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L-Deprenyl Treatment in Aged Mice Slightly Increases Life Spans, and Greatly Reduces Fecundity by Aged Males

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Male and female B6D2F1 (C57BL/6J × DBA/2J)F1 and B6CBAF1 (C57BL/6J × CBA/CaHT6J)F1 mice were injected subcutaneously 3 times a week with L-deprenyl (0.25 mg/kg) starting at mean ages of 26 months and 18.5 months, respectively. Life spans of aging mice were increased 6–9% by the drug. While none of the life span effects were significant for a single genotype and gender, life spans were significantly longer in L-deprenyl-treated animals (p = .011) when all data were combined. L-deprenyl-injected mice consumed about the same amounts of food as controls: L-deprenyl 3.1 g/day, control 3.3 g/day, after 7 months of treatment. There were no significant effects of L-deprenyl on measures of changes with age in the following biological systems: activity, excitement, red blood cell mass, collagen denaturation rate, and wound healing rate. L-deprenyl-treated B6CBAF1 males and females were significantly heavier than controls after 4–6 months of treatment. To measure fecundity, B6CBAF1 males at an average age of 750 days were each caged with two young B6 females; 10 of 17 L-deprenyl-injected males sired an average of 31.3 pups per male, while 14 of 24 controls sired 82.1 pups per male.

L-DEPRENYL has been approved by the FDA to treat Parkinson's disease, and is usually used in conjunction with L-Dopa (Knoll et al., 1989). Knoll and colleagues have reported a 30.5% increase in Wistar × Logan rat life spans with L-deprenyl injections started at 730 days; controls lived to a mean age of 1,029 days, and the L-deprenyl-treated lived to a mean age of 1,343 days. The same authors reported that male sexual performance doubled after 30 weeks of treatment, and that conditioned avoidance responses increased fourfold with the injection of L-deprenyl. Yen and Knoll (1992) reported significant increases in life span and memory function in mice injected with L-deprenyl, starting at 12 months of age, as well as using combinations of L-deprenyl and Dinh Lang (Policias Fruticosum L.). Brandeis et al. (1991) reported improvement of cognitive function by injection of L-deprenyl in 24.5-month-old Sprague-Dawley rats. Knoll (1991) also reported a threefold increase in SOD activity in the striatum of male F344 rats, after only 3 weeks of daily injections of L-deprenyl.

When Milgram et al. (1990) attempted to replicate Knoll's studies in 24-month-old male Fischer 344 rats, they found a 2.2% increase in mean life span, considerably less than the increases reported by Knoll et al. (1989), and found that body weights declined less rapidly with age in the L-deprenyl-treated rats. Ingram et al. (1993) found a marked 60% striatal MOA-B inhibition in C57BL/6J male mice given L-deprenyl in the water at 1.0 mg/kg/day starting at 18 months of age, but there was no increase in life span when the experiment ended after 6.5 months of treatment. There were also no substantial benefits from L-deprenyl treatment in a battery of six behavioral measures.

Because of inconsistencies in results from previous studies and because L-deprenyl is being promoted for self-medication as a general anti-aging therapy (Knoll et al., 1989), we tested its effects on longevities in two F1 hybrid mouse types often used in studies on aging. B6D2F1 mice are a standard genotype, and B6CBAF1 mice combine two standard long-lived inbred strains; in our hands both are long-lived for their species (Harrison and Archer, 1983, 1987). We also compared genders, and our studies are the first that we are aware of to define effects of L-deprenyl in females. Since all individuals in each inbred strain or F1 hybrid are genetically identical, it is vital to test diverse genotypes in order to distinguish effects unique to a particular strain from effects general for a species. L-deprenyl treatment is potentially interesting because it has been reported to increase maximum life spans in rats to beyond those normally found in that species. To increase maximum life spans, all biological systems must function for longer periods than normal, since individuals live only until the first vital biological system fails. Therefore, a treatment that increases maximum life span appears to increase functional periods in all vital biological systems that may fail. This suggests alterations in underlying mechanisms affecting aging in multiple biological systems. Changes in such mechanisms may also allow rapid evolutionary changes in longevities such as those reported by Austad (1993). Prior work leading to the hypothesis that L-deprenyl retards basic aging processes predicts that it should increase life spans in general, and old male fecundity in particular, in our long-lived F1 hybrid mice. However, we found only slight benefits in life span and strong deleterious effects on male fecundity.

