBP, and MAP, which were significantly lower than those caused by the 10 mg kg^{-1} day^{-1} dose of selegiline.

5 These findings indicate that rasagiline, when given at doses equivalent to selegiline, is less likely to be hypotensive.

British Journal of Pharmacology (2004) **143,** 371–378. doi:10.1038/sj.bjp.0705962

Keywords: Monoamine oxidase (MAO) A and B; deprenyl (selegiline); rasagiline; irreversible inhibitors; Parkinson's disease; dopamine

Abbreviations: ANOVA, analysis of variance; CBF, carotid blood flow; CVR, carotid vascular resistance; COMT, catechol-*O*-methyltranferase; DBP, diastolic blood pressure; HR, heart rate; L-DOPA, L-dihydroxphenylalanine; MAO, monoamine oxidase; MAP, mean arterial pressure; SBP, systolic blood pressure; TVP-136, aminoindan; TVP-1022, *N*-propargyl-1*S*(−)aminoindan

Introduction

Rasagiline, a potent, selective monoamine oxidase (MAO) B inhibitor, is being developed for Parkinson's disease as monotherapy or as an adjunct to L-dihydroxphenylalanine (L-DOPA) therapy (Youdim *et al*., 2001; Finberg & Youdim, 2002; Parkinson Study Group, 2002; 2004; Gassen *et al*., 2003). Phase III controlled studies have shown that rasagiline is effective with a dose of as low as 1 mg kg^{-1} in monotherapy (Parkinson Study Group, 2002) and as an adjunct to L-DOPA, comparable in its effect to the anti-Parkinson catechol-*O*-methyltranferase (COMT) inhibitor, entacapone (Brooks & Sagar, 2003). Rasagiline exhibits neuroprotective activities both *in vitro* and *in vivo* (for a review, see Mandel *et al*., 2003; Youdim, 2003), which may contribute to its possible disease-modifying activity (Parkinson Study Group, 2004). It is metabolized to its major metabolite aminoindan (Youdim *et al*., 2001), which also has neuroprotective activity against serum deprivation and L-methamphetamine-induced neurotoxicity in partially differentiated PC-12 cells (Am *et al*., 2004). By contrast, selegiline (l-deprenyl), a selective MAO-B inhibitor, which is a useful anti-Parkinson drug both in monotherapy (Parkinson Study Group, 1989) and as an adjunct to L-DOPA therapy, and has L-DOPA sparing action (Birkmayer *et al*., 1977; Parkinson Study Group, 1989; Riederer & Rinne, 1992), is a propargyl derivative of L-methamphetamine. Thus,

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Advance online publication: 31 August 2004

the major metabolite of selegiline, L-methamphetamine (Shin, 1997; Szoko *et al*., 1999; Kraemer & Maurer, 2002), is neurotoxic (Abu-Raya *et al*., 2002; Am *et al*., 2004). In contrast to aminoindan, L-methamphetamine prevents the neuroprotective activities of rasagiline and selegiline in partially differentiated cultured PC-12 cells (Am *et al*., 2004). Selegiline and methamphetamine, unlike rasagiline and aminoindan, have sympathomimetic activity (Simpson, 1978) that increases heart rate (HR) and blood pressure (BP) (Finberg *et al*., 1980; 1999). Recent studies by Glezer & Finberg (2003) have indicated that the sympathomimetic action of selegiline can be attributed to its L-methamphetamine and amphetamine metabolites. These properties are absent in rasagiline and in its metabolite aminoindan. Parkinsonian patients receiving combined treatments with selegiline plus levodopa have been reported to have a higher mortality rate than those treated with levodopa alone (Lees, 1995). This is not related to its MAO-B inhibitory activity, but rather attributed to its sympathomimetic action and methamphetamine metabolites (Reynolds *et al*., 1978; Lavian *et al*., 1993). Since rasagiline is a new anti-Parkinson drug with no sympathomimetic activity and promising clinical value (Parkinson Study Group, 2002; 2004), our major aim was to compare for the first time the acute and chronic cardiovascular actions of these drugs and their respective major metabolites in rats.

Methods

Studies were conducted on Sprague–Dawley rats (Harlan Laboratories, Ltd., Jerusalem, Israel), weighing 290–330 g. The animals were kept in a temperature-controlled room, and were fed standard rat chow containing 0.5% NaCl and tap water *ad libitum*. All experiments were performed according to the guidelines of the committee for the supervision of animal experiments, Technion, IIT.

Drug administration and experimental protocols

Acute cardiovascular effects of selegiline, rasagiline, or their active metabolites administered intravenously to rats This protocol was designed to examine the cardiovascular effects of either selegiline, rasagiline (1 or 10 mg kg^{-1}), or their metabolites, L-methamphetamine and aminoindan (1 mg kg^{-1}) administered intravenous (i.v.) to normal rats. These doses were chosen to give a 10 : 1 ratio of these drugs employed in the clinic (Kalir *et al*., 1981; Parkinson Study Group, 2002; 2004). Rats were anaesthetized with inactin (thiobutabarbital sodium, 100 mg kg^{-1} i.p.; Sigma Chemical Company, St Louis, MO, U.S.A.), and placed on a thermoregulated surgical table to maintain their body temperature at 37°C. The advantage of inactin when administered i.p. to rats is the rapid induction of anaesthesia (usually within few minutes), regular respiration, lack of BP changes, as well as long-standing anaesthesia (7–8 h) which enables to perform any kind of acute experiments without additional anaesthesia administration (Andreucci, 1978).

