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GROWTH HORMONE AND AGING

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ABSTRACT

The potential usefulness of growth hormone (GH) as an anti-aging therapy is of considerable current interest. Secretion of GH normally declines during aging and administration of GH can reverse age-related changes in body composition. However, mutant dwarf mice with congenital GH deficiency and GH resistant GH-R-KO mice live much longer than their normal siblings, while a pathological elevation of GH levels reduces life expectancy in both mice and men. We propose that the actions of GH on growth, development, and adult body size may serve as important determinants of aging and life span, while the age-related decline in GH levels contributes to some of the symptoms of aging.

INTRODUCTION

The subject of growth hormone (GH) and aging was discussed in many recent reviews (1-7) and received considerable attention in the news media. Thus, the reader might well ask what possible purpose could be served by taking up this topic one more time. Previous reviews dealt primarily with the effects of aging on GH release, with the issue of the utility of GH in the treatment of the elderly, and with the controversy of whether GH acts to prevent or to accelerate aging. What we will try to do is to place the available information in the broader context of the multiple interactions between neuroendocrine signaling and aging. We will also summarize the newest information, including data on the effects of GH resistance on longevity.

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Neuroendocrine system and aging.

We believe that the interaction of endocrine, or more precisely, neuroendocrine, signaling and aging involves three related but clearly separable issues:

1. Changes in the neuroendocrine function that coincide with and are presumably caused by aging. These changes include alterations in the rates of hormone release and in responsiveness of target tissues to hormonal signals and thus could be viewed as consequences or symptoms of aging.
2. Effects of altered neuroendocrine control on body composition and functions. These effects apparently contribute to the age-related decline in physical, mental, and reproductive fitness and thus could be viewed as mechanisms of aging.
3. Role of hormones as mediators or effectors of the genetic program that influences the rate of aging and the life span. There is growing evidence that genetically determined differences in the release and/or action of hormones during development and adult life correlate with aging and longevity.

Growth hormone is importantly involved in each of the interactions listed above. Thus, GH release and the function of the "somatotropic axis" are suppressed during aging and reduced GH levels contribute to structural and functional alterations that accompany aging, while naturally occurring or experimentally-induced changes in GH release or action can have a major impact on the life span and apparently also on the rate of aging. Below, we will summarize the evidence for these generalizations and identify some findings that fail to support them. Thus, we hope to provide a balanced view of this topic which is of intense biological interest and considerable clinical significance.

Growth hormone release and signaling during aging.

In the human, peripheral GH levels are maximal during the peripubertal period of accelerated growth and begin

to decline shortly thereafter. This decline continues throughout life and plasma GH levels in elderly individuals are much lower than in young adults (3, 4, 6). The decline in GH levels with aging is not unique to the human and is well documented to occur in other species, including dogs, rats, and mice (1, 2, 8, 9). The age-related decrease in plasma GH levels is believed to reflect reduced GH release from the pituitary, most likely as a consequence of declining stimulatory and increasing inhibitory inputs from the hypothalamus (6). The consequences of the age-related reduction in GH levels may be augmented by reduced responsiveness of target organs to GH. Reduced GH signaling leads to decline of peripheral levels of insulin-like growth factor-I (IGF-I), the main mediator of GH action (2, 10). These changes have been referred to as "somatopause" to emphasize parallelism to the age-related decline in gonadal function (menopause and andropause).

