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Chronic Treatment of Syrian Hamsters With Low-Dose Selegiline Increases Life Span in Females But Not Males

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STOLL, S., U. HAFNER, B. KRÄNZLIN AND W. E. MÜLLER. *Chronic treatment of Syrian hamsters with low-dose selegiline increases life span in females but not males.* NEUROBIOL AGING **18**(2) 205–211, 1997.—The only intervention conclusively shown to prolong life span in mammals is caloric restriction. Selegiline, a selective, irreversible inhibitor of monoamine oxidase B (MAO-B), is the first drug reported to reproducibly increase mean and maximum life span in animals, although this has only been demonstrated in male rats and mice. The effect on life span is commonly assumed to depend on MAO-B inhibition, but final experimental proof is missing. Therefore, we investigated the possible relationship between selegiline's effect on life span and MAO-B by monitoring survival data and MAO activity in Syrian hamsters of both sexes. Selegiline (0.05 mg/kg) significantly increased life span in female Syrian hamsters, but not in males. In contrast, MAO-B was inhibited equally in both sexes by about 40%, although females had a higher baseline MAO-B activity. No increase in MAO-B with age was observed. Female control hamsters had a shorter life span than male controls. Interestingly, this sex difference dissapeared in the selegiline-treated animals. These findings suggest that the increase of life span by selegiline might be independent of MAO-B inhibition, but is possibly related to mechanisms determining sex differences of life span. © 1997 Elsevier Science Inc.

Selegiline Life span Survival Monoamine oxidase B Sex differences

SELEGILINE (L-deprenyl) is the first selective MAO-B inhibitor introduced into clinical use (2). Today, it is part of the standard treatment regimen of Parkinson's disease (PD) as a safe therapeutic agent (46). Further studies also indicate modest but significant beneficial effects in Alzheimer's disease (AD) [for review see (46)]. Some of the clinical studies suggest that selegiline may not only alleviate symptoms of PD but might even retard the progression of the disease (38) and increase survival of treated patients (3).

Experimental data on the life span of animals are only available for male mice and rats, where long-term treatment with selegiline can increase mean (19,21,30) and maximum life span (21,30) and keeps sexual vigor (24) and learning performance (40) at the level of younger controls. An increase in life expectancy has recently also been reported in male nude mice (11). These findings support the view of a therapeutic potential of selegiline not only against neurodegenerative diseases but also against normal aging and make selegiline the first drug with consistant effects on life expectancy. Up to now, caloric restriction is the only experimental condition conclusively shown to prolong life span in mammals (34).

There still is a controversy whether the inhibition of MAO-B is also responsible for selegiline's effects on life span described above. The nigrostriatal dopaminergic system is known to degenerate rapidly with aging. An initial and widely accepted hypothesis assumes that there might be a fatal threshold in the number of dopaminergic neurons that is reached at the maximum life span of a species (21). Free radical formation resulting from dopamine metabolism by MAO-B has been associated with the age-related decline of dopaminergic neurons (29). Therefore, selegiline-mediated MAO-B inhibition was suggested to slow down the neurodegenerative process by reducing free radical production. Even though there is evidence that selegiline protects dopaminergic neurons from age-related changes (23), it is by no means certain whether the protection is due to the inhibition of MAO-B. Moreover, it is not known whether protecting dopaminergic neurons or inhibiting MAO-B alone increases life span. In contrast, selegiline has recently been demonstrated to rescue rat facial