After tracheostomy, polyethylene catheters (Portex Ltd, Hythe, Kent, U.K.) were inserted into the left carotid artery and jugular vein, for measurements of mean arterial pressure (MAP), and infusion of various solutions, respectively. A solution of normal saline (0.9% NaCl) was infused at a rate equal to 1.5% of body weight throughout the experiment. After an equilibration period of 30 min, the following experimental protocols were performed. For measurements of total carotid blood flow (CBF), the right carotid artery was exposed through a mid-neck incision ($n=6$), and an ultrasonic flowprobe (type 1RB) connected to an ultrasonic flowmeter (model T206, Transonic Corp Inc., Ithaca, NY, U.S.A.) was placed around the carotid artery. Arterial BP was continuously monitored with a pressure transducer (model 156PC05GWL; Microswitch, Freepoint, IL, U.S.A.) connected to the right carotid arterial line. The data of CBF and MAP were continuously recorded by a computerized data acquisition system, using the Labtech Notebook® software. Carotid vascular resistance (CVR), which reflects cerebral perfusion, was calculated on-line by the standard formula (CVR = MAP/CBF). Choosing CBF, rather than renal, mesenteric, or hindquarters blood flow is of physiological relevance to selegiline, since it is known to produce orthostatic hypotension. After surgery and equilibration, baseline measurements were obtained for 20–30 min. Selegiline, rasagiline, L-methamphetamine, or aminoindan were then administered i.v. as bolus injections, at 1 or 10 mg kg^{-1} ($n=4$–6 rats), followed by a ~100 min recording period after each dose administration.

Cardiovascular effects of selegiline or rasagiline given orally to rats This protocol was designed to examine the cardiovascular effects of low and high doses of selegiline or rasagiline (1 or 10 mg kg^{-1} day^{-1}) given orally. Rats were treated daily (at 10:00 h) by gavage with 1 or 10 mg kg^{-1} of rasagiline or selegiline for 21 days, and systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, and HR were measured in conscious rats by the tail cuff technique (IITC, Model 31, Woodland Hills, CA, U.S.A.) before (baseline value) and every 3–4 days following oral administration of each drug. Importantly, although the original method for measuring arterial BP using the tail-cuff provides only SBP values, the equipment used in this study, the IITC Model 31, has a high sensitivity pulse transducer coupled with an accurate microprocessor program, which enabled us to distinguish between SBP and DBP. Rats treated with vehicle (saline) served as controls.

Statistical analysis One-way analysis of variance (ANOVA) for repeated measures, followed by the Dunnett test, were used to compare treatment values with the corresponding control group. For comparison of the graphs representing control and experimental groups, two-way ANOVA was used. A value of $P<0.05$ was considered statistically significant. Data are presented as mean ± s.e.m.

Results

Cardiovascular effects of intravenously administered selegiline or rasagiline

In order to compare the cardiovascular effects of selegiline to those of rasagiline, similar doses of these compounds were administered i.v. Figure 1 summarizes the effects of a bolus i.v. injection of selegiline or rasagiline at a dose of 1 mg kg^{-1} on MAP, CBF, and CVR. Intravenous injection of selegiline gradually decreased MAP from 132 ± 6 to 120 ± 6 mmHg 120 min after administration, CBF was decreased from

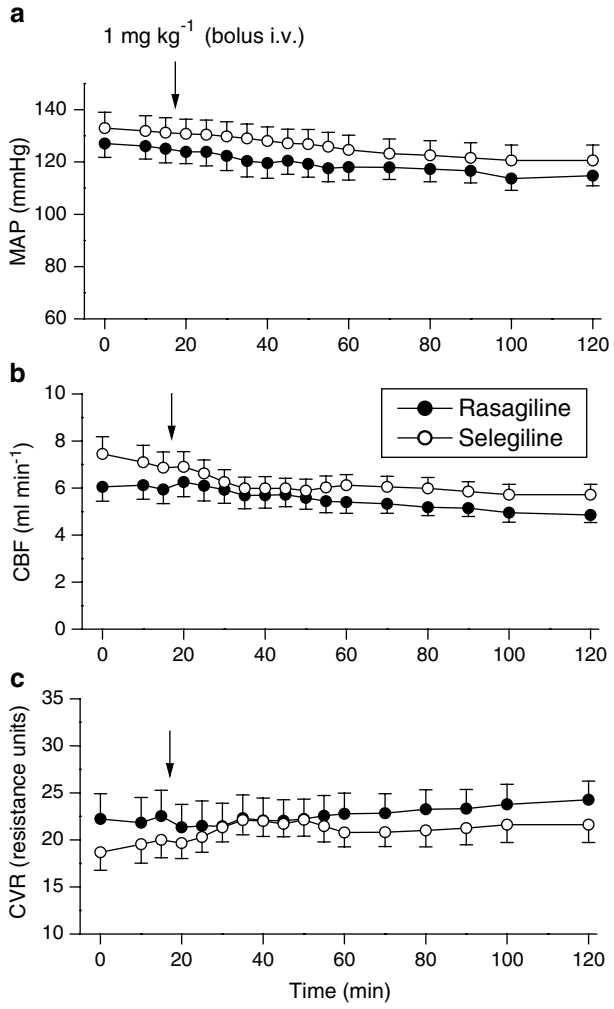

Figure 1 Effects of a bolus i.v. administration (1 mg kg^{-1}) of selegiline or rasagiline on (a) mean arterial pressure, MAP; (b) carotid blood flow, CBF; and (c) CVR, carotid vascular resistance. $N=6$ rats in each group.

