

Review

# Why (–)deprenyl prolongs survivals of experimental animals: Increase of anti-oxidant enzymes in brain and other body tissues as well as mobilization of various humoral factors may lead to systemic anti-aging effects

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## Abstract

(–)Deprenyl, a monoamine oxidase B (MAO B) inhibitor is known to upregulate activities of anti-oxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) in brain dopaminergic regions. The drug is also the sole chemical which has been repeatedly shown to increase life spans of several animal species including rats, mice, hamsters and dogs. Further, the drug was recently found to enhance anti-oxidant enzyme activities not only in brain dopaminergic regions but also in extra-brain tissues such as the heart, kidneys, adrenal glands and the spleen. We and others have also observed mobilization of many humoral factors (interferone (INF)- $\gamma$ , tumor necrosis factor (TNF)- $\alpha$ , interleukine (IL)-1 $\beta$ , 2, 6, trophic factors, etc.) and enhancement of natural killer (NK) cell functions by (–)deprenyl administration. An apparent extension of life spans of experimental animals reported in the past may be better explained by these new observations that (–)deprenyl upregulate SOD and CAT activities not only in the brain but also in extra-brain vital organs and involve anti-tumorigenic as well as immunomodulatory effect as well. These combined drug effects may lead to the protection of the homeostatic regulations of the neuro-immuno-endocrine axis of an organism against aging. © 2002 Elsevier Science Ireland Ltd. All rights reserved.

**Keywords:** Superoxide dismutase; Catalase; Life span prolongation; Cytokines

## 1. Introduction

The ‘free radical theory of aging’ was proposed almost half a century ago by Harman (1956) and has been increasingly supported as the most realistic possibility. Recent research achievements by

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means of different approaches are all supportive for this thesis (Orr and Sohal, 1994; Migliaccio et al., 1999; Melov et al., 2000).

To date, however, there has been no direct proof for this theory. Accordingly, attempts have been made based on this thesis to prolong the life span of animals by means of so-called anti-oxidant strategies. Most of these approaches are to administer so-called anti-oxidant chemicals, pharmaceuticals and more recently so-called nutraceuticals in an attempt to prolong the life span of animals. However, there is no single convincing study which demonstrated the definitive and reproducible success in prolonging the life span of animals by these approaches (e.g. Lipman et al., 1998). There are many reasons for this failure in these attempts and one of the authors has repeatedly discussed that the failure in prolonging the life span of animals does not disprove this thesis, however, certainly does not prove it (Kitani, 1998). At the beginning of the 21st millennium, it is still the consensus of experimental gerontologists that the only reliable means of prolonging the mean and maximum life span of animals is the 'caloric restriction (CR)' (Masoro, 1995; Yu, 1996). Most of the data on CR have been generated from studies on laboratory animals, rodents in particular (Masoro, 1995; Yu, 1996). In order to know whether results of these rodent studies can be projected to primates, humans in particular, efforts have been conducted in the US using non-human primates (Henry et al., 2000; Roth et al., 2000). Studies appear to be promising, but it will be another decade before we have definitive results.

(-)-Deprenyl is a MAO B inhibitor (Knoll, 1980) and is currently used as an agent to retard the progression of Parkinson's disease (Tetrud and Langston, 1989; The Parkinson Study Group, 1989, 1993). The drug is known to have an anti-apoptotic potency and some neuroprotective effects (Tatton et al., 1994; Olanow, 1996; Paterson et al., 1997; Maruyama and Naoi, 1999). However, precise underlying mechanisms for these effects remain unclear.

Knoll who was originally involved with the

development of (-)-deprenyl reported that the repeated administration of the drug could prolong the life span of aging male rats (Knoll, 1988). Since then, several attempts including our own have been reported with inconsistent results (Milgram et al., 1990; Ingram et al., 1993; Kitani et al., 1993; Piantanelli et al., 1994; Bickford et al., 1997; Gallagher et al., 1998). Despite some studies which did not succeed in prolonging the life span of animals (Ingram et al., 1993; Piantanelli et al., 1994; Bickford et al., 1997; Gallagher et al., 1998), rather convincing results demonstrating a significant increase in life spans of at least four different animal species by the drug can be found in the literature (Knoll 1988; Milgram et al., 1990; Kitani et al., 1993; Archer and Harrison, 1996; Ruehl et al., 1997; Stoll et al., 1997). The mechanism(s) underlying the effect of (-)-deprenyl on the survival of animals, however, remains unelucidated. The authors have long suggested that the upregulation of activities of anti-oxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) induced by the drug may be causally related to the effect of the drug on the survival of animals primarily because of the parallelism of the dose-response efficacies of deprenyl on these two seemingly different effects of the drug (Kitani et al., 1996, 1998, 1999, 2000). The purpose of this paper is to further support the contention providing additional data on animal survivals as well as the humoral events induced by the administration of the drug.

## 2. Materials and methods

Some of the results presented here have been obtained in the Tokyo Metropolitan Institute of Gerontology (TMIG, Tokyo, Japan) using Fischer 344/Du (F344/Du) rats originally purchased from Japan Charles River (Atsugi, Japan) and BDF1 and C57BL mice from SLC (Shizuoka, Japan).