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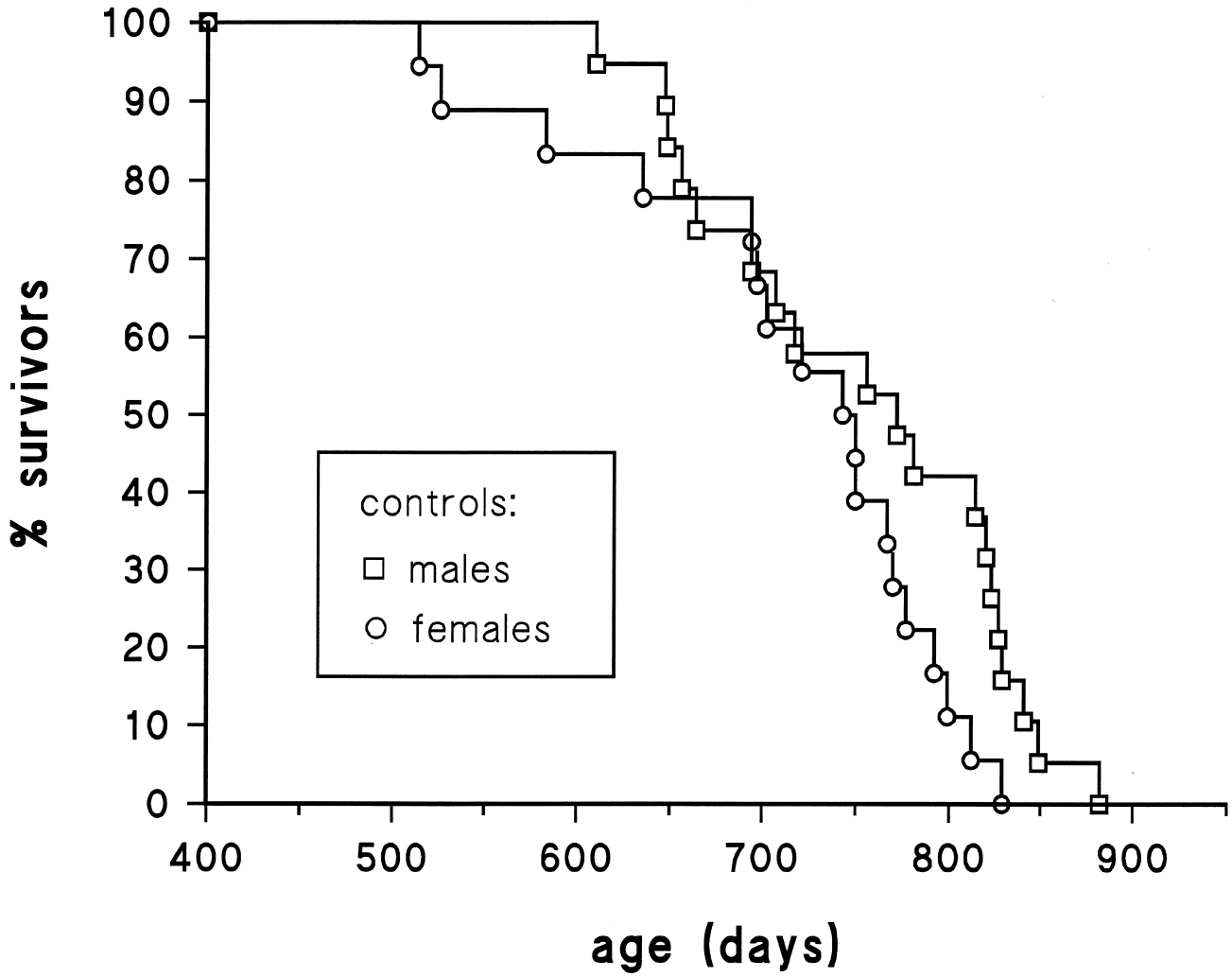

FIG. 1. Survival curves of male (n = 19) and female (n = 18) control hamsters. Male animals tend to live longer than females. Survival analysis was performed with the nonparametric log rank test of SAS 6.10 for windows (p = 0.058).

motorneurons after axotomy at doses two orders of magnitude lower than required for MAO-B inhibition (1). This effect exhibited a 2000-fold greater stereoselectivity than inhibition of MAO-B does (42). Further, low doses of selegiline not sufficient to inhibit MAO-B, show neuronal growth factor-like effects (37) and reduce apoptosis in vitro (43). Taken together, these observations suggest that selegiline's effects on life span might be independent of MAO-B inhibition.

In earlier survival studies in rats, 0.25 mg/kg selegiline SC was usually given three times per week for continous maintanance of MAO-B blockade, because it was previously shown that this treatment exerts almost complete MAO-B inhibition in rat brain (7,28), while MAO-A is not affected. However, no data are available from longevity studies verifying a relationship between MAO-B inhibition and life span.