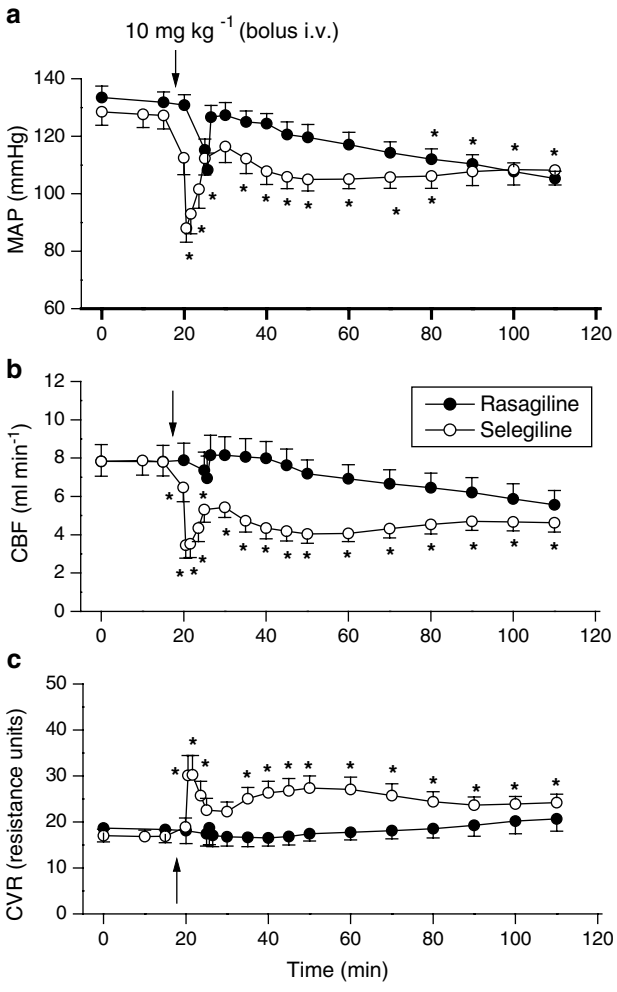

Figure 2 Effects of a bolus i.v. administration (10 mg kg^{-1}) of selegiline or rasagiline on (a) mean arterial pressure, MAP; (b) carotid blood flow, CBF, and (c) carotid vascular resistance, CVR. *$P<0.05$ compared to basal values in both groups. $N=6$ rats in each group.

7.0 ± 0.7 to 5.7 ± 0.4 ml min^{-1}, and CVR was increased from 17.0 ± 1.4 to 22 ± 1.9 RU ($P>0.05$ for each parameter). Administering an identical dose of rasagiline insignificantly decreased MAP from 127 ± 6 to 115 ± 4 mmHg (at 120 min after administration), and CBF from 6.1 ± 0.6 to 5.0 ± 0.4 ml min^{-1}, and increased CVR from 22.2 ± 2.7 to 24.3 ± 2.0 RU. Hence, both drugs affected similarly the cardiovascular parameters measured.

Intravenous administration of selegiline at a dose of 10 mg kg^{-1} caused a marked transient depressor effect, followed by a prompt and sustained recovery of MAP. In fact, 80 min after selegiline administration, MAP was only slightly decreased compared to predrug levels (Figure 2). At the same dose, rasagiline decreased MAP from 134 ± 4 to 108 ± 6 mmHg ($P<0.01$). CBF was markedly reduced by selegiline in a biphasic manner, from 7.8 ± 0.8 to 4.0 ± 0.5 ml min^{-1} (at 120 min, $P<0.05$), but was unaffected by rasagiline. Finally, CVR was increased considerably by selegiline, but was unchanged by rasagiline. To facilitate the analysis of the effect of each drug (at both doses), and the comparison between rasagiline and selegiline, the data were expressed as % change from baseline values. As seen in Figure 3, at a dose of 1 mg kg^{-1}, both drugs affected MAP similarly. In contrast to rasagiline, at a dose of 10 mg kg^{-1}, selegiline immediately after administration caused a marked transient hypotensive effect, whereas at 120 min both drugs induced a similar decline in MAP. As for CBF (Figure 4), at the low dose, both drugs induced a slight ($P>0.05$) decline. At 10 mg kg^{-1}, selegiline caused a marked decline in CBF, while the effect of rasagiline was statistically significant only at 120 min. Finally, at 1 mg kg^{-1} of both drugs, CVR was unaffected (Figure 5). At 10 mg kg^{-1}, selegiline markedly increased CVR, whereas rasagiline was ineffective.

