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Review

Growth Hormone and Aging

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Although age-related decline in plasma growth hormone (GH) levels is well documented, the possible role of GH in the control of aging is controversial. Overexpression of GH in transgenic mice is associated with reduced life expectancy and numerous symptoms of premature aging. Ames dwarf mice with hereditary GH, prolactin, and thyrotropin deficiency live much longer than their normal siblings. In contrast to these indications that GH may accelerate aging, some physiological changes in the elderly resemble symptoms of GH deficiency and can be corrected by GH replacement.

It is suggested that these seemingly contradictory observations are related to the dose–response characteristics of GH action, and to negative correlation between body size and life expectancy within a species. Physiological mechanisms linking plasma GH levels and body size with aging remain to be identified.

Key Words: Growth hormone; aging; body size; life-span.

Introduction

The levels of growth hormone (GH) and insulin-like growth factor-I (IGF-I, the main mediator of GH actions) progressively decline during aging *(1–3)*. There is also evidence that some of the age-related changes in body composition, serum lipids, and muscle performance closely resemble symptoms of adult-onset GH deficiency *(3–5)* and that they can be mitigated or even reversed by administration of GH to elderly subjects *(6)*. However, the broader issue of the possible effects of GH on the process of aging and on life expectancy is poorly understood and fraught with controversy. For example, prolonged elevation of GH levels above the physiological range is associated with reduced life-span in transgenic mice *(7,8)* and in patients with acromegaly *(9,10)*. Curiously, hypopituitarism and GH deficiency in the human were reported to be associated with increased markers of cardiovascular risk and reduced life expectancy *(9,11)*, whereas mice with congenital hypopituitarism (including GH deficiency) were recently reported to live much longer than normal animals *(12)*. This brief article will summarize findings that suggest that GH may advance aging, as well as the findings that suggest the opposite, attempt to explain these contradictions, and suggest physiological mechanisms that may link GH and life expectancy. The issues of the risks and benefits of GH treatment in the elderly and the influence of GH therapy on the quality of life are outside the scope of this article.

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Does GH Advance Aging?

As mentioned above, acromegalic patients with GH-secreting pituitary tumors have reduced life expectancy *(9,11)*. This is owing to increased incidence of cardiovascular disease, diabetes, and perhaps also tumors *(10,11)*. Although a clear distinction between age-related changes in the incidence of diseases and aging *per se* is very difficult—if not impossible—reduced life expectancy of acromegalic patients is generally not regarded as evidence for accelerated aging. Studies of the effects of lifelong excess of GH in experimental animals may be more pertinent to the issue of the effects of GH on aging. Transgenic mice overexpressing rat, bovine, or human GH die much earlier than their normal siblings *(7,13–16)*. In lines of mice in which plasma levels of heterologous GH are very high, approx 0.5 μg/mL or greater, transgenic animals rarely reach half of the normal life-span (*7,8*; Bartke et al., unpublished observations). Reduced life expectancy in these animals is accompanied by reduced replicative potential of their cells in culture *(14)*, increased free radical processes *(16)*, deficits in learning and memory (Meliska et al., unpublished observations), and increased astrogliosis in the brain *(8)*. These animals also exhibit early onset of pathological changes in the kidney *(7,17,18)* and of decline in hypothalamic catecholamine turnover *(13)*. Age-related changes in the kidney, glomerulosclerosis, and glomerulonephritis deserve particular attention because they appear to represent a leading

cause of death in both normal and GH-transgenic mice *(7,17,19)*.

In spite of the above-mentioned findings, the conclusion that transgenic mice overexpressing GH experience accelerated aging is not generally accepted. Some of the age-related changes listed above can be interpreted as GH-induced pathology rather than aging. It can also be argued that pharmacological levels of GH reduce life expectancy by increasing plasma corticosterone levels *(8,20,21)*, inducing insulin resistance *(22,23)*, or by other mechanisms not directly related to "physiological aging." The interpretation of findings obtained in transgenic mice will be difficult to resolve. For example, plasma corticosterone levels are consistently elevated in GH transgenics as compared to normal mice *(20)*, but mean basal corticosterone levels are not correlated with life-span of mice from a particular line *(20)*. Moreover, the role of glucocorticoids in normal aging is a matter of considerable controversy in its own right *(21,24,25)*. Another example of detrimental effects of overexposure to GH was provided by a report that treatment of rats with very high doses of GH can cause mortality *(26)*. However, the mechanisms involved in this effect remain to be identified.