METHODS

Mice. — Male and female B6D2F1 and B6CBAF1 mice were produced and maintained at The Jackson Laboratory, which is fully accredited by the American Association for Accreditation of Laboratory Animal Care. All mice were virgins, and were introduced into the research colony when

weaned at 4 weeks of age and housed 4 per side in filter-hooded, double-sided plastic cages.

The mice were kept in an isolated animal colony under positive air pressure, with filtered air, room temperatures of 22 ± 2 °C, and light from 7 a.m. to 7 p.m. Quarterly, at least 20 middle-aged or old mice from this colony were used for routine animal health assessment by The Jackson Laboratory's diagnostic laboratory. In addition, pathologists screened any mice that appeared ill without explainable cause, such as extreme age or experimental treatment. Details of the testing procedures have been published (see Harrison and Archer, 1983). No pathogenic organisms have been detected, since a single positive test for mouse hepatitis virus in December, 1982.

Mice consumed a pasteurized diet (Emory Morse Co., Jackson Laboratory diet 96WA) containing 357 C/100 g, 22% protein, 7% fat, and 50% nitrogen free extract; they received ad libitum food and chlorinated water, acidified to prevent growth of *Pseudomonas*. The mice were untreated until 16–28 months of age; at that point, they were gently restrained by picking them up and inverting them once each day for a week to acclimate them to handling before starting injections. Ages were matched in the treated and control groups.

Males and females were injected subcutaneously (sc) with .25 mg/Kg of L-deprenyl 3 days per week — on Monday, Wednesday, and Friday — for the rest of their lives; the saline controls were injected in the same way. Food consumption was measured once a month in both groups, to determine whether L-deprenyl caused any alteration in food consumption.

The rationale for the starting time, route of administration, and amount of L-deprenyl administered was to duplicate Knoll's studies as closely as possible (Knoll, personal communication, 1990). The L-deprenyl was a gift from Somerset Pharmaceuticals (Tampa, FL). L-deprenyl solutions were made up once a month as in Knoll et al. (1989), then frozen at –20 °C. Mice were weighed monthly to ascertain possible differences in weight due to the drug, or to the injections, and also to help monitor the health of animals. Aging mice were monitored starting at the time of the first injection and continuing, daily during the week, and once on the weekend, for the rest of their life span. Therefore, life span is expressed in days (± 1 day).

Measures of aging in various biological systems. — Only mice appearing healthy to an experienced observer were used for tests of age effects on a variety of different biological systems. This assessment was based on normal activity, normal responses to handling, and external appearance (including eyes and pelt), and on the absence of discharges, recent weight loss, and palpable lumps. More importantly, the tests did not harm the subjects, so subsequent longevities were determined after testing.

The following tests have been described previously (Harrison and Archer, 1987):

Voluntary activity was measured using the open field test (OF) as the number of squares crossed in a lighted box in 5 minutes. Excitement (boli) was measured as the number of fecal boli deposited during the 5-minute open field test. Hematocrit (HCT) was determined on blood samples from the retro-orbital sinus. Extracellular macromolecular aging was measured as the tail tendon collagen (TTC) denaturation rate using single fibers immersed in a bath of 7 M urea at pH 7.5 and 45 °C, while holding a 2 g weight (Harrison and Archer, 1978). Wound healing (WH) was the time required for the wound to heal over smoothly after the extraction of about half of the fibers in one of the lateral tail tendons.

In testing fecundity, male B6CBAF1 mice were injected starting at 569 days for L-deprenyl-treated groups and at 562 days for saline-treated groups, giving average ages for the mice that produced litters. Fecundity was tested after 181 days of treatment, so that when males averaged about 750 days old, each was caged separately with two 4-week-old C57BL/6J females. Cages were checked for litters 3 times a week, and pups were counted and removed as soon as they were found, until no more litters were produced. The females remained with the males for the rest of the males' life spans, and cages were checked at least once a week.

Since histograms of our life span and other data appeared roughly Gaussian, statistical treatment effects were assessed with the unpaired *t*-test, three-way ANOVA, and general descriptive statistics (means, standard error, and graphics), all from Statview, version 4.0 (Abacus Concepts, Berkeley, CA).