*Cardiovascular effects of i.v. administration of TVP-136 (aminoindan), TVP-1022 (*N*-propargyl-1S(−)aminoindan), and* L*-methamphetamine*

The aim of these experiments was to compare the cardio vascular effects of the active metabolite of selegiline, L-methamphetamine, with the rasagiline metabolites TVP-136 and TVP-1022. To accomplish this aim, 1 mg kg^{-1}

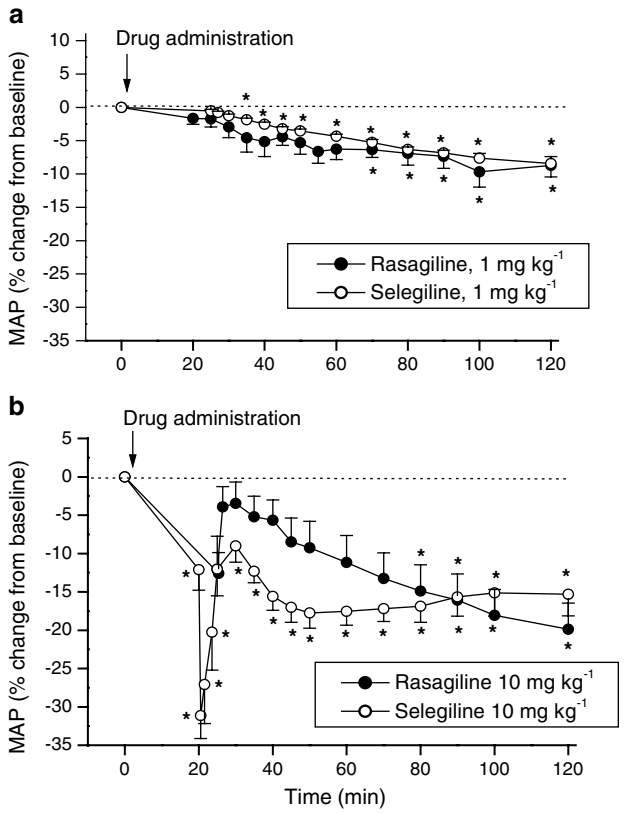

Figure 3 Effects of a bolus i.v. administration of equal doses of selegiline and rasagiline on MAP. Data are expressed as % change from absolute baseline values presented in Figures 1 and 2. The curves representing MAP did not differ between the rats treated with selegiline and rasagiline at $1\,mg\,kg^{-1}$ (by two-way ANOVA), but were statistically different at $10\,mg\,kg^{-1}$.

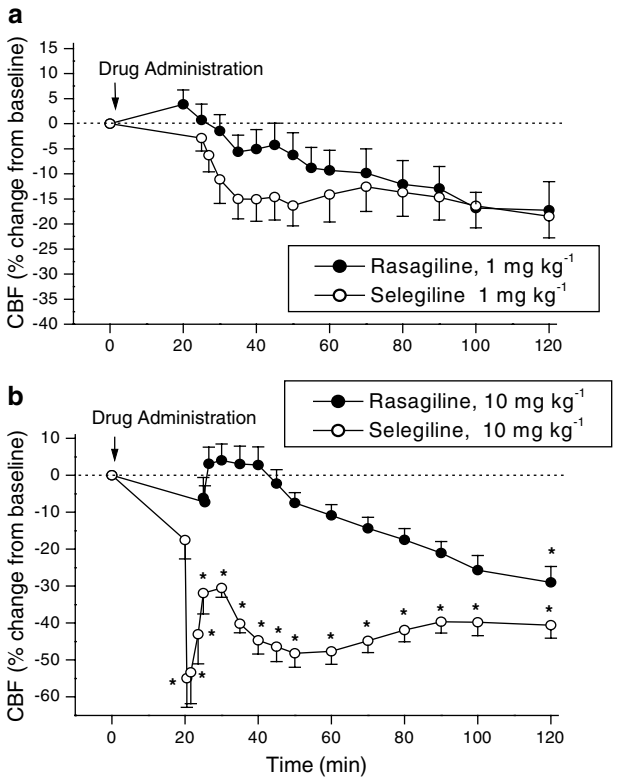

Figure 4 Effects of a bolus i.v. administration of equal doses of selegiline and rasagiline on CBF. Data are expressed as % change from absolute baseline values presented in Figures 1 and 2. The curves differed significantly between rats treated with selegiline and rasagiline at both 1 and $10\,mg\,kg^{-1}$ (two-way ANOVA).

of each compound was administered intravenously, and the cardiovascular changes were monitored. As seen in Figure 6, L-methamphetamine caused a dramatic reduction in MAP, which decreased in a biphasic mode from 135.1 ± 5.8 to 109.6 ± 4.1 mmHg (at 30 min after drug administration). In contrast, both TVP-136 and TVP-1022 (at a similar dose) caused a much milder effect on MAP, which attained statistical significance only from 50 min onwards. Similar to the effect of selegiline (Figure 6), L-methamphetamine decreased CBF and increased CVR along a similar time course (i.e., a transient increase or decrease followed by a decline to a semi-steady-state level). In contrast, both TVP-136 and TVP-1022 caused a much smaller change in CBF and CVR, achieving statistical significance only at time points >50 min after drug administration. The relative effect of each drug on the measured cardiovascular parameters are illustrated in Figure 7.

