ELSEVIER

Mechanisms of Ageing and Development
123 (2002) 121–130

mechanisms of ageing and development

www.elsevier.com/locate/mechagedev

The Snell dwarf mutation *Pit1*^{dw} can increase life span in mice

Kevin Flurkey [a,*], John Papaconstantinou [b], David E. Harrison [a]

[a] *The Jackson Laboratory, Bar Harbor, ME 04609, USA*
[b] *The University of Texas Medical Branch, Department of Human Biological Chemistry & Genetics, Galveston, TX, USA*

Abstract

Over the past 30 years, the Snell dwarf mutation (*Pit1*^{dw}) has been reported to shorten, to have no effect on, or to increase life span in various colonies; however, few details of these disparate results have been published. We now report that mean, median, and maximum life spans are increased by 40–50% for Snell dwarf (*Pit1*^{dw}/*Pit1*^{dw}) DW/J females, and 25–50% for dwarf DWC3F1 males and females with the compound heterozygous *Pit1*^{dw}/*Pit1*$^{dw-J}$ genotype. We previously observed aspects of delayed senescence in Snell dwarf (*Pit1*^{dw}/*Pit1*^{dw}) DW/J *males*; however, their median life span was shortened by about 25% (*Genetic Effects on Aging II*, 1990, The Telford Press, Caldwell, NJ, pp. 435–456). This short life span was not an intrinsic effect of the mutation, but a consequence of housing male dwarfs with normal-sized male littermates; our present results demonstrate that Snell dwarf males attain very long life spans when housed with normal-sized females. We conclude that the dwarf mutation interacts with environmental factors to alter life spans and, probably, rates of ageing, over an extremely broad range. We propose that this variation in the effect of the Snell dwarf mutation results from a tradeoff between physical vigor and life span that is mediated by pituitary hormones, and that growth hormone, thyroid hormone, and possibly prolactin regulate mechanisms that schedule mortality in mammals. © 2002 Published by Elsevier Science Ireland Ltd.

Keywords: Snell dwarf; *Pit1*; Life span; Gene; Ageing

1. Introduction

The Snell dwarf mutation, which prevents the development of the pituitary cells that secrete growth hormone, thyrotrophin and prolactin, has been of interest to gerontologists for decades. The presentations on the Snell dwarf in each of the three Genetics Effects on Aging meetings, beginning 25 years ago (Piantanelli and Fabris, 1978; Flurkey and Harrison, 1990; this paper), reflect an evolving understanding of the complex interaction of pituitary hormone deficiency with senescence. We now report that, under low stress husbandry conditions, the Snell dwarf mutation consistently increases life span.

The Snell dwarf mutation, designated *Pit1*^{dw}, is a point mutation in *Pit1* on mouse chromosome 16 that prevents DNA-binding of its gene product Pit1, a transacting POU domain protein which is necessary for the differentiation of pituitary thyrotrophs, somatotrophs and lactotrophs (Li et al., 1990). Mice that are homozygous for the muta-

* Corresponding author.

0047-6374/02/$ - see front matter © 2002 Published by Elsevier Science Ireland Ltd.
PII: S0047-6374(01)00339-6

tion do not produce thyroid hormone, growth hormone or prolactin (Cheng et al., 1983; Sinha et al., 1975; Bartke, 1964, 1965), are about half the weight of their normal littermates at weaning, and about one-third normal weight as young adults. The phenotype includes effects on maturation, for example, the skeleton of Snell dwarf mice does not complete adult maturation (Silberberg, 1973). The mutation is maintained on the DW/J genetic background, which was inbred at The Jackson Laboratory in 1966.

Initial studies of immunological impairment in Snell dwarf mice, maintained in conventional non-barrier colonies, indicated that within two months of weaning some T cell-dependent functions were impaired, although B cell-dependent functions were unaffected. In Snell–Bagg dwarf mice, these impairments were associated with an apparent wasting disease and early death at around five months of age, just 25% of the life span for their normal littermates (Fabris et al., 1972); life span for DW/J Snell dwarfs was reported to be even shorter (Chen et al., 1972). The preferential impairment of T cell-dependent functions, which is comparable to the pattern of impairment during immunologic ageing, and the early death suggested to Fabris et al. (1972) that putative growth hormone and thyroid hormone deficiencies of ageing may promote immunological senescence. They proposed the Snell dwarf as a model for accelerated senescence (Fabris et al., 1972; Piantanelli and Fabris, 1978).