More recent studies were performed at the National Institute for Longevity Sciences (NILS, Obu, Japan). Rats used at NILS were F344/6JNia purchased from Harlan Sprague Dawley

(Indianapolis, IL, USA) which had been raised under the contract between the National Institute on Aging (NIA, Bethesda, USA) and the company. Husbandry conditions of animals in the two institutes have been described elsewhere for TMIG (Nokubo, 1985) and NILS (Tanaka et al., 2000).

Procedures for tissue preparations and enzyme activity measurements are described in detail elsewhere (Carrillo et al., 1991, 1992a,b). In brief, SOD activities were determined by the method described by Elstner and Heupel (1976). In some recent studies, the original method of McCord and Fridovich (1969) was used. Mn-SOD activities were defined as the fraction which can be inhibited by the addition of KCN at a concentration of 0.5 mM (McCord and Fridovich, 1969). CAT activities were determined immediately after the preparation of tissue samples by the method described by Beers and Sizer (1952). Protein concentration was determined by the method reported by Lowry et al. (1955).

### 3. Results and discussion

#### 3.1. The effect of (–)deprenyl on survival of animals

Fig. 1 shows survival curves of control and deprenyl-treated rats. Male F344/Du rats began receiving s.c. injections of (–)deprenyl solution (0.5 mg/kg, three times a week) at the age of 18 months. There was a definitive modification of the survival curve of the treated group in comparison to that of the control group yielding a 33.8% increase in the average life expectancy as calculated at the age of 24 months (Kitani et al., 1993). This value is much smaller than that initially reported by Knoll (1988) on male Logan–Wistar cross rats which started to receive the drug at the age of 24 months at a dose of 0.25 mg/kg (s.c.), three times a week, the increase in the average life expectancy at 24 months being more than 100%. On the other hand, the second study reported from Canada (Milgram et al., 1990) demonstrated

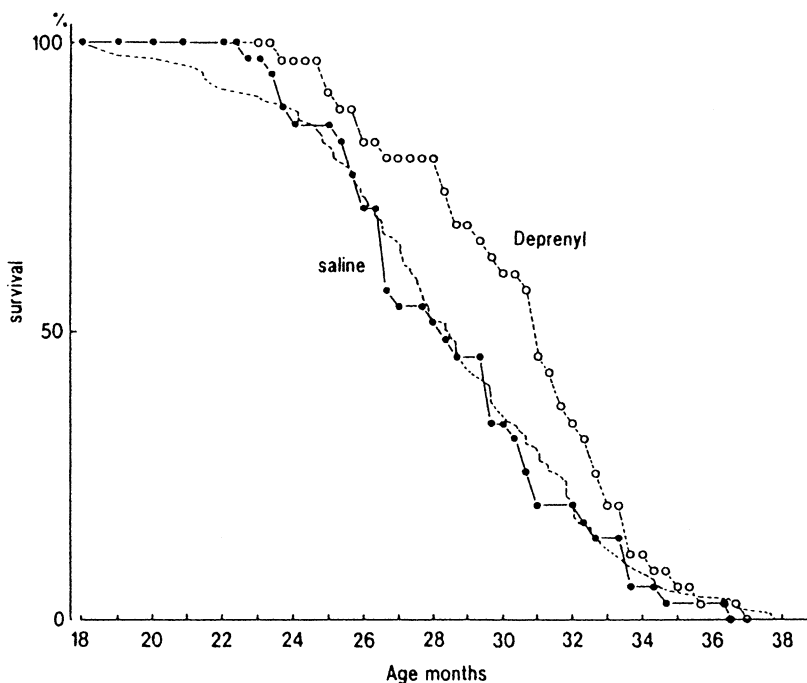


Fig. 1. Survival curves of control (closed circles) and deprenyl-treated (open circles) rats as expressed from pooled data of three cohorts. Broken line without symbols indicates data from 100 animals raised in the specific pathogen-free farm of the institute (TMIG) as reported previously (Kitani et al., 1993 with permission from Life Sciences).

Table 1  
Effect of deprenyl on life span of rats

Strain (sex), effect	Dose, authors
Logan–Wistar(M), > +100% <sup>a</sup>	0.25 mg/kg, s.c. (3 ×, a week) <sup>b</sup> , Knoll, 1988
F-344(M), +16% <sup>a</sup>	0.25 mg/kg, s.c. (3 ×, a week) <sup>b</sup> , Milgram et al., 1990
F-344(M), +34% <sup>a</sup>	0.5 mg/kg, s.c. (3 ×, a week) <sup>c</sup> , Kitani et al., 1993
F-344(M), no significant effect	0.5 mg/kg, p.o. (daily) <sup>d</sup> , Bickford et al., 1997
Wistar(M), adverse effect (shortening of life span)	0.5 mg/kg, s.c. (3 ×, a week) <sup>e</sup> , Gallagher et al., 1998

<sup>a</sup> Average life expectancy after 24 months of age.

<sup>b</sup> After 24 months of age.

<sup>c</sup> After 18 months of age.

<sup>d</sup> Between 54 and 118 weeks.