Cardiovascular effects of oral administration of selegiline and rasagiline

Since rasagiline and selegiline are orally administered drugs, the present protocol was designed to investigate their effects when given orally to rats. Moreover, since the effective clinical dose of rasagiline is about one-tenth of that of selegiline, we compared the cardiovascular effects of $1\,mg\,kg^{-1}\,day^{-1}$ of rasagiline with those of $10\,mg\,kg^{-1}\,day^{-1}$ of selegiline (Figure 8). Vehicle (saline) administration did not affect BP or HR. Daily oral administration of selegiline ($10\,mg\,kg^{-1}\,day^{-1}$) caused a statistically significant depressant effect on SBP, DBP, and MAP (Figure 8), which was evident at early time points. This dose of selegiline did not affect HR significantly. Importantly, administration of $1\,mg\,kg^{-1}\,day^{-1}$ of rasagiline, which is equivalent to $10\,mg\,kg^{-1}$ selegiline, resulted in a moderate but significant decrease in SBP, DBP, and MAP. The curves representing the changes in SBP, DBP, and MAP, but not HR, in response to rasagiline administration throughout the treatment period differ significantly ($P<0.001$, determined by two-way ANOVA) from the corresponding parameters obtained in rats treated with the clinically relevant dose of selegiline ($10\,mg\,kg^{-1}\,day^{-1}$). At this low dose, rasagiline did not affect HR ($P>0.05$) (Figure 8). These findings suggest that rasagiline may be less hypotensive than selegiline.

Discussion

The irreversible MAO-B inhibitor selegiline (l-deprenyl) was identified as an anti-Parkinson drug (Birkmayer *et al.*, 1975; 1977; Lees *et al.*, 1977). Selegiline is widely employed as a monotherapy and as an adjunct to levodopa, together with peripheral decarboxylase inhibitors (Birkmayer *et al.*, 1977). Selegiline is a sympathomimetic amine derived from L-methamphetamine, which increases BP and HR, and its major metabolite, L-methamphetamine has a similar action. Recently,

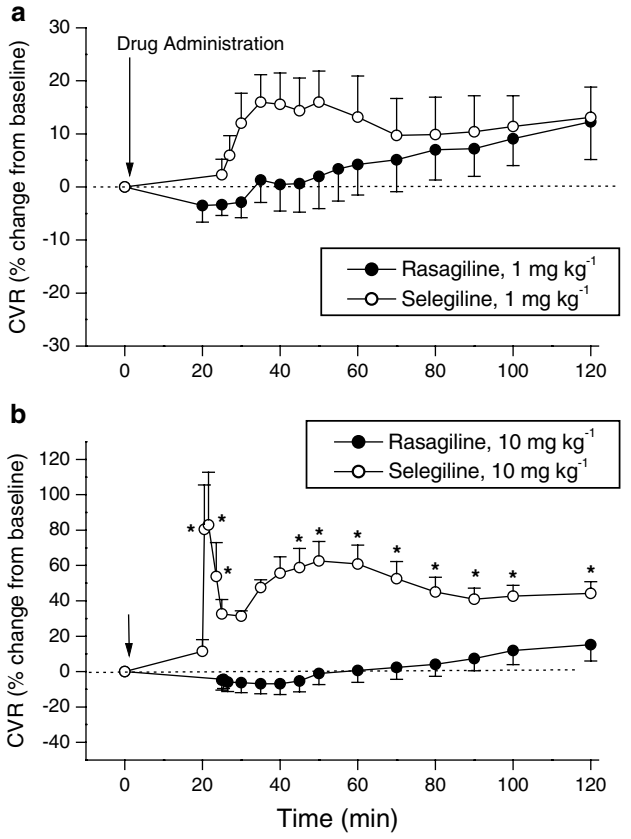

Figure 5 Effects of a bolus i.v. administration of equal doses of selegiline and rasagiline on CVR. Data are expressed as % change from absolute baseline values presented in Figures 1 and 2. The curves differed significantly between rats treated with selegiline and rasagiline at both 1 and 10 mg kg^{-1} (two-way ANOVA).