However, not all researchers observed accelerated senescence and shortened life span in Snell dwarfs, despite the dwarfs' well-known frailty. For example, a number of researchers found no evidence for advanced immunologic ageing in adult Snell dwarf mice either in vitro (Dumont et al., 1979; Flurkey and Harrison, 1990; Cross et al., 1992) or in vivo (Baroni et al., 1972; Schneider, 1976). Eicher and Beamer (1980) reported that Jackson dwarf mice outlive their normal-sized littermates. Jackson dwarf mice have a mutation at the *Pit1* locus ($Pit1^{dw-J}$) that arose spontaneously on the C3H/HeJ inbred background and produces the same dwarfing phenotype as the Snell dwarf mutation. Silberberg reported that ageing of the knee joint and vertebral column were greatly retarded and that age-related osteoarthritis, which is characteristic of the DW/J strain, was completely prevented in 'long-lived' Snell dwarf mice (Silberberg, 1972, 1973). In fact, Silberberg considered the Snell dwarf a model of delayed senescence, partly because individual dwarfs could survive past 3.5 years. Unfortunately, she never published survival data.

Interestingly, in colonies where dwarfs thrived, special husbandry precautions often were used. Therefore, we re-examined the effect of the Snell dwarf mutation on life span in greater detail using precautions to ensure that the dwarfs were warm (by housing them with normal, non-dwarf littermates), had access to food and water, and were reared in specific pathogen-free conditions (Flurkey and Harrison, 1990). We reported that male Snell dwarfs housed with normal DW/J male littermates lived well beyond five months, to a median life span of about 18 months, which was, nonetheless, shorter than the 24 month median life span of the normal DW/J male littermates. However, in a subsequent pilot study, we found that female Snell dwarf mice housed with normal DW/J female littermates had a median life span of about 29 months, which was a 50% increase in life span compared to the 19 month median of the normal DW/J females (Flurkey and Harrison, 1994). In addition, Brown-Borg et al. (1996) reported that both male and female Ames dwarf mice ($Prop1^{df}$), which exhibit a dwarfing phenotype that is comparable to that of Snell dwarfs, live at least 50% longer than their normal-sized littermates, achieving median life spans of around 38 months, and Miller (1999) presented preliminary evidence that dwarf DWC3F1 $Pit1^{dw}/Pit1^{dw-J}$ mice live longer than their normal littermates. We now present complete life span data for female Snell dwarf mice, confirming their extended life span. We also present data indicating that the shorter life span we observed previously for male Snell dwarfs resulted from housing with normal-sized male littermates, not from an intrinsically shortened survival. Furthermore, to determine if *Pit1* mutations also increase life span on a more robust genetic background, we crossed DW/J $Pit1^{dw}/+$ mice with C3H/HeJ $Pit1^{dw-J}/+$ mice.

The median life span of these DWC3F1 dwarf mice was increased by about 40% over that of normal DWC3F1 littermates, to about 38 months. We conclude that Snell dwarfs can live longer than normal under protective environmental conditions.

Our results demonstrate that pituitary hormones mediate important tradeoffs between life span and other components of reproductive fitness, including youthful vigor. Whereas normal hypophyseal function is important for optimal vigor, health maintenance, and survival in less than ideal environments, it limits the potential to attain maximal life span; however, in protective environmental contexts, the frailty that results from hypophyseal deficiency does not compromise survival, the beneficial effects of hypophyseal deficiency on senescence rates can be expressed, and life span is increased.

2. Materials and methods

2.1. Mice

All mice were reared at The Jackson Laboratory in a limited access specific pathogen-free colony. Pathogen testing is described in Harrison et al. (1982); the pathogen status of the colony has not changed since then.

DW/J $Pit1^{dw}/Pit1^{dw}$ (designated $Pit1^{dw/dw}$) dwarf mice were produced by mating DW/J $Pit1^{dw}/+$ heterozygotes. Heterozygotes are phenotypically indistinguishable from normal wild type homozygotes, and we used both as controls, which we designate 'normal littermates' or 'normal-sized controls', symbolized as $Pit1^{+}/?$. DW/J mice were on a 12 h light cycle at 22–24 °C, given autoclaved Purina 96W chow and sterilized acidified tap water ad lib. Dwarf mice were housed with same sex normal-sized controls ('caretakers') to provide warmth; special water bottles or extra shavings were provided to ensure that the dwarfs could reach their water. Cages were checked three times each week for deaths.

Toward the end of this study, when three middle-aged dwarf males were still alive, it became clear that female, but not male, dwarfs were living longer than normal. Because of the possibility that aggression by normal male caretakers could affect survival of the male dwarfs, the male caretakers were replaced with normal female caretakers for these three male dwarfs through the remainder of the study.