Therefore, the present study was carried out with the objective to assess the possible relationship between increase of life span and MAO-B inhibition in hamsters of both sexes chronically treated with selegiline by combining the following approaches: 1) The use of a dose regimen expected to yield only low MAO-B inhibition. During prolonged SC treatment with 0.05 mg/kg MAO-B inhibition accumulates up to 75% (28). The inhibition of MAO-B by oral doses of selegiline is about one-third less than the inhibition found by equivalent SC doses in rats (10). Thus, we expected less than 50% inhibition of MAO-B by our schedule of 0.05 mg/kg body weight/day provided in the food. 2) The use of the Syrian hamster (*Mesocricetus auratus*) as a species with low MAO-B activity in the brain (31), which might be specifically sensitive for small changes in MAO-B activity. 3) Monitoring MAO-B inhibition in each animal taking part in the study. 4) Comparison of both sexes as an intraspecies control. This is particularly important because female Syrian hamsters live shorter than male ones (18), contrasting the situation in experimental mice and rats where life expectancy is usually not different in both sexes (12).

METHOD

Animals

Middle-aged Syrian hamsters were purchased as 9-month-old couples of retired breeders from the German Federal Health Administration (Bundesgesundheitsamt). At the age of 13 months

the animals were randomly divided into a group receiving 1.0 mg selegiline per kg food equalling about 0.05 mg selegiline per kg body weight daily (n = 35, 17 males, 18 females) and a control group (n = 37, 19 males, 18 females). Controls got food from the same production lot without selegiline. Food intake and body weight were measured regularly. Animal facilities were checked for dead hamsters twice daily. Deceased animals were immediately frozen for later biochemical assessment of brain MAO activity and for autopsy. In some cases, animals could not be investigated due to cannibalism or strong autolysis.

MAO Assay

Whole-brain MAO-A and MAO-B activities were measured according to a method previously described (47). Briefly, postmortem brains were removed as rapidly as possible and homogenized in 40 ml ice-cold 5 mmol/l potassium buffer pH 7.5 containing 10 mmol/l dithiothreitol, 2.5 mmol/l EDTA, and 0.5 mg/ml bovine serum albumin. After centrifugation of the crude homogenates the resulting pellets were resuspended in potassium buffer at a final concentration of 75 mg wet weight/ml. Brain homogenates were stored at −20°C until use.

For MAO-B assay, tissue homogenates were diluted 1:16 (vol./vol.) with 50 mmol/l potassium–phosphate buffer pH 7.5. The enzymatic reaction was started by adding 30 μl of increasing concentrations of ^{14}C-β-phenylethylamine to 110 μl aliquots of the homogenates. After incubation of the samples for 6 min at 37°C the reaction was terminated with 250 μl 4 mol/l HCl. The ^{14}C-labeled deaminated reaction product was extracted with 1 ml toluol/ethylacetat (1:1; 2 min). Radioactivity of 600 μl of the organic layer was quantified by liquid scintillation counting. "Blank" samples were prepared in analogy after a preincubation for 15 min at 95°C. For MAO-A activity ^{14}C-5-hydroxytryptamine was used as substrate.

Statistics

Survival data of aging populations are not distributed normally. Instead, age-dependent mortality rises exponentially over a large part of the life span following the Gompertz equation (12,13,35). Recent evidence, however, suggests the Gompertz equation does not necessarily hold true at old ages (4,5,12,14). The age-dependent mortality of the oldest individuals of a population does not always increase exponentially, but can increase at a slower rate, stay constant, or even decrease. A parametric statistical test could give misleading results. Therefore, we analyzed the survival data with the log rank test of SAS 6.10 for Windows. The log rank test is a nonparametric test of lifetime data detecting differences in the right tail of the distributions very effectively (27). This is important, as the right tail of the survival curves reflects differences in maximum survival that are more important for aging processes than mean life expectancy (15).

RESULTS

One of the reasons to use hamsters for the present experiments has been the different life expectancy of male and female animals (31). This was already evident in our rather small sample of female and male control animals (Fig. 1), where the latter outlived the females. A more striking sex difference emerged under selegiline treatment. Compared to female controls the survival curve of the chronically treated female hamsters is markedly and significantly shifted to the right (Fig. 2a). Animals dying after the age of 50% mortality appear to profit more than those which die earlier. Maximum life span (the maximum 20% of age) was increased from 408 ± 16 days (controls) to 475 ± 37 days (selegiline) ($p <$ 0.02, t-test). The oldest treated subjects outlived the controls by