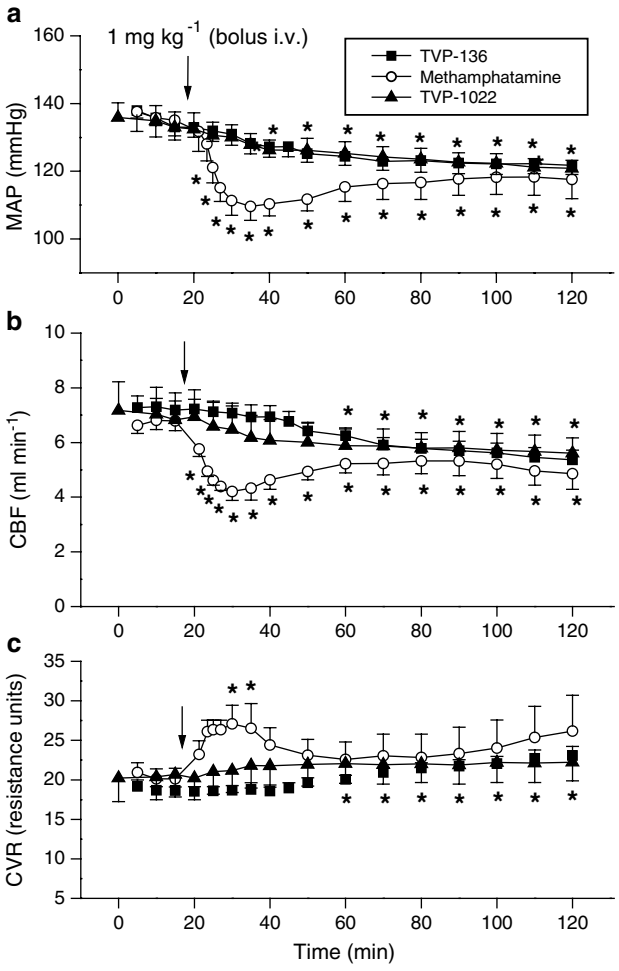

Figure 6 Effects of bolus i.v. administration (1 mg kg^{-1}) of either TVP-136 or TVP-1022 (rasagiline metabolites), or L-methamphetamine, a selegiline metabolite on (a) mean arterial pressure, MAP; (b) carotid blood flow, CBF; and (c) carotid vascular resistance, CVR. *$P<0.05$, compared to basal values. The curves representing MAP, CBF, and CVR differed significantly between the rats treated with L-methamphetamine compared with either TVP-136- or TVP-1022-treated animals (by two-way ANOVA). $N=4$–6 rats in each group.

it was reported that Parkinsonian patients receiving combined treatments with selegiline plus levodopa have a higher mortality rate than those treated with levodopa alone. This has been attributed to its sympathomimetic activity and to the well-recognized orthostatic hypotension side effects of selegiline and levodopa, and is an independent risk factor for mortality in elderly subjects. The newly developed anti-Parkinson drug, rasagiline (Youdim *et al*., 2001; Finberg & Youdim, 2002; Parkinson Study Group, 2002), is a highly potent selective irreversible inhibitor of MAO-B, with $\sim$10 times the potency of selegiline *in vivo* (Kalir *et al*., 1981; Youdim *et al*., 2001; Parkinson study Group 2002; 2004). Unlike selegiline, rasagiline has no sympathomimetic activity, nor is it metabolized to amphetamine or amphetamine-like derivatives, but rather to its major metabolite, aminoindan. Based on the importance of these drugs as anti-Parkinson agents, our major aim was to compare for the first time, the cardiovascular actions of selegiline, rasagiline, and their active metabolites.

The comparison of the cardiovascular effects of i.v. administration of selegiline and rasagiline has been performed taking into consideration that the clinical dosage of selegiline and rasagiline are 10 and 1 mg kg^{-1} day^{-1}, respectively. Thus, our study demonstrates that at 1 mg kg^{-1}, neither drug affected MAP, CBF, or CVR. Since MAO-A is responsible for norepinephrine metabolism, any possible release of noradrenaline by rasagiline would have had a profound effect on the cardiovascular system. By contrast, the 10 mg kg^{-1} equivalent dosage of selegiline profoundly reduced MAP and CBF, and increased CVR. These effects were biphasic, composed of a marked transient effect lasting 5–10 min, followed by a smaller steady-state effect that lasted for the length (120 min) of the experiment. At this i.v. dosage (10 mg kg^{-1}), rasagiline induced a reduction in MAP and CBF, but did change CVR. The comparison of selegiline and rasagiline actions on MAP, CBF, and CVR at the two i.v. dosages are better illustrated in Figures 3–5, where the percentage changes of the cardiovascular effects are presented. This difference between the cardiovascular actions of selegiline and rasagiline may be attributed to the amphetamine action of selegiline from which it is derived. Indeed, i.v. injection of L-methamphetamine, the major metabolite of selegiline, induced changes in MAP, CBF, and CVR, similar to those caused by selegiline (Figures 6 and 7). These results cannot be attributed to the MAO inhibitory activity of methamphetamine, since the latter is a poor reversible inhibitor of MAO-A or -B *in vitro* and not