To determine if null mutations at *Pit1* also could increase life span on a robust hybrid genetic background, we crossed DW/J $Pit1^{dw}/+$ mice with C3H/HeJ $Pit1^{dw-J}/+$ mice to produce compound mutant $Pit1^{dw}/Pit1^{dw-J}$ (designated $Pit1^{dw/dw-J}$) dwarfs and normal DWC3F1 littermates. The $Pit1^{dw-J}$ mutation (the Jackson dwarf) arose spontaneously on the inbred C3H/HeJ background, is allelic to the Snell dwarf mutation, and produces the same phenotype (Eicher and Beamer, 1980). Both directions of the cross were used, producing both DWC3F1 and C3DWF1 mice. There was no effect of the direction of the cross on life span for either dwarfs or normal littermates; therefore, 'DWC3F1' will be used throughout this paper to designate mice from either direction of the cross.

DWC3F1 mice were fed the NIH-31 diet, 4% fat and they were maintained at an ambient temperature of 26–28.5 °C. All DWC3F1 dwarfs were housed with normal DWC3F1 females throughout the study. When a normal female died, it was replaced with a young normal DWC3F1 female.

2.2. Statistics

Effects of the mutation on mean life span were determined by ANOVA, and on median life span by the Mann–Whitney *U* test, using the statistical package STATVIEW 4.5 (Roth et al., 1992).

For DW/J mice, an estimate of maximum life span is given by the ages of the two longest-lived mice (Table 1). The small number of mice in each group precludes a more precise estimate; however, we note that the probability of underestimating maximum life span increases as group size decreases; therefore, actual maximum life spans are probably greater. For the larger populations of DWC3F1 mice, the mean of the longest-lived 10% of each population is given as an estimate of maximum life span. When the longest-lived 10%

was not an integer, it was rounded up to the next integer to determine the number of mice used for the calculation, and the life span of the youngest mouse of this group was weighted according to its fractional contribution.

3. Results

3.1. Life span in DW/J mice

Under specific pathogen-free conditions, the median life span of female Snell dwarf mice, housed with female caretakers, is increased by 50% over the median life span for normal-sized controls (heterozygote and wild type homozygote littermates) (Fig. 1, Table 1, $P = 0.0003$, Mann–Whitney U test). For male Snell dwarf mice housed with normal-sized DW/J males, the median life span was 6% less than for the normal DW/J controls (Fig. 1, Table 1); the difference was not significant. Three middle-aged dwarf males were rehoused with normal female caretakers (at 15, 19 and 22 months of age); survival of these three was tripled over the expected survival, which was calculated using data from a much larger study in which male DW/J dwarfs were housed with normal male littermates throughout their lives (Flurkey and Harrison, 1990) (Table 2, $P = 0.01$, ANOVA, expected versus actual remaining life span).

3.2. Life span in DWC3F1 mice

To determine if dwarfing mutations at *Pit1* increase life span on a genetic background that is more robust than the DW/J background, we assessed life span in DWC3F1 *Pit1*$^{dw/dw-J}$ dwarfs and their DWC3F1 *Pit1*$^{+}$/? littermate controls. In this study, male dwarfs were housed with female caretakers throughout their lives beginning at weaning. The life span of both male and female DWC3F1 *Pit1*$^{+}$/? controls was increased, over that of DW/J *Pit1*$^{+}$/? controls, to more than 800 days. The median life span was increased further in DWC3F1 *Pit1*$^{dw/dw-J}$ dwarfs, by 51% in females and 29% in males (Fig. 2 and Table 3: $P < 0.0001$, females; $P = 0.001$, males, Mann–Whitney U test).

4. Discussion

The DW/J inbred strain is considered a high tumor strain (Chen et al., 1972); its life span is relatively short compared to that of standard strains typically used for gerontological studies. Others and we have demonstrated that pituitary

Table 1
Survival characteristics for DW/J mice

	Median	Mean ± SEM	Two Oldest [a]	*n*
Females				
DW/J *Pit1*$^{+}$/? controls	579	571 ± 37	754, 789	16
DW/J *Pit1*$^{dw/dw}$ dwarfs	*872* [b]	*844 ± 44* [c]	*1061*, *1100*	18
Percent difference	51	48	40	
Males				
DW/J *Pit1*$^{+}$/? controls	671	613 ± 44	816, 819	17
DW/J *Pit1*$^{dw/dw}$ dwarfs	*634*	*618 ± 87* [d]	*1007*, *1022* [d]	12
Percent difference	−6	1	24	

[a] Used to estimate maximum life span from small populations.
[b] Differs from female controls, $P = 0.0003$, Mann–Whitney U test.
[c] Differs from female controls, $P < 0.000$l, ANOVA.
[d] All of the male dwarfs were housed with normal males throughout their life except for three dwarfs that were rehoused with normal females at 15, 19 and 22 months of age. These three lived much longer than expected if they had been left with normal males (see Table 2), and they include the two longest-lived males of this group.