RESULTS

Life spans. — We performed two experiments, the first using B6D2F1 males and females, and the second using B6CBAF1 males and females. In the first, L-deprenyl injections were initiated at 26 months of age, and in the second, treatment began at 18.5 months of age. Compared to controls injected with saline, mice given L-deprenyl had mean life spans increased 9% for 22 B6D2F1 males, 9% for 21 B6D2F1 females, 6% for 21 B6CBAF1 males, and 7% for 21 B6CBAF1 females (Table 1). None of these increases alone was statistically significant. A three-way ANOVA on all the data showed a significant gender effect ($p = .0003$) and treatment effect ($p = .001$); none of the other main effects or interactions was significant, with all p's $>.40$ (Table 1).

Calories eaten and weights. — Food consumption for both males and females was identical in L-deprenyl and control groups. The average food consumption per mouse per day for B6CBAF1 males and females after 7 months of treatment was 2.6 ± 0.2 g (42) for groups given L-deprenyl, and 2.9 ± 0.2 g (38) for controls. L-deprenyl-treated B6D2F1 females and controls had nearly identical body weights, but the female B6CBAF1 mice and male mice of both F1 hybrids tended to weigh more in the L-deprenyl group compared to the controls during the first 10.5 months of treatment (Table 2). Thus, there was no evidence that L-deprenyl treatment might increase life span by reducing food consumption.

Aging in different biological systems. — There were no significant effects of L-deprenyl treatments in several differ-

Table 1. Life Spans of L-Deprenyl-Treated and Control Mice (B6D2F1 and B6CBAF1)

Strain and Treatment	Sex	Mean	*SE*	*n*	Median	Max. 10%
B6D2F1						
Deprenyl	M	1056	35.2	22	1064	1325
Control	M	972	37.5	20	1036	1149
Deprenyl	F	975	28.4	21	949	1198
Control	F	898	45.4	22	950	1207
B6CBAF1						
Deprenyl	M	1050	46.6	21	1073	1327
Control	M	994	32.4	28	1003	1235
Deprenyl	F	931	38.7	21	933	1295
Control	F	872	19.9	17	898	987

Three-way ANOVA comparing genotypes and genders and treatment.

	df	Sum of Square	Mean Square	*F*-value	*p*-value
Strain	1	7049.6	7049.6	.2	.631
Gender	1	413466.4	413466.4	13.5	.0003
Strain × Gender	1	19482.9	19482.9	.6	.4253
Treatment	1	200115.1	200115.1	6.6	.011
Strain × Treatment	1	5583.2	5583.2	.2	.669
Gender × Treatment	1	43.6	43.6	<.1	.97
Stran × Gender × Treat.	1	269.2	269.2	<.1	.93
Residual	163	4971681	30501.1		

Note: Life spans are given in days as mean, standard error, number of mice, median, and the longest lived 10 percent.

ent biological systems that are known to change with age or that are affected by food restriction or both (Harrison and Archer, 1987). Voluntary activity, excitement, hematocrit, and tail tendon collagen denaturation all gave similar results in groups treated with L-deprenyl and in controls. Wound healing rates appeared marginally faster in L-deprenyl-treated groups, but the difference was not significant (Table 3). The large variations in collagen fiber denaturation times resulted from the wide range of ages when tested. However, ages were matched for treated and control mice, and there were no effects of treatment at any age.

Reproductive ability. — Effects of L-deprenyl on fecundity were measured using B6CBAF1 males by the timing and frequency of litters, starting at an average age of about 750 days after treatment for 181 days. Ten of 17 L-deprenyl-injected males sired pups by young females, as did 14 of 24 control males; neither percentages of successful males nor ages when pups were sired differed significantly (Table 4). However, the numbers of pups were greatly reduced by treatment with L-deprenyl: controls averaged 82.1 pups/father, while the L-deprenyl treated fathers averaged only 31.3 pups/father. This effect was highly significant ($p < .0001$), as measured by the *t*-test (Table 4). The bar graph in Figure 1 shows that the duration of fecundity was similar in both groups, despite the much larger numbers of pups born to fathers treated with saline rather than L-deprenyl.