It is also pertinent to ask whether the effects of pathologically elevated GH levels in acromegalic patients and transgenic mice represent physiological actions of this hormone. Biphasic dose–response relationships for GH actions in vitro have been reported *(27)* and are consistent with the requirement for dimerization of GH receptors in GH signaling *(27,28)*. There is also considerable evidence that some hormones (including prolactin [PRL], which is closely related to GH) may exert qualitatively different effects, depending on the ,concentration (for a review of this issue concerning PRL, please *see* ref. *29*). Therefore, studies of individuals with GH deficiency will be necessary to clarify whether or not GH normally influences aging.

There is very little information on life expectancy of humans with GH deficiency or resistance. Anecdotal reports indicate that "dwarfs may live longer than giants" *(30)*. Hypopituitarism, including GH deficiency, was recently associated with cardiovascular disease and reduced life expectancy *(9,11)*. These findings will be discussed later in this article.

Caloric restriction, which produces impressive prolongation of life in laboratory rodents *(31)* and appears to have similar effects in nonhuman primates (Roth, personal communication), was reported to be associated with suppression of GH release *(32)*. In rats, food deprivation and malnutrition disrupt the normal pulsatile pattern of GH release *(33)*. However, other investigators found that GH release is increased rather than suppressed in mildly calorically restricted approx 2-yr-old rats, in comparison to old, ad libitum-fed controls *(34,35)*, in keeping with the effects of caloric-restriction on GH release in other species *(36–38)*. Moreover, interpretation of the findings on calorie-restricted animals is confounded by the fact that the control animals in these studies have food available ad libitum and little need or opportunity for physical exercise. Thus, it could be argued that the calorie-restricted animals may be closer to the "normal" condition of animals living in their natural habitat, and that differences in the life-span of the restricted and the control groups are at least partially owing to the life-shortening effects of sedentary life style, overeating, and obesity.

Effects of hypophysectomy on life-span and aging depend on the age at which the surgery is performed, replacement therapy, nutrition, etc. *(39,40)*, and there are obvious difficulties in ascribing the effects of hypophysectomy to deficiency of GH or of any particular pituitary hormone. However, suppression of various pathological changes normally associated with aging and significant extension of the life-span were recorded in rats hypophysectomized early in life and provided with glucocorticoid replacement *(40)*.

In laboratory mice and rats there are well-characterized mutations that produce GH deficiency or resistance, but data on the life-span of these animals compared to their normal siblings are surprisingly scarce. Dwarf mice (Snell dwarfs, dw/dw), which are GH-, PRL-, and thyroid stimulating hormone-(TSH) deficient *(41,42),* were reported to die at a very early age owing to deficient immune function *(43)*. After publication of these results, several other workers reported that dwarf mice in their colonies survive much longer, but no data on mean or maximal life-span were reported *(44–47)*. In recent and ongoing studies, Flurkey and his colleagues find that Snell dwarf mice in their colony live significantly longer than their normal siblings (Flurkey and Harrison, personal communication). We have recently examined life-span in Ames dwarf mice (df/df). Ames dwarfs have the same endocrine phenotype as Snell dwarfs, i.e., GH, PRL, and TSH deficiency *(41,48)* owing to a mutation on a different chromosome acting at an earlier stage of fetal pituitary development *(48,49)*. Dwarfs outlived their normal siblings by more than a year with average age at death being 723 and 718 d in normal males and females, and 1076 and 1206 d in dwarf males and dwarf females, respectively *(12)*. It is unknown if prolonged survival of dwarf mice is a result of GH deficiency, because as indicated above, these animals are also PRL-deficient and hypothyroid. Interpretation of findings in dwarf mice is further complicated by their hypogonadism, which can range from mild to severe, apparently depending on the genetic background (*50*; and unpublished observations) and a delay or absence of sexual maturation.

It is intriguing that transgenic mice with a dwarf phenotype resulting from expression of a GH antagonist *(51)* apparently live longer than normal animals from the same strain (Chen and Kopchick, unpublished observations). Data on longevity of these animals as well as mutant

mice and rats with isolated GH deficiency or GH resistance are needed to determine whether GH has a physiological role in determining life expectancy. Information on the life-span of animals with targeted disruption ("knockout") of the GH receptor gene and other genes involved in the function of the GH-IGF-I axis should become available within the next few years, and may clarify many of the issues raised in this article.

Does GH Prevent Aging?