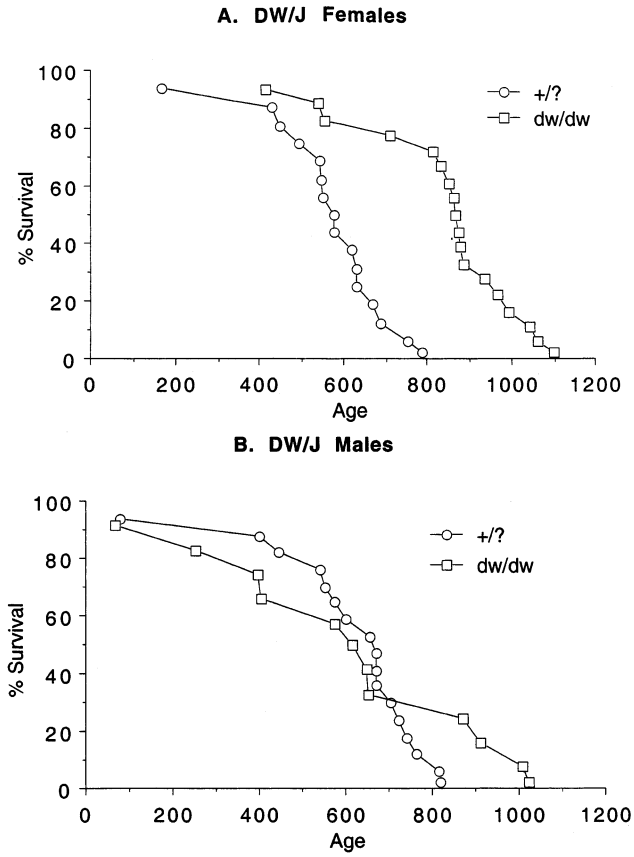

Fig. 1. Survival of DW/J mice. Each point represents one mouse. Statistics are given in Table 1. All dwarf males were continuously housed with normal DW/J males except the three longest-lived dwarf males, which were rehoused with normal females caretakers at 15, 19 and 22 months of age. The survival of these rehoused dwarfs was significantly greater than expected for Snell dwarf males housed with normal males (Table 2).

endocrine deficiencies produced by hypophysectomy can retard age-related tumorigenesis in rodents (Flurkey et al., 1995; Everitt et al., 1980). Thus, it is possible that the Snell dwarf mutation increased the life span of DW/J mice simply by withdrawing endocrine support of some strain-specific tumor. To determine if the dwarf mutation could also increase survival on a genetic background that has a normal life span, we produced dwarf mice on a more robust F1 hybrid background by crossing DW/J $Pit1^{dw}/+$ mice with C3H/HeJ $Pit1^{dw-J}/+$ mice. In these studies, we housed male dwarf mice continuously with normal female, rather than male, caretakers. As expected, the normal DWC3F1 mice lived about 30% longer than normal DW/J mice. Additionally, life span in the DWC3F1 dwarfs was increased even further (by 25–50%) over that of the normal DWC3F1 controls, confirming a report by Miller (Miller (1999), expanded in Flurkey et al. (2001)) for the same DWC3F1$^{dw/dw-J}$ hybrid, and demonstrating that the life extension effect of the dwarf mutation does not result simply from normalizing a short life span. On both genetic backgrounds, the dwarf mutation shifted the entire survival curve to the right, indicating that the expression of all causes of mortality was delayed. Preliminary results of a histopathologic evaluation of DWC3F1 dwarfs and control littermates indicate that the dwarfing mutation eliminates or delays the expression of most of the age-related lesions found in the normal littermates at death, including most malignancies that are the probable causes of death for this genotype (Flurkey et al., unpublished). It appears that among the elements

Table 2
Effect on survival of rehousing DW/J male dwarfs with female caretakers [a]

Age when mouse was rehoused (days)	Expected remaining life span [b]	Actual remaining life span	Total life span
444	230	466	910
575	119	447	1022
672	*53*	*335*	1007
Mean ± S.E.M.	134 ± 52	412 ± 40 [c]	$n = 3$

[a] Normal male 'caretakers' were removed and replaced with normal female caretakers.
[b] Expected survival was calculated from life span data on male DW/J Snell dwarfs that were continuously housed with DW/J male caretakers (Flurkey and Harrison, 1990).
[c] Greater than expected survival, $P = 0.01$, ANOVA.