<sup>e</sup> Between 3 and 23 months.

a significant effect of a 16% increase, one half of what we obtained in F344 rats. The study by the Canadian group also used male F344 rats but they treated animals exactly as was done in the study by Knoll (1988), beginning treatment at 24 months. Several other studies using rats, however, have reported negative results in terms of life span prolongation of animals by the drug (Ingram et al., 1993; Bickford et al., 1997; Gallagher et al., 1998). Some of these positive or negative studies in rats are summarized in Table 1. Discrepancy among different studies will be discussed later in this article. (–)Deprenyl was also shown to prolong the life spans of dogs (Ruehl et al., 1997), mice (Archer and Harrison, 1996) and hamsters (Stoll et al., 1997). These events have been extensively discussed elsewhere by the authors (Kitani et al., 1996, 1998, 1999, 2000).

### 3.2. The effect of (–)deprenyl on anti-oxidant enzyme activities

Knoll (1988) also originally reported that a continuous 3 week treatment with the drug increases (total) SOD activities in striatum of rats. Later, however, he could not reproduce the phenomenon in another strain of rats and cautioned that it may not be a universal effect of the drug.

We have extensively studied this effect of (–)deprenyl.

Fig. 2 shows a part of the observations made by our group (Carrillo et al., 1992b). It is clear that a 3 week s.c. continuous infusion (or consecutive injections) definitely increases enzyme activities of CAT and SOD selectively in brain regions of primarily dopaminergic nature. However, an optimal dose for increasing enzyme activities varied widely depending on ages and sexes of rats (for review, see Kitani et al., 1996). An optimal dose is ten times greater in male than female rats of young age (Carrillo et al., 1992a). Interestingly, aging caused a decrease in an optimal dose in male (Carrillo et al., 1993) but an increase in optimal dose in female rats (Carrillo et al., 1992a). Reasons for differences in optimal dose among different sexes and ages have been discussed extensively (Kitani et al., 1996, 1998, 1999). Further as seen in Fig. 2, there is a clear region and tissue selectivity for this phenomenon. In rats, mice and dogs, we have found that this effect of the drug is limited to primarily dopaminergic regions in the brain (S. nigra, striatum, and cerebral cortical regions) but is not seen in hippocampus and cerebellum (Carrillo et al., 1992a,b). Further we confirmed repeatedly that it does not happen in the liver (Carrillo et al., 1992a,b). From these observations, we have believed until recently that the deprenyl-mediated upregulation of activities of SOD and CAT is limited to certain brain regions. We will discuss later that this was not true and in some primarily catecholaminergic organs outside of the brain, enzyme activities of SOD and CAT are significantly increased by the drug.

### 3.3. Parallelism of the dose–efficacy relationships for the effect on anti-oxidant enzymes and survivals of animals

Fig. 3 shows the results of SOD and CAT activity changes with various doses of (–)deprenyl administration for 1 month (s.c. injection three times a week) in 27 month-old male F344/Du rats (Carrillo et al., 2000a). As has been repeatedly emphasized (Kitani et al., 1996, 1998, 1999), there is a clear inverse U shape dose effect

of the drug on SOD and CAT activities showing that there is a dose dependent increase in enzyme activities, but then, a greater dose becomes less effective from a certain dose point and an excessive dose adversely affects (decreases) activities (Carrillo et al., 1992a,b; Kitani et al., 1996). We have shown that there is an optimal dose range for the drug in terms of its effect on SOD and

CAT activities in rats (Carrillo et al., 1992a,b, 1993) and mice (Carrillo et al., 1996) of both sexes and at different ages. As is clear in Fig. 3, 1.0 mg/kg/inj. is in the middle of an optimal dose range in old male F344/Du rats when they are treated only for 1 month (Carrillo et al., 2000a). However, when male F344/Du rats were treated for 13 months from 18 to 31 months of age with