Table 2. Weights of L-Deprenyl Treated Mice Compared With Controls[a]

Strain-Group	Sex	Start	2 Months	4–6 Months	10–11 Months
B6D2F1-L-dep	M	38.8 ± 6 (22)[a]	35.6 ± 5 (20)	34.2 ± 3 (15)	32.8 ± 3 (10)
B6D2F1-Cont	M	37.3 ± 5 (19)	34.3 ± 5 (18)	32.6 ± 5 (13)	31.9 ± 6 (4)
B6D2F1-L-dep	F	32.1 ± 5 (20)	30.9 ± 5 (20)	31.1 ± 6 (17)	32.8 ± 4 (5)
B6D2F1-Cont	F	32.5 ± 6 (22)	30.2 ± 5 (20)	31.1 ± 5 (13)	33.8 ± 4 (4)
B6CBAF1-L-dep	M	45.0 ± 5 (21)	44.2 ± 5 (21)	42.8 ± 5 (19)	38.3 ± 5 (17)
B6CBAF1-Cont	M	43.0 ± 3 (27)	42.0 ± 3 (27)	39.4 ± 5 (26)*	35.6 ± 4 (22)
B6CBAF1-L-dep	F	42.0 ± 7 (21)	39.0 ± 7 (21)	40.2 ± 5 (20)	39.7 ± 6 (16)
B6CBAF1-Cont	F	43.0 ± 3 (17)	36.2 ± 4 (17)**	35.9 ± 4 (16)**	37.2 ± 6 (14)

Note: Probabilities of observing differences between deprenyl (L-dep) and control (Cont) groups by chance: $*p < .05 > .01$, $**p < .01$, and all others $p > .05$ when comparing groups of the same age, strain, and gender, using the unpaired *t*-test.

[a] Weights given as Mean ± *SE* (*n*) after time periods of 2 months, 4–6 months, and 10–11 months.

Table 3. L-Deprenyl Effects on Biological System Aging in Male and Female B6D2F1 Mice[a]

Group	Open Field	Boli No.	Hematocrit	Collagen Fiber	Wound Healing
L-dep-F	99 ± 10 (9)[a]	1.4 ± 0.5 (9)	45 ± 1 (8)	276 ± 78 (9)	15 ± 1 (7)
Cont-F	94 ± 11 (10)	0.9 ± 0.5 (10)	42 ± 2 (9)	301 ± 42 (10)	19 ± 4 (7)
L-dep-M	108 ± 9 (11)	1.1 ± 0.5 (11)	45 ± 0.9 (12)	418 ± 99 (13)	20 ± 3 (13)
Cont-M	76 ± 15 (6)	1.2 ± 0.8 (6)	45 ± 2 (6)	245 ± 66 (5)	25 ± 6 (5)

Notes: Mice in the deprenyl (L-dep) and control (Cont) groups were matched in age, although ages ranged from 830–1260 days when tested. Voluntary activity in the open field, numbers of fecal boli deposited during the open field test, hematocrit, tail tendon collagen fiber denaturation times, and wound healing time after fiber removal were tested. None of the tests showed significant effects of L-deprenyl; $p > .05$ by chance comparing L-dep and Cont of the same gender, by the unpaired *t*-test.

[a] Data given as mean ± *SE* (*n*).

Table 4. L-Deprenyl Effects on Male B6CBAF1 Fecundity

	Maximum Age When Pups Sired		Mean Age When Pups Sired		No. of Pups per Father	
	L-deprenyl	Control	L-deprenyl	Control	L-deprenyl	Control
Mean	983	1002	924	905	31.3	82.1
SE	21.6	25.2	16.8	17.4	12.9	15.6
n[a]	10	14	10	14	10	14

[a]Number of 750-day-old males that successfully sired pups after each was housed with two 4-week-old C57BL/6J females. Total numbers of males tested were 17 treated with L-deprenyl, and 24 controls. The higher number of pups per sire in controls was statistically significant as measured by the unpaired *t*-test, $p < .0001$.