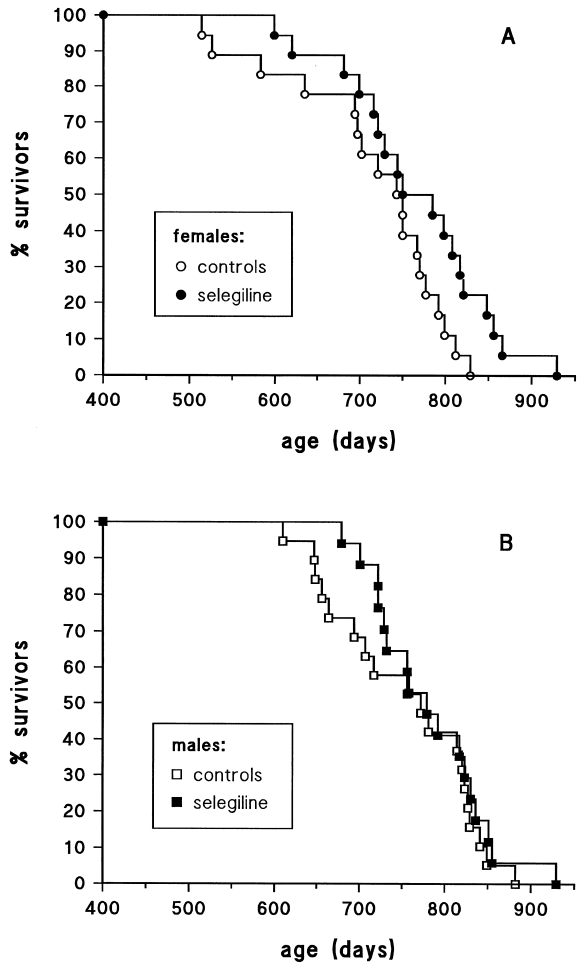

FIG. 2. Survival curves of female (A) and male (B) Syrian hamsters (female control: n = 18, female selegiline: n = 18, male control: n = 19, male selegiline: n = 17). Selegiline was provided at a dose of 0.05 mg selegiline per kg body weight per day by the diet starting at the age of 13 month until natural death. The slopes of the curves of the female hamsters were significantly different ($p < 0.05$, $\chi^2(1) = 3.85$) analyzed by the log rank test.

almost 3 months. This is nearly 10% of their total life span. In contrast to all previous longevity studies with selegiline in male rats and male mice, we did not see any significant effect of selegiline on the survival rates of male hamsters (Fig. 2b). Maximum life span was not different between control (450 ± 23 days) and selegiline treated (468 ± 42 days) males. After selegiline treatment, the significant difference of life span between male and female hamsters (Fig. 1) disappeared (Fig. 3).

Macroscopic pathologic findings were not different between control and selegiline-treated animals (Table 1). In many cases more than one diagnosis per animal was made. Therefore, the number of findings exceeds the number of hamsters examined. The most frequently observed pathologic findings involved the lung, kidneys, liver, or adrenal glands as already described as common causes of spontaneous death in Syrian hamsters (36).

Body weights were recorded every month. The results are summarized in Fig. 4 and indicate no differences between selegiline and control groups for both sexes. In all groups body weight decreases at advanced age, which is consistent with findings of