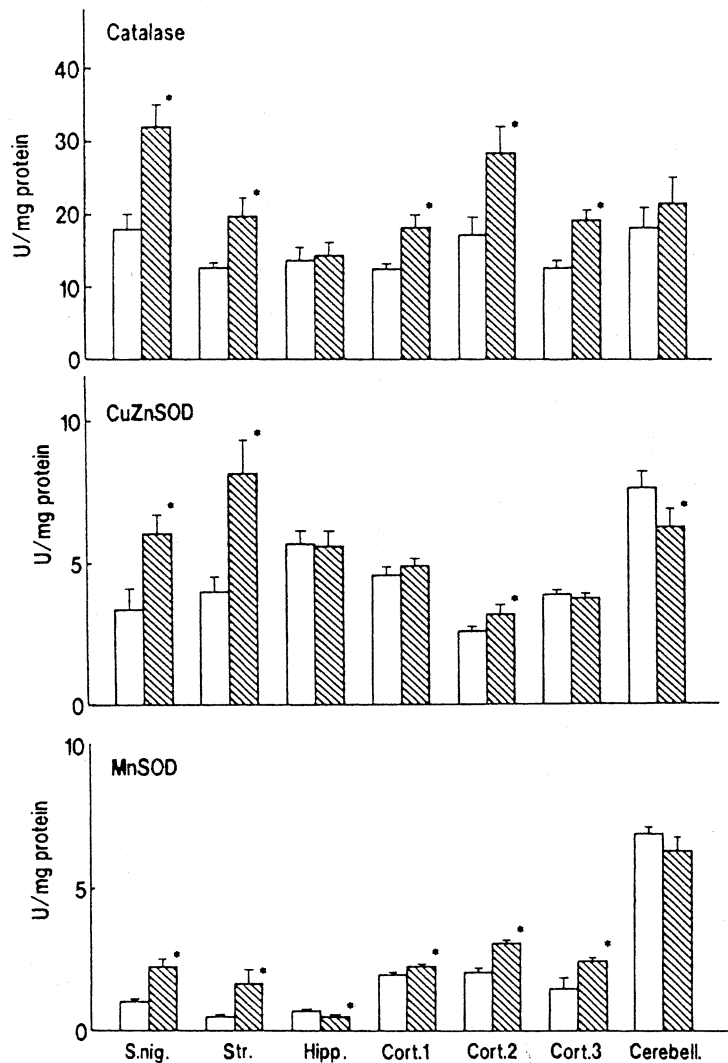


Fig. 2. Catalase (upper panel) Cu, Zn-SOD (middle panel) and Mn-SOD (lower panel) activities in different brain regions and the liver in young male rats treated with saline solution (white column,  $n = 6$ ) and rats treated with deprenyl infusion at a rate of 2.0 mg/kg per day for 21 days (shaded column,  $n = 4$ ). \*Significantly different from corresponding control values ( $P < 0.05$ ,  $t$ -test). (S.nig., substantia nigra; Str., striatum; Hipp., hippocampus; Cort 1, frontal cortex; Cort 2, parietotemporal cortex; Cort 3, occipital cortex; Cerebell, cerebellum). (Reproduced from Carrillo et al., 1992b with the permission of the publisher.)

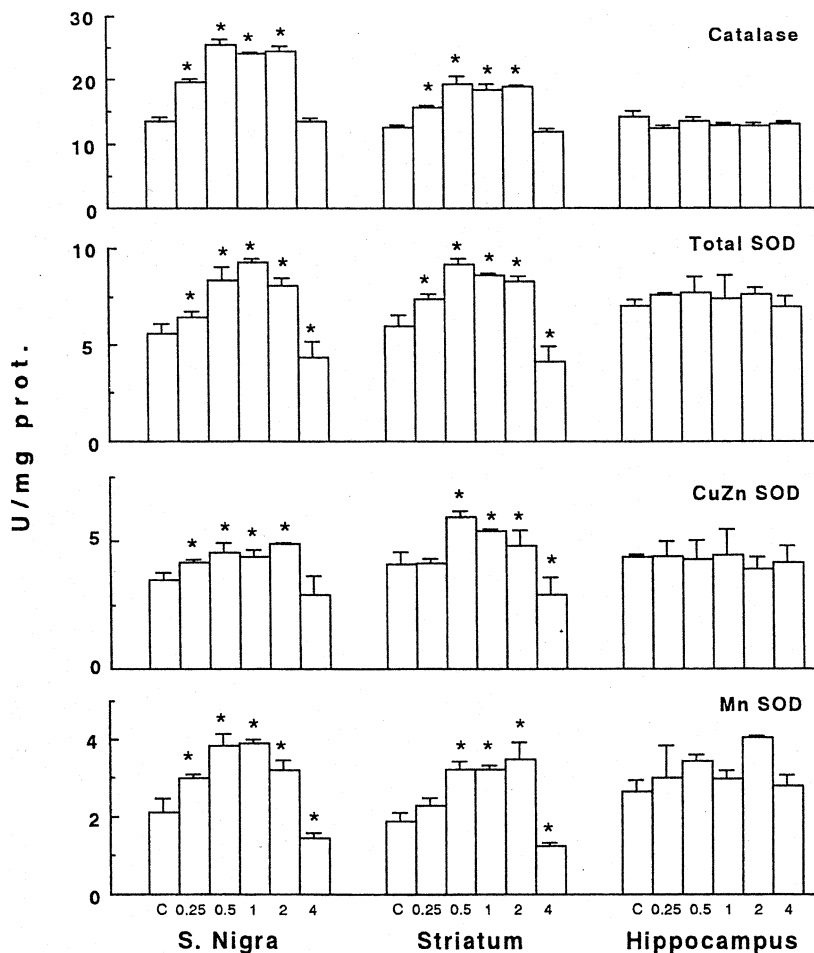


Fig. 3. Catalase (CAT) and superoxide dismutase (SOD) activities in three different brain regions of 27-month-old male F-344 rats treated with various doses of deprenyl for 1 month before sacrifice. C: control rats given saline injections, 0.25–4 indicate doses of (–)deprenyl (mg/kg/injection, three times per week) for 1 month. \*Significantly different from respective control values ( $P < 0.05$ , Scheff's  $F$  test). (Reproduced from Carrillo et al., 2000a with the permission of Life Sciences.)

this dose (1.0 mg/kg/inj.), this positive effect was totally abolished. As shown in Fig. 4, both CAT and SOD activities were almost identical for control and (–)deprenyl treated old rats for 13 months at a dose of 1.0 mg/kg/inj. (Carrillo et al., 2000a).