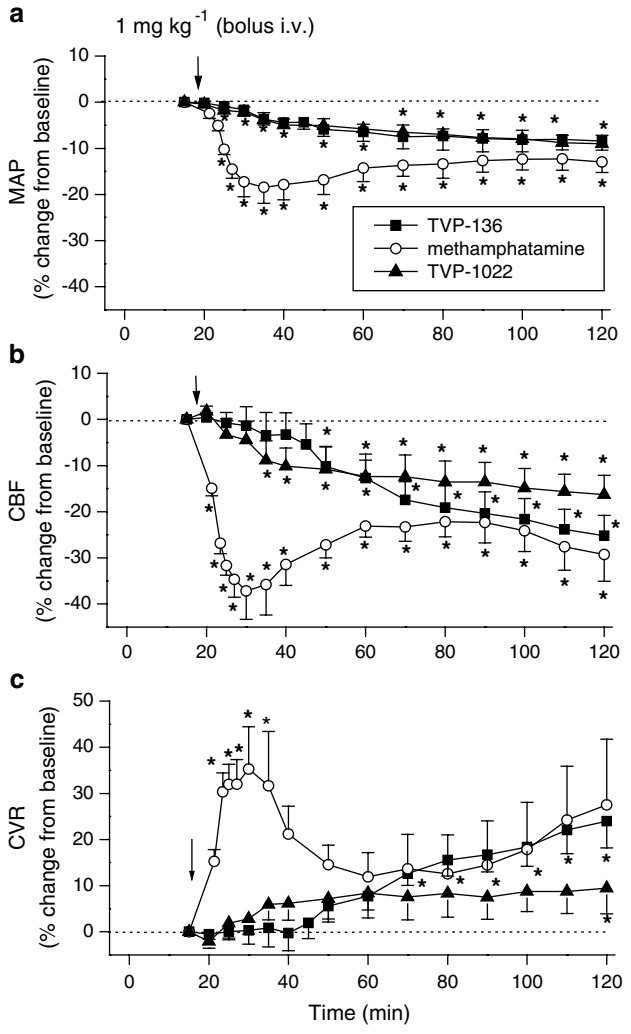

Figure 7 Effects of bolus i.v. administration (1 mg kg^{-1}) of either TVP-136 or TVP-1022 (rasagiline metabolites), or L-methamphetamine, a selegiline metabolite on (a) mean arterial pressure, MAP; (b) carotid blood flow, CBF; and (c) carotid vascular resistance, CVR. Data are expressed as % change from absolute baseline values presented in Figure 6. *$P<0.05$, compared to basal values. $N=4$–6 rats in each group.

in vivo, but rather to its catecholamine-releasing and -uptake inhibitory properties. This is better illustrated by fewer cardiovascular effects induced by aminoindan (TVP-136), the major metabolite of rasagiline and the latter's non-MAO inhibitor S-optical isomer, TVP-1022 (Youdim *et al*., 2001).

Oral treatment of rats for up to 21 days showed a significant difference between selegiline and rasagiline. Oral administration of both drugs caused a significant reduction in SBP, DBP, and MAP from baseline, and compared with the control group. However, when one compares the 1 mg kg^{-1} dosage of rasagiline with 10 mg kg^{-1} equivalent dosage of selegiline in the 21-day chronic treatment studies, profound differences between the actions of the two drugs becomes obvious. While administration of 1 mg kg^{-1} of rasagiline resulted in a mild ($P<0.05$) reduction in SBP, DBP, and MAP, administration of 10 mg kg^{-1} selegiline produced a strong hypotensive response, which was ~2–3 times that observed with rasagiline. Neither drug at these dosages increased HR significantly. However, the slight increase in the HR by both agents suggest that they also act at the cardiovascular level; if their actions were restricted to CNS, one may predict a reduction in HR along the hypotensive effects. An additional mechanism that may have caused the increased HR is the compensatory response to hypotension. These results are in agreement with our findings in the acute protocol, and clearly support the concept that rasagiline has less side effects on the cardiovascular system (such as hypotension), when compared with selegiline at orally applied doses.

In Parkinson's disease, some patients develop impaired cardiovascular reflexes due to autonomic dysfunction leading to impaired BP and HR regulation (Mathias, 1998). This has been attributed to impaired cardiac sympathetic activity (Goldstein *et al*., 2000), but other studies also indicate both sympathetic and parasympathetic failure in Parkinsonian patients (Turkka et al., 1987; Meco *et al*., 1991; Mathias, 1998). The studies of Pavese *et al*. (2004) on the cardiovascular effects of methamphetamine in Parkinson's disease suggests that there is an impairment of catecholamine release from peripheral sympathetic presynaptic terminals.

The mechanisms underlying the hypotensive action of selegiline, in comparison with rasagiline, are not known, and are beyond the scope of the current study. However, the involvement of the sympathetic system is appealing. The observations that the most dramatic declines in MAP and CBF were observed during the first few minutes after i.v. administration of selegiline suggest that the inhibitory actions of selegiline do not involve new protein synthesis/degradation, and probably stem from changes in the autonomic reflexes of the cardiovascular system. Whereas it is well known that all MAO inhibitors induce hypotension with varying potency, the underlying mechanism has not been fully characterized. This may be attributed to α2-adrenoreceptor blockade (Finberg *et al*., 1990), or as Fischer *et al*. (1968) and Kopin *et al*. (1969) have proposed, to the possibility of false neurotransmitter octopamine. Moreover, as mentioned above, reduced activity of the central and peripheral sympathetic nervous system and catecholamine uptake by methamphetamine may be an attractive explanation (Youdim *et al*., 2001). Furthermore, altered baroreceptor function may contribute to the observed severe hypotension (Churchyard *et al*., 1997). The depressant effect of methamphetamine, the active metabolite of selegiline, can be ascribed to its ability to reduce the activity of the sympathetic nervous system, thus leading to a fall in BP, and subsequently to reduced CBF. The latter, especially when lasting for a long period (over 60 min), as seen following selegiline administration, may affect the CNS function, thus aggravating the abnormal regulation of BP. In contrast, rasagiline at comparable doses affected CBF only mildly, thus preserving the CNS from hypoperfusion. A similar vasodepressant effect of selegiline was reported in Parkinsonian patients by Montastruc *et al*. (2000). According to these authors, analysis of the French pharmacovigilance database between 1989 and 1997 (Montastruc *et al*., 2000) revealed that the most often reported adverse drug reaction of selegiline were as expected, psychiatric and orthostatic hypotension. The possible mechanism that may be involved in the exaggerated hypotensive response of selegiline is stimulation of central α-adrenoreceptors activated by elevated levels of dopamine (Pazos *et al*., 1982). The amphetamine metabolites of selegiline may be involved in these processes.