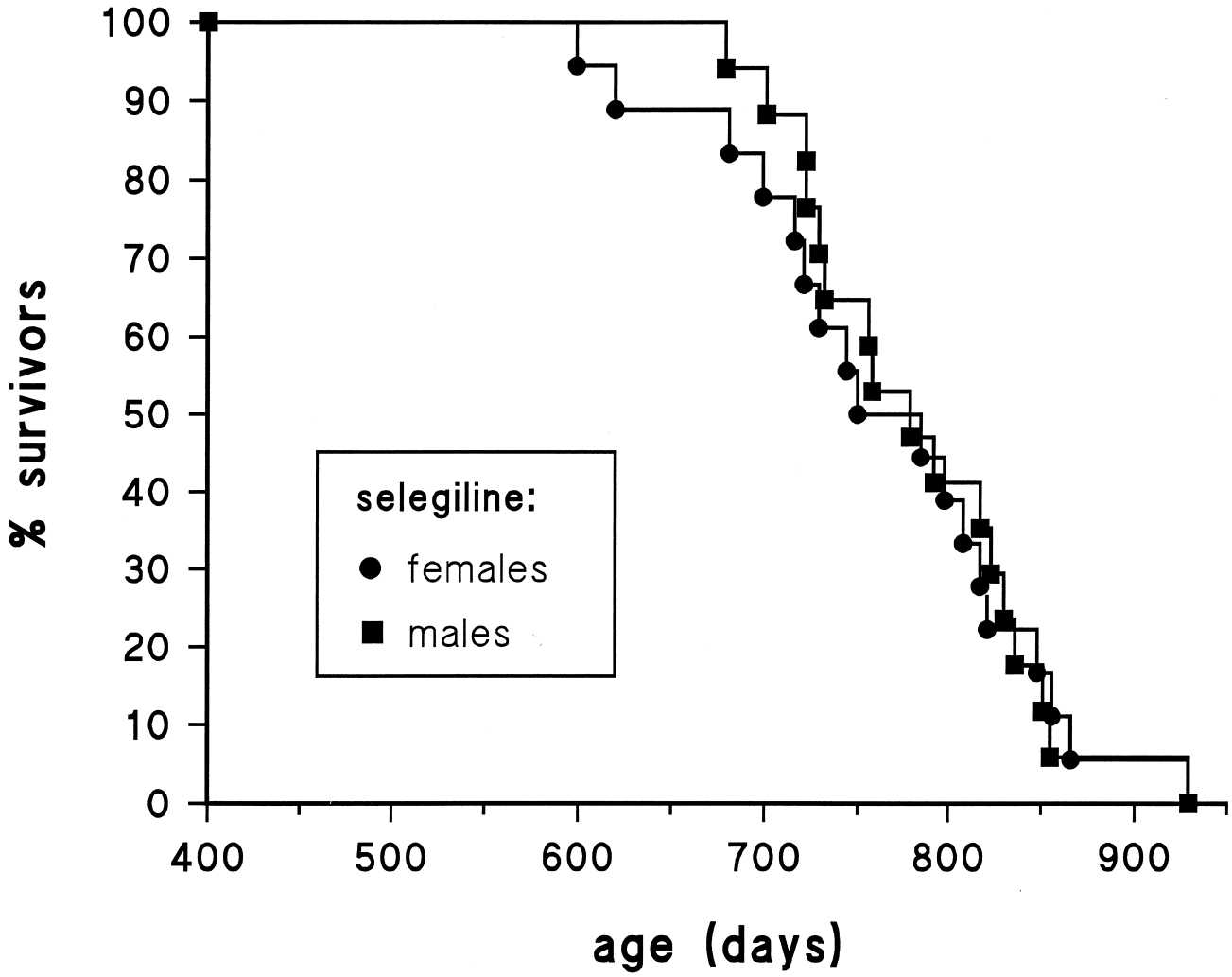

FIG. 3. Comparison between the survival curves of the selegiline-treated animals of both sexes. The slopes of the curves were not significantly different.

other investigators (19,30). In contrast, average food consumption per gram of body weight was constant during the whole treatment period and did not differ between selegiline-treated animals and controls. The mean values ± SD were 0.331 ± 0.017 g and 0.340 ± 0.022 g, respectively.

For the animals investigated (see Table 2) we found no age-related changes of MAO-B and A in hamster whole brain, because neither V_{max} nor K_m values of both enzymes did significantly correlate with age in the control group ($n = 25$) (V_{max} MAO-B: $r = 0.07$, $p = 0.33$; K_m MAO-B: $r = 0.21$, $p = 0.33$; V_{max} MAO-A: $r = 0.07$, $p = 0.75$; K_m MAO-A: $r = 0.01$, $p = 0.96$). No correlations of MAO activity with age existed also in the selegiline-treated group ($n = 21$) (V_{max} MAO-B: $r = -0.23$, $p = 0.31$; K_m MAO-B: $r = 0.03$, $p = 0.88$; V_{max} MAO-A: $r = -0.10$, $p = 0.65$; K_m MAO-A: $r = 0.09$, $p = 0.71$). This parallels findings of (16) in mice, where an age-related increase of MAO-B activity also was not found. In contrast, human brain MAO-B is known to rise with age (9). Similar to observations in mice (44), female hamsters showed significantly higher levels of MAO-B in the brain (Table 2). However, there was only a tendency towards higher MAO-A activity. Nevertheless, selegiline inhibited MAO-B activity equally in both sexes with about 40% inhibition of V_{max} but no effect on K_m (Table 2). MAO-A activity was not altered in both groups (Table 2).