It is very well documented that peripheral GH levels decline with aging. This is true of all species that have been examined to date, including the rat *(52)*, the dog *(53)*, and the human *(1–3,54)*. Moreover, changes in body composition that normally accompany aging, i.e., increased adiposity, reduced lean body mass, and decline in muscle volume and performance, resemble findings in patients with GH deficiency *(3,55)* and are, in general, opposite to changes described in acromegalic patients *(10,36,56,57)*. Thus, it can be suspected that aging or at least some of its symptoms are related to a physiological decline in GH levels with age. Strong support for this possibility was provided by results of treatment of elderly subjects with recombinant human GH *(6)*. The results of GH treatment were beneficial and included increased lean body mass, reduction in adiposity, improved general well-being, and a reduction in the rate of age-related decline of bone density *(6)*. Not surprisingly, these results received a great amount of both scientific and news media attention, and raised an exciting possibility that GH replacement may delay, prevent, and/or reverse aging. However, it should be pointed out that these studies were relatively short term, and that the results available to date do not allow any firm conclusions or even meaningful predictions regarding the possible effect of GH on life expectancy. Moreover, the results of some of the subsequent studies have been less clear *(58,59)* and long-term double-blind, placebo-controlled studies may be necessary to remove doubts about the beneficial effects and advisability of GH therapy in the elderly.

The possibility that GH may act to prevent or postpone aging receives some support from observations in patients with GH deficiency. In these individuals, cardiac function is negatively affected *(5,9)*, and life expectancy was reported to be reduced *(11)*. Replacement of GH in GH-deficient patients is beneficial for cardiac health *(5,9)* and thus presumably also for life expectancy. However, Bates et al. *(60)* suggested that in hypopituitary patients, the observed increase in mortality is owing mainly to pituitary tumors and effects of their treatment. Profound GH deficiency in patients caused by premature aging with Werner's syndrome *(61)* would seem to fit with the concept that GH may normally function to prevent aging. However, premature aging is not seen in other states of GH deficiency.

The reported association of prolonged survival with the stimulation of pulsatile GH release in rats exposed to mild caloric restriction *(34,35)* would also be compatible with the concept that age-related decline in GH levels may be causally related to aging. The fact that life-span of hypophysectomized rats and dwarf mice was reduced in some of the studies *(40,43)* supports the hypothesis that GH may prevent, whereas GH deficiency may accelerate aging. However, most of the studies in the same animal models indicate prolonged rather than reduced survival (*12,40*; Flurkey and Harrison, unpublished data). Intermittent administration of GH to inbred Balb/c mice was reported to prolong their survival *(62)*. However, this effect was not replicated in a recent study (D. N. Kalu, personal communication).

Can These Discrepancies Be Reconciled?

Cogent arguments can be made to support the conclusion that GH acts to accelerate aging and to support the opposite conclusion that GH delays aging. Clinical and experimental evidence for each of these opposing conclusions appears to be substantial, even if indirect, and, in some cases, difficult to refute. However, we believe that at least some of these contradictory data can be reconciled by viewing the available evidence in light of the relationship of aging to body size and by interpreting the effects of GH on aging purely in this context. There is considerable evidence that within species, life-span is negatively correlated to body size. Thus, dogs from small breeds live longer than dogs from large breeds *(63)*, small mice live longer than large mice *(64–66)*, and short people apparently tend to outlive tall people *(67)*. Data on the relationship of height to life expectancy in humans are somewhat less convincing than the data derived from dogs or mice, but include comparisons of both different cohorts and of individuals within a cohort *(67)*.

Impressive differences in the life-span between animals calorically restricted during most of their life-span and those fed ad libitum *(31)* obviously fit this concept, because food-restricted animals are much smaller. Similarly, animals in which the life span was extended by hypophysectomy early in life combined with glucocorticoid replacement *(40)* exhibit very little, if any growth after removal of the pituitary, and thus increasingly lag behind the sham-operated or untreated controls in terms of their body weight.

Congenital absence of GH in dwarf mice is associated with diminutive body size (approx $^1/_3$ of the body wt of their normal siblings) and prolonged survival. Massive elevation of GH levels in GH transgenic mice leads to accelerated and prolonged growth with adult body weight ranging from 50–100% above normal in most of the lines that have been examined, and is associated with drastically reduced life span.

Because growth hormone, directly or via insulin-like growth factor I (IGF-I), affects a multitude of targets and functions, only some of which are directly related to growth,

and since it may exhibit biphasic dose–response relationships for each of these actions, it should not be surprising that the relationship among GH levels, body size, and longevity does not always hold. For example, detrimental effects of GH deficiency on cardiac function in humans *(9)* may mask the potentially beneficial effects of this condition on life expectancy. Deficiency or excess of GH developing after bone maturation in humans affects body composition but has virtually no effect on height and relatively modest effects on body weight. Thus, alterations in life expectancy in the affected individual may reflect GH actions on cardiac function, carbohydrate homeostasis, and so forth, rather than the postulated growth-mediated effects of this hormone on longevity.