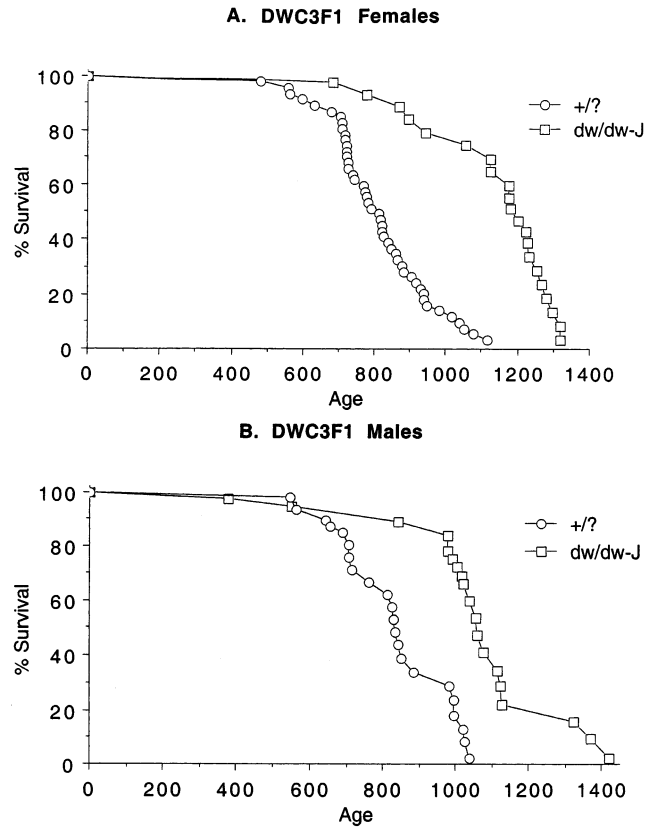

Fig. 2. Survival of DWC3F1 mice. Each point represents one mouse. Statistics are given in Table 3.

Table 3
Survival characteristics for DWC3F1 mice

	Median	Mean ± S.E.M.	Mean of the longest-lived 10%	*n*
Females				
DWC3F1 *Pit1*$^{+}$/? controls	814	811 ± 20	1061	48
DWC3F1 *Pit1*$^{dw/dw-J}$ dwarfs	*1231* [a]	*1148 ± 39* [b]	*1313*	23
Percent difference	51	42	24	
Males				
DWC3F1 *Pit1*$^{+}$/? controls	827	822 ± 34	1101	23
DWC3F1 *Pit1*$^{dw/dw-J}$ dwarfs	*1068* [c]	*1037 ± 53* [d]	*1394*	20
Percent difference	29	26	27	

[a] Differs from female controls, $P < 0.0001$, Mann–Whitney U test.
[b] Differs from female controls, $P < 0.0001$, ANOVA.
[c] Differs from male controls, $P = 0.0005$, Mann–Whitney U test.
[d] Differs from male controls, $P < 0.00$l, ANOVA.

of delayed senescence in the dwarf (see below) are the mechanisms that schedule mortality.

In the studies of the male DWC3F1 dwarfs, the effect of the dwarf mutation is confounded with the presence of normal female caretakers, and we must consider an alternative hypothesis that longevity in males, independent of the presence of the dwarfing mutation, is promoted by housing them with normal females. Although housing any males with females may improve the males' longevity, the importance of the dwarf mutation is formally demonstrated in the females, where life span is increased by 40–50% for both DWC3F1 and DW/J genotypes.

Another mutation that produces a phenotype virtually identical to the Snell dwarf mutation is the Ames dwarf mutation (*Prop1*^{df}), which is maintained on a mixed genetic background. This mutation inactivates a transactivator of *Pit1*, and, like the Snell dwarf mutation, it prevents the development of pituitary somatotrophs, lactotrophs, and thyrotrophs; it also increases both median and maximum life span compared to littermate controls (Brown-Borg et al., 1996). Thus, two different mutations, each of which produces a combined deficiency of growth hormone, thyroid hormone, and prolactin, increase life span on various genetic backgrounds. These observations indicate that it is the endocrine deficiencies, rather than the specific mutation or interaction with genetic background, that increase life span.