Thus, a duration of the treatment is also a strong determinant for the optimal dose of the drug on enzyme activities. This property appears to be more prominent in mice than in rats. In mice only a 3-month-treatment considerably decreased the optimal dose range as well as the

magnitude of an increase in enzyme activities (Carrillo et al., 1996). In female F344 rats, a 6-month-treatment still maintained enzyme activities significantly higher than in control animals (Carrillo et al., 1994).

The dose–response relationship for the effect on survival of animals is more difficult to obtain, because of the requirements of facilities, time and labor. However, we have recently confirmed that 0.25 mg/kg/inj. three times per week, s.c. beginning at 18 months of age significantly increased the remaining life expectancy in both male and

female rats (Kitani et al., unpublished observation), while in C57BL male mice, with two different doses (0.25 mg/kg/inj. or 0.50 mg/kg/inj.), we were unable to obtain a significant increase of the average life expectancy (Kitani et al., unpublished observations), although the 0.50 mg/kg dose prolonged the average life expectancy at 24 month of age by 20% (Kitani et al., unpublished observations). Interestingly, with the dose of 1.0 mg/kg/inj. for 13 months in male F344/Du rats, starting from 18 months of age, the survival rate was greater in control (7/12) than treated (3/12) rats (Carrillo et al., 2000a).

It is possible although not proven that the drug-treated animals which died earlier than 31 months of age had had even lower enzyme activities than corresponding control animals, since an excessive dose has been shown to reduce enzyme activities to levels lower than control values (Carrillo et al., 1992a,b, 1993, 2000a). Interestingly, when we examine reports by other scientists, we can recognize probably the same phenomena as introduced above. Gallagher et al. (1998) reported that (–)deprenyl at a dose of 0.5 mg/kg/inj., three times a week which is exactly the same dose

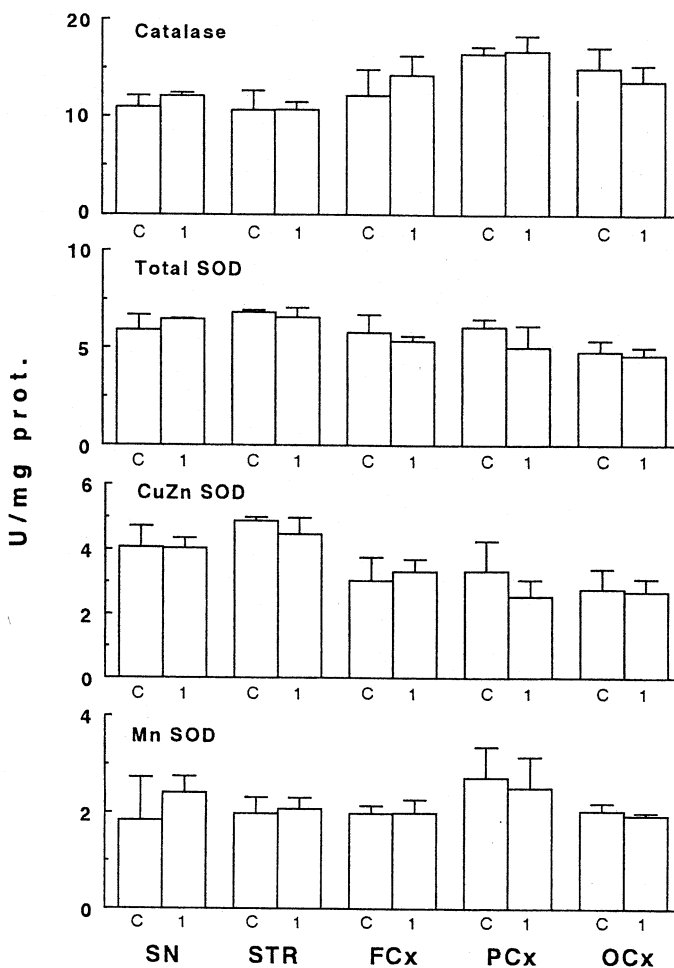


Fig. 4. Catalase (CAT) and superoxide dismutase (SOD) activities in substantia nigra (SN), striatum (STR), frontal cortex (FCx), parietotemporal cortex (PCx) and occipital cortex (OCx) in 31-month-old male F-344 rats treated with saline (c) or deprenyl solution at a dose of 1.0 mg/kg/injection (1), three times a week for 13 months starting from the age of 18 months. (Reproduced from Carrillo et al., 2000a with the permission of Life Sciences.)