In GH transgenic mice, drastic reduction in life expectancy may represent summing up of the effects of GH on adult size, resource allocation *(68)*, adrenocortical secretion *(20)*, and kidney function *(7,17)*. Conversely, drastic reduction of adult body weight in hereditary dwarf mice may overshadow the negative effects of GH and PRL deficiency on immune function *(43,69,70)*. In calorically restricted rats and mice, it could be suspected that the beneficial effects of reduced body size owing to reduced food intake could mask the potentially negative impact of elevated GH levels on the life span. To summarize this line of reasoning, GH may affect life expectancy only in as much as it serves as one of the determinants of adult body size. Evolution of optimal body size and biological meaning of differences in body size between and within species are topics of considerable current interest in theoretical biology *(71–73)*.

What Mechanisms May Link Body Size, GH Levels, and Life Span?

Proponents of the cause:effect relationships between body size and aging suggest that small body size confers bioenergetic and cardiovascular advantages *(67,74)*. Detailed discussion of these arguments and the mathematical formulae used to calculate the relative advantage of small individuals are outside the scope of this article. However, we would like to emphasize that this line of reasoning fits well with the entropy theory of aging *(74–76)*. If aging is viewed as a progressive failure to maintain organization and prevent entropy, it can be argued that small individuals expend less energy for growth and, therefore, have more energy available for "maintaining order" *(68)*. Transgenic mice overexpressing GH may present an excellent, and perhaps extreme, example of this relationship. It has been documented that these animals utilize disproportional amount of food energy for growth, fail to compensate for this by increasing food intake, and thus have insufficient energy for maintenance, including repair processes *(68)*. In strong support of this reasoning, transgenic MT-rGH mice were reported to live longer when they were encouraged to eat more by offering them carbohydrate supplement (*16*, Rollo, personal communication).

In the human and other species in which growth ceases after attainment of adult body size, these arguments would obviously not apply to adult individuals. There is little reason to suspect that anabolic and thermogenic actions of GH *(4,77,78)* could divert significant amounts of energy from repair mechanisms.

The well-documented anabolic and proliferative effects of GH and IGF-I suggest additional mechanisms for their effects on life-span. Stimulation of cell division is believed to set the stage for increased probability of neoplastic changes, and incidence of tumors was reported to be increased in individuals with abnormally elevated GH levels and reduced in states of GH deficiency *(5,10,41,56)*. However, the relationship of GH levels to neoplastic changes is poorly understood and controversial. Stimulation of metabolic processes increases generation of free radicals, and free radical damage is believed to represent one of the major, if not the cardinal, mechanisms of aging. It was recently reported that free radical processes are enhanced in transgenic mice overexpressing GH *(16)*.

These associations and putative mechanisms linking the levels of GH, an anabolic hormone, to regulation of life span appear to be consistent with older theories, which viewed aging as primarily "wear and tear" *(79)* that could be accelerated by "living fast" *(80)*. The entropy theory of aging and focus on the role of free radicals may put these ill-defined relationships into the context of measurable physiological processes.

The effects of GH on cell division and the control of somatic growth may also explain how altered levels of GH during early development can affect life expectancy. Pioneering studies of life span of cultured cells by Hayflick and Morehead *(81)* and extensive work on this subject that followed, link aging to the number of cell divisions. In GH-deficient dwarf mice, cell number is reduced and cell divisions cease earlier than in normal individuals *(82)*, thus perhaps setting the stage for their prolonged survival (*12*; Flurkey and Harrison, unpublished).

In closing, it should be mentioned that this or any attempt to provide a uniform explanation for the relationships of GH levels, body size, and life expectancy is based on an unproven and possibly faulty assumption that causal relationships among these factors are similar in different species. Clearly, more research is needed to provide the answers to questions posed in this article, to validate or reject the presented theories, and to identify the mechanisms involved. Current and contemplated use of GH in the treatment of short stature *(4)*, obesity *(83)*, and various catabolic states *(84)* emphasizes the need for more information on the effects of chronic exposure to elevated GH levels.

Note Added in Proof

An intriguing possibility that the GH-IGF-I axis may be linked to longevity via energy metabolism and insulin signaling was suggested by the recent demonstration that the "longevity gene" of the worm, *Caenorhabditis elegans*, is related to the insulin receptor gene in higher organisms *(85)*.

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