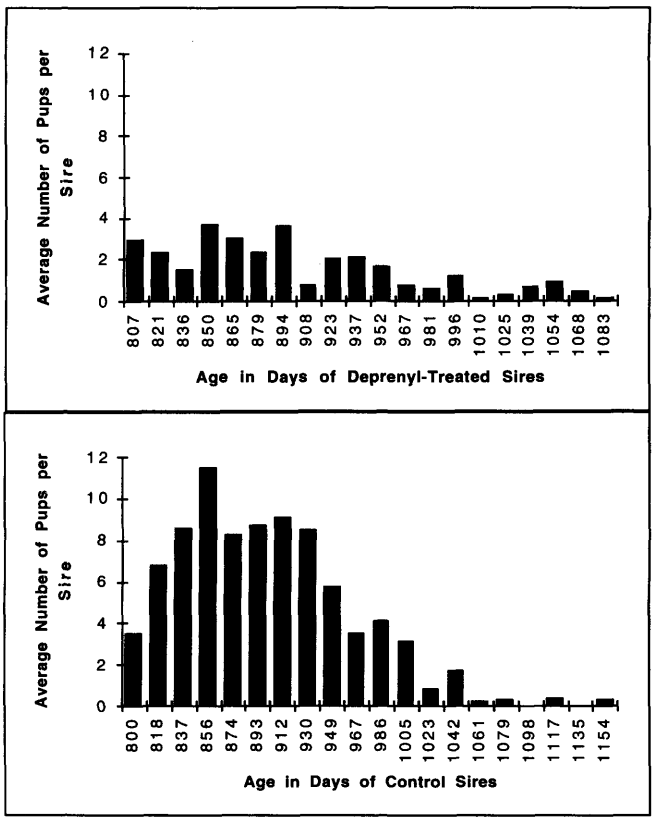

Figure 1. Bar graphs showing numbers of pups born per successful B6CBAF1 sire in L-deprenyl- and saline-injected mice. Ten out of 17 L-deprenyl-treated mice sired pups, and 14 out of 24 saline-treated mice sired pups. Offspring were produced for 333 days with the L-deprenyl-treated males and for 404 days with the saline-treated males. Three saline-treated females were lost after 180–240 days, but none was lost during this period in the L-deprenyl-treated group. L-deprenyl-treated males sired on the average 31.3 ± 12.9 (10) pups per father, while saline-treated males sired on the average 82.1 ± 15.6 (14) pups per father [data given as mean ± *SE*, (*n*)]. The higher litter sizes in controls were statistically significant as measured by the unpaired *t*-test $p < .0001$.

DISCUSSION

Figure 2 summarizes all current life-span studies with L-deprenyl in both rats and mice; Table 5 summarizes details of these studies: ages in months when L-deprenyl injections began; life spans, *SE* and *n* for L-deprenyl-injected animals and for controls; number of days life spans were increased; percentages life spans were increased; and statistical significances. Our results (current in Table 5) showed much smaller increases in life span than found by Knoll and his colleagues; in fact, our results were similar to those of Milgram et al. (1990), Piantanelli et al. (1994), and Kitani et al. (1994). For a comparison with a well established manipulation that increases survival in the same B6CBAF1 genotype used in the current study, life spans were 985 ± 35 (35) for control males, and 1185 ± 36 (34) for food-restricted males giving mean ± SE (*n*) from Harrison and Archer (1987).

We selected starting ages to test effects on mice after fractions of the normal life span that were similar to those used in studies reporting strong positive effects. Our first experiment with B6D2F1 mice started at 26 months of age, 81% and 88% of total male and female life spans, respectively. There was a 77-day increase in mean female life span, and an 84-day increase in mean male life span (Table 1). In prior studies showing the largest benefits of the drug, Knoll et al. (1989) started with rats at 24 months, 71% of normal life spans, while Yen and Knoll (1992) started with mice at 12 months, 58% of normal life spans. Therefore, in the second experiment with B6CBAF1 mice, we tested the hypothesis that starting treatment sooner would increase the effects, and started L-deprenyl injections 6 months earlier, at 18 months of age, 55% and 63% of normal life spans in males and females, respectively. The hypothesis was not supported, as mean longevities were only increased 59 days in females, and 56 days in males.

Nevertheless, L-deprenyl treatments appeared to result in a statistically significant increase in life span when we combined all the data, $p = .011$ in a three-way ANOVA comparing genotypes and genders and treatment (Table 1). There was no significant effect of genotype, and there were no interactions of genotype with treatment in life spans, so it is reasonable to combine the data. The effect was far less significant than the effect of gender ($p = .0003$), since in our groups, males lived significantly longer than females.