Both growth hormone and thyroid hormone deficiencies may contribute individually to the increased life span in dwarf mice. Genetically based deficiencies of the somatotrophic axis are associated with increased life span in mice: Ghrhr-defective 'little' mice (*Ghrhr*^{lit}/*Ghrhr*^{lit}) can live 20–25% longer (Flurkey et al., 2001), and growth hormone receptor knock out mice live 40–50% longer than controls (Coschigano et al., 2000). The effect of somatotrophic deficiency on life span may depend on interactions of environmental factors with genetic background; the 'little' mutation had inconsistent effects on life span in earlier studies in our lab that employed diets with higher fat content (Flurkey and Harrison, 1990). Chronic thyroid hormone deficiency degrades general health under normal circumstances, and extreme thyroid hormone deficiency can shorten life span due to eventual thyrotroph hypertrophy that physically disrupts the hypothalamus; however, chronic thyroid deficiency that was produced by neonatal treatment with thyroid hormone increased longevity in rats (Ooka et al., 1983). It appears that prolactin deficiency is not necessary for the increased life span in dwarf mice; chronic prolactin-replacement by heterotopic pituitary transplantation into dwarf DWC3F1 mice did not shorten their life span (Flurkey et al., 2001).

Endocrine deficiencies have been shown to retard specific aspects of senescence, e.g. estradiol deficiency retards ageing of the luteinizing hormone neuroendocrine axis in female rats and mice (Aschheim, 1976; Mobbs, 1990; Finch et al., 1984), and thyroid hormone deficiency retards collagen ageing (Everitt and Delbridge, 1976; Giles and Everitt, 1967). Furthermore, in Snell or Ames dwarf mice, multiple facets of ageing are retarded, including skeletal and joint ageing (Silberberg, 1972, 1973), T cell ageing (Flurkey et al., 2001), and metabolic aspects of ageing (Bartke, 2000). Thus, normal levels of growth hormone, thyroid hormone, and, perhaps, prolactin appear to advance the expression of multiple aspects of senescence, including aspects that determine life span. We propose that such hormones promote senescence and influence life span as they continue to promote tissue remodeling and differentiation, i.e. to promote their organizational effects, after sexual maturity is attained, eventually extending maturational change beyond the adaptive range. We borrow a term from developmental biology used to describe the exaggeration of characteristics during phylogeny (for example, the elongation of the giraffe's neck as it evolved) and suggest that senescence is a consequence of progressive hypermorphosis in adults (Flurkey, 2001). In this context, hormones that promote maturation, such as thyroid hormone and growth hormone, are agents of senescence when their organizational effects persist and accumulate throughout the life span.

The idea that hormones contribute to senescence by promoting adult hypermorphosis appears to contrast with the well-supported idea that senescence results from endocrine deficiency

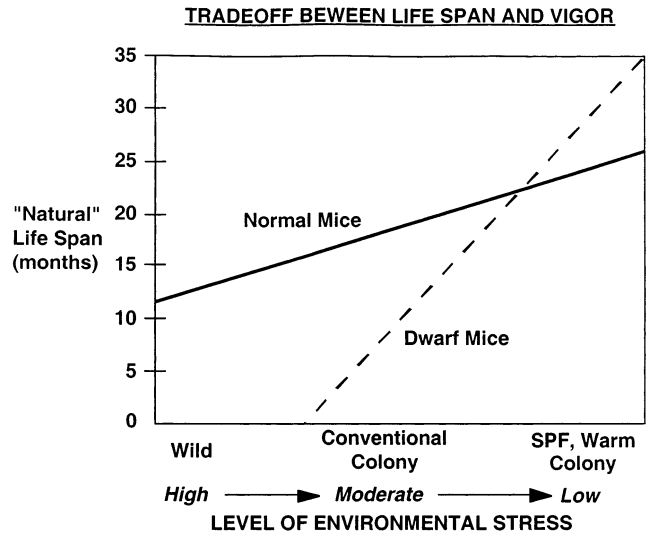

Fig. 3. The interaction of endocrine deficiencies with environmental stresses determines survival. Growth hormone, thyroid hormone and prolactin may mediate a tradeoff between ability to survive environmental stresses and maximum potential life span. These hormones are necessary to achieve optimal vigor, which is progressively less important for survival as environments become less challenging. Highly protective environments unmask the potential of extreme endocrine deficiencies, such as those of the Snell dwarf, to delay senescence and increase life span.