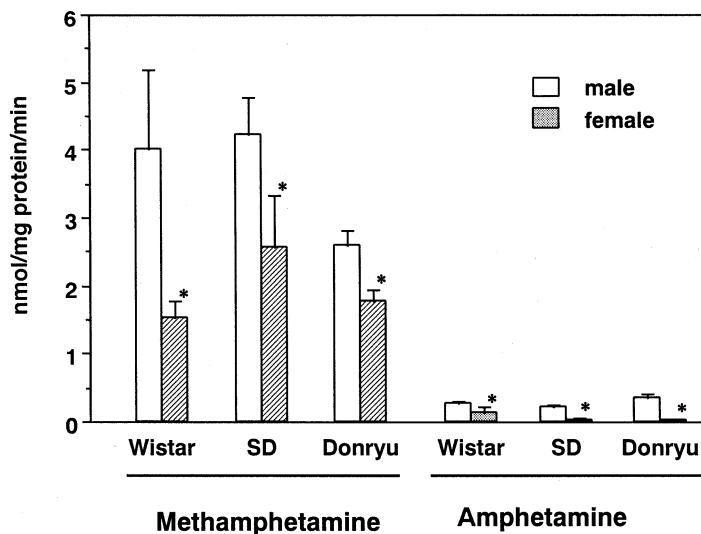


Fig. 5. Differences in metabolism of (–)deprenyl in rat liver microsomes between different sexes and strains of rats. The figure was drawn from the data reported by Yoshida et al., 1987. Formation of methamphetamine by means of depropargylation (left panel) and amphetamine by further *N*-demethylation (right panel).

as we successfully used in our previous study in prolonging the life span of male F344 rats (Kitani et al., 1993) actually shortened the life span of male Wistar rats. Further, the same group more recently reported that the same dose of the drug did not increase SOD activities, although they observed a significant increase in CAT activities (Gallagher et al., 1999). The duration of treatment was 20 months for the survival study (Gallagher et al., 1998) and 9 to 15 months for enzyme studies (Gallagher et al., 1999). Since it has been clearly shown that metabolism of (–)deprenyl is mediated mainly by microsomal P-450 system in the liver by means of *N*-demethylation and depropargylation (Yoshida et al., 1986, 1987), and that the metabolic potency is very different among different rat strains (Yoshida et al., 1987) (see Fig. 5) it is well conceivable that this dose was too high in this strain. If we assume that the rate of metabolism of the drug by the liver is two times greater in F344/Du rats than in the Wistar rats which Gallagher et al. (1998, 1999) used, and if we further take it into consideration that a much longer treatment was used, we can interpret without difficulty that the group of Gallagher et al. has created a similar phenomenon as we have

shown in F344/Du rats with only two times difference in the dosage used (Carrillo et al., 2000a). If we assume that not only with regard to enzyme activities but also survival of animals, the rule is that at certain dose point the drug works less effectively and finally works adversely with excessive doses, most of the past reports on survivals of rats and mice undergoing (–)deprenyl administration can be quite reasonably explained (for review, see Kitani et al., 1996, 1998). These data are consistent with our past notion that animals can live for a longer period, as long as anti-oxidant enzyme activities are maintained higher by (–)deprenyl than corresponding control levels (Kitani et al., 1996, 1998, 1999, 2000).

#### 3.4. Neurohumoral events induced by (–)deprenyl

Assuming that the upregulation of SOD and CAT activities in selective brain regions makes animals live longer as insisted by the authors (Kitani et al., 1996, 1998, 1999, 2000), the thesis lacks more direct explanation for mechanisms underlying the extension of life span of animals by the drug. When we look at pharmacologies of the drug, we notice that many humoral factors are



mobilized by the drug. These include neurotrophic factors (Semkova et al., 1996; Li et al., 1998; Tang et al., 1998; Kontkanen and Castren, 1999) and other interleukins such as IL-2 (ThyagaRajan et al., 1998b), IL-6 (Müller et al., 1996) etc. (Table 2).

Some of these humoral events and deprenyl's anti-tumorigenic and immunomodulatory effects are extensively discussed by ThyagaRajan and Felten (2002) in this volume. ThyagaRajan et al. (1998a,b, 2000a,b) have shown that deprenyl enhances natural killer (NK) cell activities and restores both neuroadrenergic innervation and norepinephrine concentration in the spleen and, importantly, that these effects appear to be related to the effect of the drug on survival of animals. In this regard, we ourselves recently confirmed that TNF- $\alpha$  concentrations are significantly increased by a 3-week treatment with the drug in the extra-brain tissues such as the heart, kidneys, adrenal glands and the spleen and IL-1 $\beta$  in renal medulla and adrenal glands (Minami et al., 2001), where we have found an increase in SOD and CAT activities with elevated messenger RNA (mRNA) levels of SODs (Minami et al., 2000, 2001). Interestingly however, we found no increase in TNF- $\alpha$  level in brain striatum where increases in activities of SOD and CAT are evident. Although TNF- $\alpha$  is considered to be a cause for elevating Mn-SOD activities (Wong and Goeddel, 1988), it remains to be elucidated how these humoral events and up-

regulations of SOD and CAT are causally interrelated. We have also observed that effects of (–)deprenyl on SOD and CAT activities in brain dopaminergic regions as well as extra-brain catecholaminergic tissues such as the heart and kidneys is shared by other propargylamines such as rasagiline (Carrillo et al., 2000b) and *N*-2-heptyl *N*-methylpropargylamine (2-HMP) (Minami et al., 2000).