Unintended food restriction due to the drug did not appear to be an important factor in our studies. Body weights were similar but tended to be slightly higher in the L-deprenyl-treated groups (Table 2), and amounts of food consumed were not affected by L-deprenyl. This may not have been the case with other studies; for example, Knoll et al. (1989) did not report food intake or body weight, so caloric restriction may have occurred due to the L-deprenyl treatment. Although food restriction is not expected to be as effective late in life as when started early, Weindruch and Walford (1982)

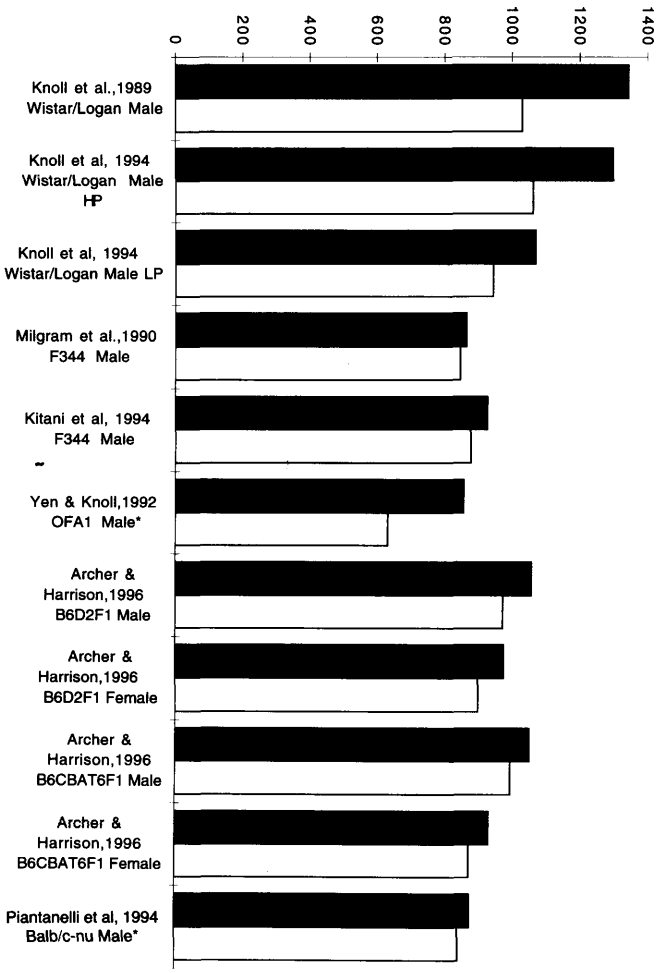

Figure 2. Summary of life span studies with L-deprenyl in rats and mice. Mean longevities for the animals in each study are shown as histograms for groups treated with L-deprenyl (dark bar) and controls (light bar). For comparison in our laboratory, food-restricted B6CBAF1 males lived for 1185 ± 36 (34) days while controls lived for 951 ± 35 (35) days, data given as mean ± *SE (n)*. *Median life spans were extrapolated from life-span curves.

found significant increases in life spans with caloric restriction started at 12 months of age. Thus, it is important to consider whether unintended food restriction might cause some of the effects of L-deprenyl. Barber et al. (1993) recently showed a depressed rate of weight gain in L-deprenyl-treated male mice, although this study was not lifelong. Yen and Knoll (1992) measured food intake and body weight in OFA-1 male mice; they found no difference in food consumption, but did report a slower loss of weight later in life.

Ingram et al. (1993) and Amenta et al. (1994) reported no effects on body weight, while Knoll et al. (1989), Milgram et al. (1990), and the current report found slightly increased body weights in mice treated with L-deprenyl. Furthermore, we found that amounts of food consumed were not significantly different in the groups given L-deprenyl and the controls. Thus, there is no support for the hypothesis that L-deprenyl acts by food restriction to reduce body weight.

There were no significant differences in the five physiological measures of changes with age tested in the current study: activity (open field), excitement (boli), hematocrit, tail tendon collagen denaturation rate, and wound healing. Although ages were matched between mice receiving L-deprenyl and controls, the large age range used may have increased the noise in this study (Table 3). Ingram et al. (1993) also found minimal effects of L-deprenyl on six behavioral tests, even though after 6 months of treatment MOA-B was 60% blocked in the striatum. Ingram and colleagues also used C57BL/6J mice, which have shorter life spans compared to our F1 mice.