In the context of the possible cause:effect relationship between the decline in GH levels and aging, the effects of caloric restriction (CR) on GH release are of particular interest. It is well documented that in laboratory strains of rats and mice, CR delays aging and significantly prolongs both the average and the maximal life span in comparison to ad libitium fed (AL) controls. There is also evidence that CR can delay aging in other species, apparently including also non-human primates (G. Roth & M. Lane, personal comm.). Similarly to the well documented suppressive effects of starvation on GH release (11), reducing caloric intake by 30-40% in CR studies leads to reduction of plasma GH and IGF-I levels (12). However, Sonntag and his colleagues (13) made an intriguing and potentially important observation that in old CR rats, pulsatile GH release is preserved and thus GH levels are higher than in AL controls at the same age. These observations could be interpreted as evidence that (i) the delay in aging induced by chronic CR postpones or prevents age-related suppression of pulsatile GH-release or (ii) that enhanced GH secretion may mediate the beneficial effects of CR on aging. Thus, pulsatile GH release in old CR animals can be viewed as either a marker or one of the causes of delayed aging. These seemingly opposite interpretations are not mutually exclusive. However, IGF-I levels in animals subjected to long term CR are suppressed in spite of the preservation of GH release (13). Further studies will be necessary to explain divergent effects of long term CR on GH and IGF-I levels. This issue is further complicated by the possibility of differences in the effects of aging on systemic as compared to local (tissue) IGF-I levels.

Role of reduced GH release in aging; GH as an anti-aging agent.

Multiple actions of GH include anabolic actions in muscle and other tissues, involvement in maintenance of bone mineral density, and mobilization of fat from the adipocytes. Therefore, it is reasonable to suspect that age-related declines in lean body mass (primarily muscle mass) and bone mineral density, as well as the increase in adiposity can be causally related to reduced GH signaling. In support of this conclusion, the effects of adult GH deficiency on body composition resemble many of the symptoms of aging and can be effectively treated by GH replacement (14, 15).

In 1990, Rudman and his colleagues (16) reported that treatment of elderly men with GH reduced adiposity and increased muscle mass and bone mineral density. In spite of limitations imposed by the design of this study and by the relatively small number of subjects involved, these findings are important and widely quoted. They suggest that treatment with GH or GH-releasing agents may reduce, prevent, or reverse various symptoms of aging in endocrinologically normal (normal for age) individuals. Moreover, data obtained in GH-deficient adults suggest that GH therapy can improve various subjective and objective measures of psychological well-being and "quality of life" (14, 15). The apparent potential of GH as an anti-aging therapy generated understandably intense interest of the public as well as producers of GH and GH-related products. While studies of the risks and benefits of long term GH treatment in the elderly are ongoing, nationally advertised GH-related and GH-releasing products promise the consumer will "look and feel 10 years younger," and describe the effects of these products as "taking the ride of your life."

Results available to date and extrapolation from the results of androgen replacement in elderly men suggest that the benefits of GH therapy are likely to be negatively correlated to pre-treatment GH levels. In other words, individuals with GH levels lower than average for their age group will be far more likely to benefit from GH administration.

Side effects of GH therapy can be serious and include swelling, joint pain, carpal tunnel syndrome, gynecomastia, and reduced responsiveness to insulin (17). The effects of GH on insulin action are of particular concern because insulin resistance normally increases with aging, is considered to be an important risk factor for life-threatening cardiovascular disease and may also accelerate aging by promoting non-enzymatic glycation of proteins. There is also evidence that peripheral IGF-I levels are positively correlated with breast and prostate cancer (6) and, therefore, increasing IGF-I levels by treatment with GH may not be desirable.

While the benefits of GH replacement in GH deficient individuals are well documented, increasing GH levels above the physiological limit is likely to involve major risks. Pathological elevation of GH levels in patients with acromegaly is associated with reduced life expectancy (18) and overexpression of GH in transgenic animals reduces average and maximal life span by as much as 50% (19, 20). In interpreting these findings, it is important to point out that reduced life expectancy of acromegalic patients and GH transgenic mice may be due to pathological changes induced by abnormally elevated levels of GH rather than to accelerated aging. Acromegalics have increased incidence of cardiovascular disease, diabetes, and tumors (18, 21) and transgenic

mice overexpressing GH very often die from renal failure (14), which can be related to GH excess (22). However, several laboratories reported evidence of accelerated aging in GH transgenic mice (23, 24, 25). Moreover, aging is often characterized as enhanced susceptibility to diseases and stress and, therefore, the division between pathology and "normal aging" may be blurred. Treatment of F344 rats with low doses of GH starting at 18 months of age had no effect on their longevity or pathology (26). However, administration of large doses of GH to rats was reported to produce toxic effects (27). In a recent study of severely ill patients in intensive care units, GH therapy significantly increased mortality (28). The issue of avoiding supraphysiological GH levels during treatment of the elderly with GH is not trivial, because GH levels normally decline with age. Thus, it may be difficult to decide what amount of GH may represent "physiological" replacement as opposed to pathological excess.