Interestingly, however, the potency of increasing these anti-oxidant enzyme activities is in the order of (–)deprenyl > rasagiline > 2HMP > 2HP [demethyl(2HP)] (Minami et al., 2000). Accordingly, the efficacy of propargylamines to elevate SOD and CAT appears to be determined by chemical moiety other than their common structure of the propargylamine.

### 3.5. The mobilization of humoral factors by (–)deprenyl

It is possible (but not proven) that the protection of brain dopaminergic regions against oxidative tissue damages by means of upregulations of SOD and CAT as reported by Knollema et al. (1995) contributes to the humoral factor mobilization, since dopaminergic neurons are known to be heavily involved in regulations of these humoral factors, cytokines in particular. However, our recent findings that SOD and CAT activities and their mRNA levels of extra-brain tissues of catecholaminergic nature are also upregulated by (–)deprenyl appear to provide more realistic explanation for the links between anti-oxidant enzyme upregulation and many of the humoral events induced by the drug. As discussed by ThyagaRajan et al. (2000a), the spleen noradrenergic fibers are much rejuvenized by (–)deprenyl, although its exact mechanisms remain unelucidated. Humoral sequences discussed by ThyagaRajan and Felten (2002) can explain some of the anti-tumorigenic as well as immunomodulatory effects of the drug, although the current authors believe that the anti-tumorigenic effect of the drug is not solely mediated by means of the suppression of thalamic and serum levels of prolactin as discussed by ThyagaRajan and Quadri (1999a), ThyagaRajan et al. (1999b). We have

Table 2  
Humoral factors mobilized by (–)deprenyl administration

	Authors
Humoral factors	Semkova et al., 1996
Neurotrophic factors	Tang et al., 1998
BDNF	Kontkanen and Castren, 1999
NGF-induced changes	Li et al., 1998
TNF- $\alpha$	Minami et al., 2001
<i>Interleukins</i>	
IL-1	Müller et al., 1996; Minami et al., 2001
IL-2	ThyagaRajan et al., 1998b
IL-6	Müller et al., 1996
Interferone- $\gamma$	ThyagaRajan et al., 1999b

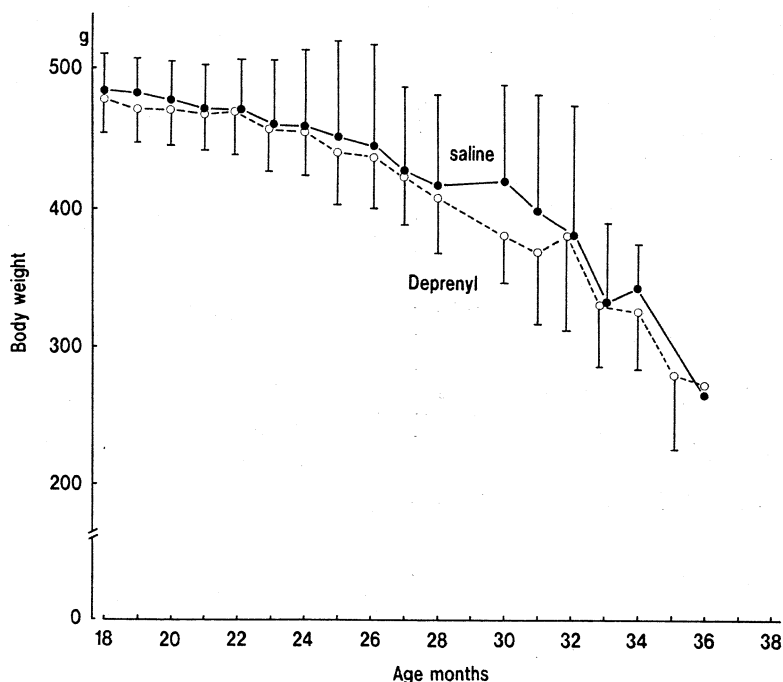


Fig. 6. Sequential changes in body weights of control (closed circles) and deprenyl-treated (open circles) rats. Despite comparable average body weights for both groups, the variation in body weight in the deprenyl-treated groups is constantly smaller than that in the control groups. Vertical bars indicate 1 SD (Kitani et al., 1993 with the permission from Life Sciences).

previously suggested and still believe that the suppressive effect of (–)deprenyl on the growth of subcutaneous benign tumors in aging male F344/Du rats can be best explained by the more general protective effect of the drug against tumor growth (Kitani et al., 1993).

As shown in Fig. 6, the average body weights were almost identical for control and (–)deprenyl-treated rat groups, while the variation of body weight tended to be greater in control rats with advancing age of animals (Kitani et al., 1993). Changes of body weight with age in F344/Du rats are determined mainly by two opposite changes. As shown in Fig. 7, after 24 months of age, animals start to bear subcutaneous tumors of benign nature. This makes animals apparently heavy, since some tumors weigh more than the rest of their body weights (>200g). Another and opposite tendency is a spontaneous emaciation with age for this rat strain leading to a decrease of body weight with age.