Control life spans are important in interpreting results of experiments reporting that life spans were extended. Treatments such as caloric restriction that extend maximum life spans for the species may retard basic mechanisms of aging, while extending the lives of short-lived individuals probably results from preventing their specific diseases. We used well-defined F1 hybrid mice that are long-lived for their species, so there would be no large increases in life span over the controls if L-deprenyl treatment merely prevented early

Table 5. Details From Previous Studies Summarized in Figure 2

Authors	Strain	Species	Sex	Age (mo)	Days Incr.	% Incr.	*p*-value	LS – Deprenyl			LS – Control		
								Mean	*SE*	*n*	Mean	*SE*	*n*
Knoll et al.,1989	Wistar/Logan	Rat	M	24	314	30.5	.001	1343	16	66	1029	4	66
Knoll et al., 1989	Wistar/Logan	Rat	M-HP	24	238	22.5	.001	1297	14	50	1059	10	49
Knoll et al., 1989	Wistar/Logan	Rat	M-LP	24	126	13.4	.001	1068	10	48	942	16	44
Milgram et al., 1990	F344	Rat	M	23–24	19	2.2	.05	864	8	66	845	8	66
Kitani et al., 1994	F344	Rat	M	18	50	5.7	.05	926	97*	35	877	109*	35
Yen and Knoll, 1992	OFA1	Mice	M	12	225	35.7	.001	855*		40	630*		40
Current study	B6D2F1	Mice	M	26	84	8.6	n.s.*	1056	35	22	972	38	20
Current study	B6D2F1	Mice	F	26	77	8.6	n.s.*	975	28	21	898	45	22
Current study	B6CBAF1	Mice	M	18	56	5.6	n.s.*	1050	47	21	994	32	28
Current study	B6CBAF1	Mice	F	18	59	6.8	n.s.*	931	39	21	872	20	17
Piantanelli et al., 1994	Balb/c-nu	Mice	M*	22	35	4.2	.01	875*		32	840*		32

Notes: Studies listed by authors, noting strain, species, and gender; age in months when injections began; days life spans were increased; percentages increased; probabilities that increases were significant; life spans (mean, *SE, n*) for groups treated with L-deprenyl, and controls. Knoll et al. HP and LP = high and low performance. All treated animals received sc injections 3 times per week of 0.25 mg/kg of L-deprenyl, except that Kitani et al. injected 0.5 mg/kg.

*Medians were reported by Piantanelli et al. and Yen and Knoll. It was unclear whether Kitani et al. gave *SE* or *SD*, and probabilities in the current study were not significant for each genotype alone, but combined gave $p = .011$ (Table 1).

deaths from diseases. Control life spans were much shorter in the study of Yen and Knoll (1992), with a median survival of only 635 days; L-deprenyl treatment increased this to 860 days, a normal life span for healthy mice, but even these treated mice lived less long than our controls. Thus, the mice studied by Yen and Knoll may have had diseases that were postponed or cured by the L-deprenyl treatment, rather than having L-deprenyl retard basic mechanisms of aging. The argument could not be used with the control Wistar × Logan rats of Knoll et al. (1989), as these were long-lived and L-deprenyl treatment substantially increased life spans, much as in food restriction studies (Figure 1).

Effects of L-deprenyl on life span may be related to activities of superoxide dismutase (SOD) and catalase, as these were increased 100% and 50%, respectively, in the cerebral cortices of 29.5-month-old male C57BL/6J SPF mice that were continuously infused for 3 weeks with 1.0 mg/kg/day of L-deprenyl (Carrillo et al., 1994). Knoll (1991) reported a threefold increase in SOD activity in the striatum of male F344 rats, after only 3 weeks of daily injections of L-deprenyl, and suggested that increases in SOD enzyme activity may cause the increase in life span. Kitani et al. (1994) sc-injected male F344 rats with 2.0 mg/kg L-deprenyl 3 times a week for 21 days; they found a threefold increase in SOD enzyme in the young males, but SOD levels did not change in old or young females.

Our studies of fecundity were performed because Knoll et al. (1989) showed a doubling of male rat sexual performance with daily injections of L-deprenyl. However, sexual performance is only one aspect of reproductive success. We measured actual production of offspring, since this measure integrates all reproductive functions, and is vital in natural selection for increased longevity. There was a highly significant decline in numbers of pups sired by old male mice that received L-deprenyl (Table 4 and Figure 1). Thus, L-deprenyl treatment diminishes fecundity in the current study.

Despite the inconsistencies between laboratories, and relatively small effects in most laboratories, we believe that the increases in life span due to L-deprenyl treatment warrant further examination. Even though effects in many studies are small, Figure 1 shows that all studies have found increased life spans. Even more importantly, the only treatment thus far given to old mammals that has shown significant benefits on life span is L-deprenyl.

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