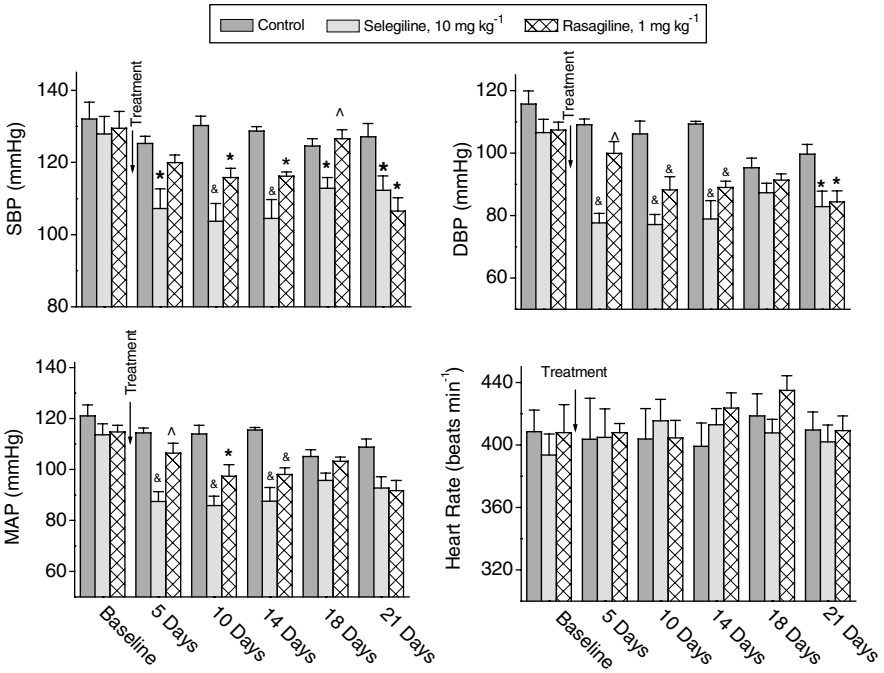

Figure 8 Comparison of the cardiovascular effects of oral administration (1 and 10 mg kg^{-1} day^{-1}) of selegiline or rasagiline. Drugs were administered daily by means of gavage for 21 days. Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR) were measured in conscious rats by means of the tail cuff technique before (baseline value), and at 5, 10, 14, 18, and 21 days of treatment. Rats treated with a saline vehicle served as controls. *$P<0.05$ and $P<0.01$ compared with basal values. #, $P<0.05$ and ^$P<0.01$ vs selegiline 10 mg kg^{-1}. $N=5$ rats in each group. The graphs representing SBP, MAP, and DBP, but not HR differed significantly between the selegiline- and rasagiline-treated rats (by two-way ANOVA).

The elevation of vascular resistance usually reflects enhanced vascular tone due to vasoconstriction. However, the present findings that CVR increased in response to selegiline despite severe hypotension does not fit with this concept. It should be emphasized that vascular resistance is derived from the ratio of BP to blood flow (BF) – (BP/BF), and therefore disproportional reduction of BP and CBF may lead to increased CVR. The fact that selegiline produced a fall in CBF far beyond the reduction in arterial BP, resulted in increased calculated CVR. Interestingly, rasagiline, which provoked mild reduction in BP with mild effects on CBF, did not change CVR.

In summary, the present study demonstrates for the first time that administration of clinical doses of selegiline, either intravenously or orally, provoked a reduction in arterial BP. In contrast, when clinically relevant comparable doses and even higher suprapharmacological doses of rasagiline were injected to normal rats, the cardiovascular response was milder. This key finding indicates that rasagiline, having milder cardiovascular effects, may be a safer therapeutic agent to Parkinson's disease compared with selegiline. In addition, our results provide new insights into the cardiovascular side effects of selegiline, which may be responsible for the few cases of sudden death among selegiline-treated Parkinson patients. The mechanisms underlying the variable hypotensive actions of both selegiline and rasagiline, and the basis for the different cardiovascular responses between these two agents remained to be explored.

This work was gratefully supported by Teva Pharmaceutical Co. (Netanya, Israel), National Parkinson Foundation (Miami, U.S.A.), and the Rappaport Family Institute for Research in the Medical Sciences at the Technion (Haifa, Israel).

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(Received April 10, 2004
Revised July 12, 2004
Accepted July 21, 2004)