DISCUSSION

It is not clear if that the small decrease of MAO-B activity found in the present experiments leads to relevant changes of dopamine content and metabolism. A recent survival study on mice (45) orally treated with 1.0 mg/kg selegiline has shown that even a reduction of striatal MAO-B by 60% did not change brain dopamine levels. On the other hand, chronic treatment of rats with a four times lower dose did elevate basal dopamine levels in the striatum (6). However, because dopamine is not a specific substrate for type B isozyme and is mainly metabolized by MAO-A in rodents (29), it seems not very likely that the weak inhibition of brain MAO-B in our study is enough to link selegiline's beneficial effects on survival exclusively to effects the drug might have on dopamine metabolism as was proposed earlier (21). It is also very unlikely that MAO-B inhibition in other organs might be relevant for the effects of this drug on the life span of hamsters, because the brain is the most sensitive organ for MAO-B inhibition by selegiline (28).

TABLE 1

INCIDENCE OF PATHOLOGICAL FINDINGS IN MALE (n = 17) AND FEMALE (n = 18) SYRIAN HAMSTERS TREATED WITH 0.05 mg SELEGILINE PER kg BODY WEIGHT IN THE FOOD AND IN CONTROLS (MALE: n = 19, FEMALE: n = 18)

	Control		Selegiline	
Diagnosis	Male	Female	Male	Female
Negative	6	4	4	5
Alveolar edema	4	1	5	3
Cerebral hemorrhage				1
Gangrene			2	
Gastritis		1	1	
Heart lesion		1		
Hepatoma			1	1
Kidney tumor	1	1	1	1
Liver cysts	2	1	4	2
Nephritis		1	1	1
Ovarian tumor				1
Pulmonary tumor	1		1	
Pancreatitis	1	1	1	
Pneumonia	2	1		3
Tumor of adrenal gland	4	2	2	
Tumor of auricular appendix	3		3	3
Thyroid tumor	1			
Urogenital diseases	3		4	

The chi-square test did not reveal any significant differences among groups.

Instead, our findings of an equally low inhibition of MAO-B in both sexes, but a significant effect on life span only in the female animals support the conclusion that the inhibition of MAO-B is not relevant in this respect. However, we cannot completely rule out at present that female hamsters have a specific susceptibility for very small changes of MAO-B activity, especially because low inhibition already protects against MPTP toxicity (17).

An alternative explanation for the effects of selegiline on aging could be the reduction of food intake, as selegiline's metabolism leads to amphetamine derivatives (28). Dietary restriction is the only intervention consistently shown to extend both median and maximal life span in many species (34), including hamsters (41). Yet, our data about food consumption and body weight (Fig. 4) strongly argue against a potential role of dietary restriction, a conclusion that is in line with several other reports on selegiline (19,21,28).

Combined overexpression of superoxide dismutase and catalase was recently shown to extend the life span of *Drosophila melenogaster* (33). Selegiline can increase SOD and CAT activities in certain brain areas of rats (especially the striatum and substantia nigra) with a dose–response relationship depending on gender and age of the animals (20). Again, this could be an attractive explanation for its effects on longevity in our animals. However, by extrapolating the data in rats, our dosage is most likely too low to enhance SOD or catalase activities substantially. Significant changes required doses of at least 0.1 mg/kg/day in F-344 rats (20) or more than 0.25 mg selegiline/kg/day in CFY rats (22), both given subcutaneously. These doses, in turn, have more pronounced effects on MAO-B activity than the ones we observed (28).

Selegiline shows neuronal growth factor-like effects in tissue cultures at doses that do not inhibit MAO-B (1). If similar properties are present in vivo, they might be relevant for its effects on maximum life span. In this case, the sex difference of its effect on survival might be related to modulating effects of sex hormones on neuronal growth factor function. In fact, a reciprocal regulation of estrogen and NGF receptors by their ligands was described recently (39).

As gonadal steroids modulate apoptosis at least in the developing brain (32), it can also be speculated that the known protection from apoptosis by selegiline (43) could be modulated by sex hormones. Especially in view of the unaltered pathology this alternative concept of selegiline increasing life span by protecting cells from genetically programmed death is very appealing, even though the findings for neuronal cells (43) do not necessarily hold true for apoptosis in all somatic cells (8).

Finally, very recent data (25,26) suggest that very low doses of selegiline might enhance the activity of catecholaminergic neurons by an yet unknown mechanism, but independent of MAO-B inhibition.