Almost comparable average body weights for control and (–)deprenyl-treated rat groups with greater variation of body weight in the control group of same ages may be explained by these two factors of opposite directions. The only explanation is that the drug tended to retard the development and progression of these benign tumors in aging animals and at the same time tended to retard the progression of emaciation. Although there is no clear description, it is notable that the same phenomenon is clearly observed in a figure in the report by Milgram et al. (1990) which used the same male F344 strain of rats. It is possible that the increase in TNF- $\alpha$  concentration in some extra-brain organs induced by the drug has contributed at least in part to the prevention of tumors of various organs. Collectively, the tumor preventive effect of the drug appears to be multifactorial, however, it may be one strong factor for the extension of life spans of aging animals which are prone to life threatening tumors. An amaz-

ingly marked effect of the drug on survival of aging female Beagle dogs (Ruehl et al., 1997) may be partly explained by this aspect of (–)deprenyl's pharmacology. Accordingly, this could be due to the intervention in an age-associated disorder, tumors.

On the other hand, age-associated deterioration of immune function is more difficult to separate from the natural aging process. Whether the decline is pathological or in part of the natural aging process, however, (–)deprenyl appears to intervene in immunological mechanisms during animal aging. In this regard, an amazingly profound effect of (–)deprenyl on survivals of nu-nu (immunosuppressed) mice (Freisleben et al., 1997) must be carefully examined with the possible mechanisms of deprenyl underlying the life span extension of different animal species kept in mind.

#### 4. Conclusions

##### 4.1. Neuro-immuno-endocrine axis for regulating homeostasis of aging

As discussed above, the upregulation of SOD and CAT activities in certain brain and extra-brain tissues may work directly to protect against oxygen induced tissue damages as shown by others in the brain (Knollema et al., 1995). Further it must be emphasized that deprenyl may be able to protect

the most vital organ (e.g. the heart) against acute oxygen crisis, such as myocardial infarction, though this has not yet been demonstrated.

Fig. 8 illustrates our idea of the homeostatic regulation of aging process as well as interventional mechanisms mediated by the administration of (–)deprenyl and probably of some other propargylamines also. It is surprising that a simple chemical, (–)deprenyl, originally developed as an anti-depressant and later proved to be a MAO B inhibitor affects so many functions of the body, primarily the neuro-immuno-endocrine axis by mutual bidirectional interactions through humoral factors.

The prevention of tumors, cancers in particular, may be regarded as an intervention in age-associated disorders. However, other aspects of (–)deprenyl's pharmacology especially in neuro-immuno-axis as discussed here as well as by ThyagaRajan (ThyagaRajan and Felten, 2002) appears to be too broad and profound to be considered as an 'intervention in age-associated disorders' per se but may possibly be intervening in the natural process of aging. Apart from the practical usefulness of propargylamines, further studies using these propargylamines, (–)deprenyl in particular, may aid us in both understanding the aging of organisms as well as with intervening in aging process with the ultimate goal of understanding and slowing the biological mechanisms of aging.

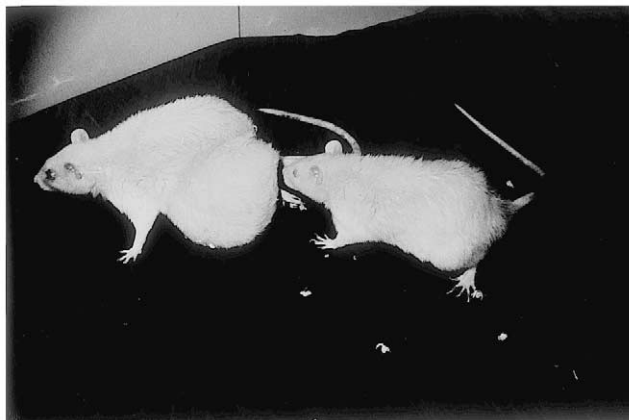


Fig. 7. Thirty-month-old male F344/Du rats with (left) and without (right) a subcutaneous tumor.

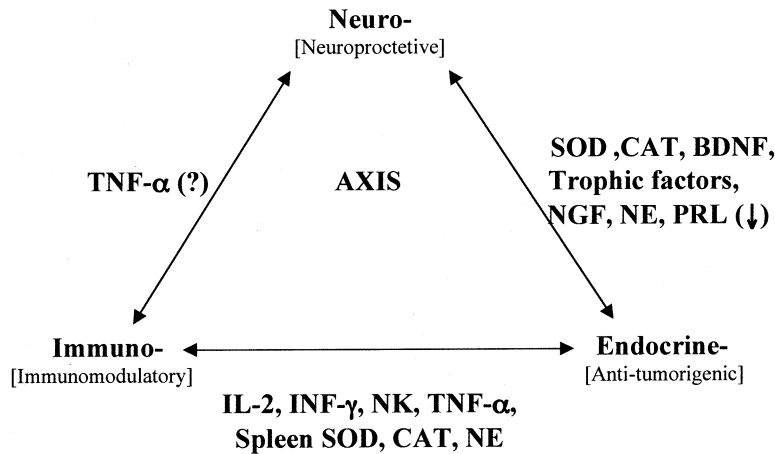


Fig. 8. Homeostatic mechanisms regulating aging and possible ways in which (–)deprenyl intervenes. Abbreviations: PRL, prolactin; NGF, neuronal growth factor. For other abbreviations, see the text.

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