(reviewed in Sonntag et al. (1999) and in Lamberts et al. (1997)). According to the view that senescence results from hypermorphosis, senescence should be ameliorated by chronic reductions of hormones that have cumulative maturational effects in adults; but, according to the 'endocrine deficiency' view, such reductions should promote senescence. These two views can be integrated by considering the interaction of endocrine deficiency with environmental challenge (Fig. 3). Whether an endocrine deficiency promotes or delays senescence depends on the stress level in the environment. For example, age-related deficiencies of anabolic hormones such as growth hormone will diminish protein synthesis, muscle mass, wound repair, and recovery from stress, all characteristics of mammalian senescence. Under conditions in the wild, where robust anabolic activity is important for survival, such endocrine deficiencies can impair health, advance 'senescence' and shorten life span. Our present results suggest that one cost of endocrine-driven optimization of fitness is a reduction of the maximum potential life span. Protective husbandry conditions do not require such vigor for survival; thus, they may be used to unmask the beneficial effects of pituitary hormone deficiencies. Such tradeoffs were anticipated over 40 years ago by Williams (1957), as a consequence of antagonistic genetic pleiotropy. Williams predicted that "senescence results from genes that increase youthful vigor at the price of vigor later on". We propose that growth hormone, thyroid hormone, and possibly prolactin are important mediators of this tradeoff.

Acknowledgements

We wish to thank Keith A. Oliver for his dedication and excellent technical assistance and Win and Douglas Savery for their generous support. This work was also supported by grants to K.F. from Polar Communications (Manalapan, NJ) and Empire Pharmaceuticals (Barbareche, SA) and by a grant from the NIA (AG-16622) to J.P. and D.E.H.

References

Aschheim, P., 1976. Aging in the hypothalamic–hypophyseal–ovarian axis in the rat. In: Everitt, A.V., Burgess, J.A. (Eds.), Hypothalamus, Pituitary and Aging. Charles C. Thomas, Springfield, IL, USA, pp. 376–418.

Baroni, C.D., Scelsi, R., Mingazzini, P.L., Cavallero, A., Uccini, S., 1972. Delayed hypersensitivity in the hereditary pituitary dwarf Snell/Bagg mouse. Nature New Biology 237, 219–220.

Bartke, A., 1964. Histology of the anterior hypophysis, thyroid and gonads of two types of dwarf mice. Anatomical Record 149, 225–236.

Bartke, A., 1965. The response of two types of dwarf mice to growth hormone, thyrotrophin and thyroxin. General and Comparative Endocrinology 5, 418–426.

Bartke, A., 2000. Delayed aging in Ames dwarf mice. Relationships to endocrine function and body size. Results and Problems in Cellular Differentiation, 29181–29202.

Brown-Borg, H.M., Borg, K.E., Meliska, C.J., Bartke, A., 1996. Dwarf mice and the aging process. Nature 384, 33.

Chen, H.W., Meier, H., Heiniger, H.J., Heubner, R.J., 1972. Tumorigenesis in strain DW/J mice and induction by prolactin of the group-specific antigen of endogenous C-type RNA tumor virus. Journal of The National Cancer Institute 49, 1145–1154.

Cheng, T.C., Beamer, W.G., Phillip, J.A., Bartke, A., Mallonee, R.L., Dowling, C., 1983. Etiology of growth hormone deficiency in little, Ames and Snell dwarf mice. Endocrinology 113, 1669–1678.

Coschigano, K.T., Clemmons, D., Bellush, L.L., Kopchick, J.J., 2000. Assessment of growth parameters and life span of GHR/BP gene-disrupted mice. Endocrinology 141, 2608–2613.

Cross, R.J., Bryson, J.S., Roszman, T.L., 1992. Immunologic disparity in the hypopituitary dwarf mouse. Journal of Immunology 148, 1347–1352.

Dumont, F., Robert, F., Bischoff, P., 1979. T and B lymphocytes in pituitary dwarf Snell–Bagg mice. Immunology 38, 23–32.

Eicher, E.M., Beamer, W.G., 1980. New mouse dw allele: genetic location and effects on life span and growth hormone levels. Journal of Heredity 71, 187–190.

Everitt, A.V., Delbridge, L., 1976. The role of the pituitary and the thyroid in the aging of collagen in the rat tail tendon. In: Everitt, A.V., Burgess, J.A. (Eds.), Hypothalamus, Pituitary and Aging. Charles C. Thomas, Springfield, IL, USA, pp. 193–208.