In conclusion, our data confirm and importantly extend the

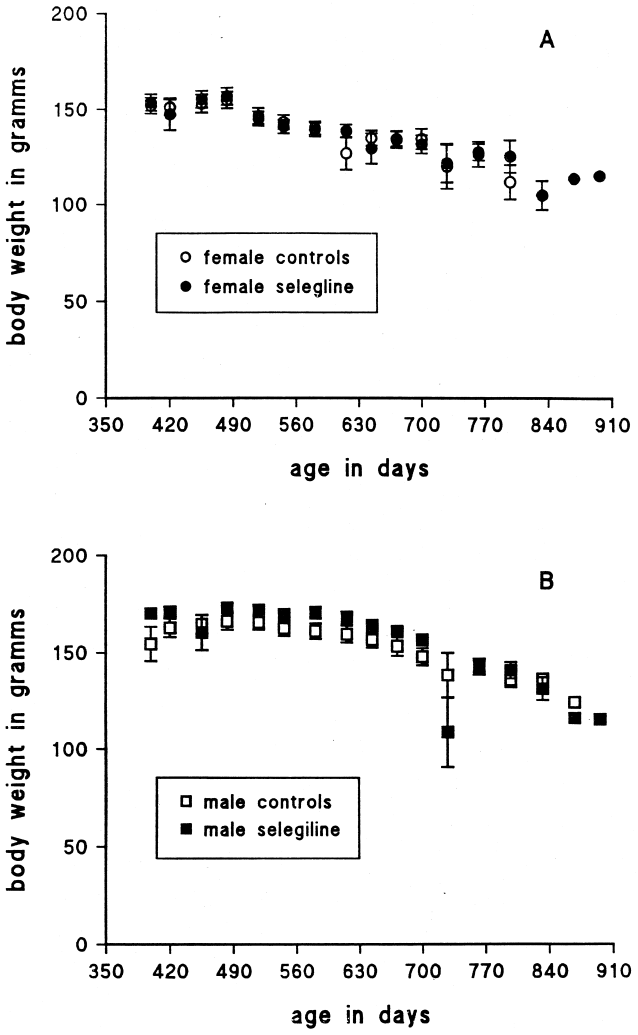

FIG. 4. Mean body weights and variances (± standard error) of female (A) and male (B) hamsters. Values were recorded monthly. No differences could be detected between selegiline groups and controls by analysis of variance.

TABLE 2

KINETIC CONSTANTS OF BRAIN MAO-A AND MAO-B IN MALE AND FEMALE SYRIAN HAMSTERS (MEANS ± SEM)

	MAO-A (5-HT)		MAO-B (PEA)	
	K_m	V_{max}	K_m	V_{max}
Males				
Control	80.69 ± 9.13	0.91 ± 0.17	12.50 ± 1.28	0.19 ± 0.02
Selegiline	91.13 ± 16.89	0.79 ± 0.11	10.51 ± 1.96	0.12 ± 0.02†
Females				
Control	112.44 ± 16.38	1.18 ± 0.22	12.47 ± 2.00	0.26 ± 0.03*
Selegiline	113.91 ± 19.94	0.88 ± 0.13	11.44 ± 1.82	0.16 ± 0.02*†

K_m values are expressed in μmol/l, V_{max} values in nmol/min/mg protein (male control: $n = 15$, male selegiline; $n = 10$, female control: $n = 10$, female selegiline: $n = 11$). Analysis of variance indicates significant sex differences in MAO-B activity (*$p < 0.0205$ vs. males, $F = 5.80$), but not of MAO-A activity and a significant treatment effect by 0.05 mg selegiline/kg body weight/day (†$p < 0.0020$ vs. controls, $F = 10.89$).

findings of a beneficial effect of selegiline on survival of experimental animals. It is the first report providing evidence that an increase of life span can still be achieved by a very low dose (0.05 mg/kg/day) of selegiline, which only partially inhibits MAO-B (40% reduction). This is only observed in females in spite of the fact that the same degree of MAO-B inhibition is achieved in both sexes. This study supports other studies suggesting that the effect of selegiline on longevity may involve factors other than MAO-B inhibition. In addition, our observation that females had higher baseline MAO-B levels than males suggest the need to consider this (together with other mechanisms determining life span between male and female animals) as potential factors influencing longevity. It is certainly premature to draw any conclusions from our data for the therapeutic potential of selegiline on longevity in human, but our findings strongly confirm the use of selegiline as a pharmacological tool in studies on aging and survival.

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