Everitt, A.V., Seedsman, N.J., Jones, F., 1980. The effects of hypophysectomy and continuous food restriction, begun at ages 70 and 400 days, on collagen aging, proteinurea, incidence of pathology and longevity in the male rat. Mechanisms of Ageing and Development 12, 161–172.

Fabris, N., Pierpaoli, W., Sorkin, E., 1972. Lymphocytes, hormones and ageing. Nature 240, 557–559.

Finch, C.E., Felicio, L.S., Mobbs, C.V., Nelson, J.F., 1984. Ovarian and steroidal influences on neuroendocrine aging processes in female rodents. Endocrine Reviews 5, 467–497.

Flurkey, K., 2001. Gerontology. In: Considine, D.M., Considine, G.D. (Eds.), Van Nostrand's Scientific Encyclopedia, 9th ed. Wiley, New York (in press).

Flurkey, K., Bronson, R., Archer, J., Coman, D., Donahue, L.R., Harrison, D.E., 1995. Hypophysectomy and age-related tumorigenesis in mice. The Gerontologist 35, 242.

Flurkey, K., Harrison, D.E., 1994. Genetic models for aging research. 15th Annual Meeting of the Southeast Pharmacological Society, Clearwater Beach, FL.

Flurkey, K., Papaconstantinou, J., Miller, R.A., Harrison, D.E., 2001. Life span extension and delayed immune and collagen aging in mutant mice with defects in growth hormone production. DNAS 98, 6736–6741.

Flurkey, K.F., Harrison, D.E., 1990. Use of genetic models to investigate the hypophyseal regulation of senescence. In: Harrison, D.E. (Ed.), Genetic Effects on Aging II. The Telford Press, Caldwell, NJ, pp. 435–456.

Giles, J.S., Everitt, A.V., 1967. The role of the thyroid and food intake in the ageing of collagen fibres. I. In the young rat. Gerontologia 13, 65–69.

Harrison, D.E., Archer, J., Astle, C.M., 1982. The effect of hypophysectomy on thymic aging in mice. Journal of Immunology 129, 2673–2677.

Lamberts, S.W., van den Beld, A.w., et al., 1997. The endocrinology of aging. Science 278, 419–424.

Li, S., Crenshaw, E.B.I., et al., 1990. Dwarf locus mutants lacking three pituitary cell types result from mutations in the POU-domain gene pit-1. Nature 347, 528–533.

Miller, R.A., 1999. Kleemeier award lecture: are there genes for aging? The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences 54 (7), B297–B307.

Mobbs, C.V., 1990. Neurotoxic effects of estrogen, glucose, and glucocorticoids: neurohumoral hysteresis and its pathological consequences during aging. Review of Biological Research in Aging 4, 201–228.

Ooka, H., Fujita, S., Yoshimoto, E., 1983. Pituitary–thyroid activity and longevity in neonatally thyroxine-treated rats. Mechanisms of Ageing and Development 22, 113–120.

Piantanelli, L., Fabris, N., 1978. Hypopituitary dwarf and athymic nude mice and the study of relationships among thymus, hormones, and aging. In: Bergsma, D., Harrison, D.E. (Eds.), Genetic Effects on Aging. Alan R. Liss, Inc., New York, pp. 315–333.

Roth, J., Haycock, K., Gagnon, J., Soper, C., Caldarola, J., 1992. STATVIEW. Berkeley, CA, Abacus Concepts, Inc.

Schneider, G.B., 1976. Immunological competence in Snell–Bagg pituitary dwarf mice: response to the contact sensitizing agent oxazalone. Journal of Anatomy 145, 371–380.

Silberberg, R., 1972. Articular aging and osteoarthrosis in dwarf mice. Pathologia et Microbiologia 38, 417–430.

Silberberg, R., 1973. Vertebral aging in hypopituitary dwarf mice. Gerontologia 19, 281–294.

Sinha, Y.N., Salocks, C.B., Vanderlaan, W.B., 1975. Pituitary and serum concentrations of prolactin and GH in Snell dwarf mice. Proceedings of the Society for Experimental Biology and Medicine 150, 207–213.

Sonntag, W.E., Lynch, C.D., Cefalu, W.T., Ingram, R.L., Bennett, S.A., Thornton, P.L., Kahn, A.S., 1999. Pleiotropic effects of growth hormone and insulin-like growth factor (IGF)-1 on biological aging: inferences from moderate caloric-restricted animals. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences 54 (12), B521–B538.

Williams, G.C., 1957. Pleiotropy, natural selection and the evolution of senescence. Evolution 11, 398–411.