Growth hormone as a putative mediator of the effects of genes on aging.

Although genetic control of aging in invertebrate animals (29, 30) and in primitive organisms (31) has been convincingly established, the amount of information on the effects of genes on aging in mammals is very limited. Several years ago, we reported that a mutation at the Prop1 locus on chromosome 11 in the mouse greatly prolongs life span (32). Animals homozygous for this mutation, the Ames dwarf mice, lack several cell types in their anterior pituitaries and are deficient in GH, prolactin (PRL), and thyroid-stimulating hormone (TSH) (33). These animals are very small, approximately 1/3 of normal body size, and hypothyroid. Females and most of the males are infertile. Ames dwarfs thrive under standard laboratory conditions, remain in excellent general health into very advanced age, and outlive their normal siblings by a remarkable 49% and 64% in males and females, respectively (32).

Importantly, the association of combined GH, PRL, and TSH deficiency with prolonged survival is not limited to the Ames dwarf mutation, to the genetic background of these animals, or to conditions in our animal colony. Similar observations were made in two different laboratories in several lines of Snell dwarf mice which have identical endocrine abnormalities due to mutation on a different chromosome and are maintained on different genetic background (34; K. Flurkey & D. Harrison, personal comm.). Survival plots of Ames and Snell dwarf mice are parallel to those of the corresponding normal controls (32, 34), suggesting that prolonged life span of dwarf mice is due to delay of aging rather than prolonged senescence or preventing early deaths.

Most intriguing is the recent report that humans with multiple pituitary hormone deficiencies due to a mutation at the same locus as Ames dwarf mice (Prop1) who were not given hormonal replacement therapy can survive to a very old age, apparently longer than normal individuals in the same population (35). We are not trying to suggest that hypopituitary children should not be treated with GH and/or thyroxine in the interest of improving their growth, development and quality of life, but want to emphasize that data concerning longevity of hereditary dwarf mice may be directly applicable to the human.

The suspected causal link between GH deficiency and aging cannot be convincingly demonstrated in Ames or Snell dwarf mice because these animals also have primary deficiency of PRL and TSH. To address this issue, we are studying aging in animals with a specific, isolated defect in GH signaling induced by targeted disruption of the GH receptor/GH binding protein gene (36). The GH receptor knock-out (GH-R-KO) "Laron dwarf mice" are GH resistant, diminutive in size, and live much longer than their normal (+/+ or +/-) siblings (37; Table 2). In GH-R-KO similarly to dwarf mice, prolonged longevity apparently represents a true delay of aging because both average and maximal life span are significantly increased. Moreover, the age-related decline in learning and memory as well as the onset of histopathological changes normally associated with aging appear to be delayed (B. Kinney, J. Mattison, & A. Bartke, unpublished observations). Thus, it can be concluded that genetic defects in GH biosynthesis or GH signaling significantly delay aging in the mouse and thus the genes involved (Prop1, Pit1, and GHR/GHBP) can be considered as "longevity genes" in mammals. However, it should be pointed out that results inconsistent with the proposed impact of reduced GH signaling on aging have also been obtained. Little (lit/lit) mice with isolated GH deficiency live longer than normal animals if they are fed a low fat diet but not when they consume "standard" (i.e. containing approx. 7% fat) laboratory chow (K. Flurkey & D. Harrison, personal comm). Growth hormone resistant transgenic mice expressing an antagonistic bGH analog do not live longer than normal animals from the same line (A. Bartke & J. Kopchick, unpublished data; Table 3) and the life span of "mini-rats" with selective GH deficiency due to expression of antisense GH-RNA is reduced rather than prolonged (38). We have no explanation for these findings but lit/lit and MT-bGH-Ant transgenic mice differ from dwarfs and GH-R-KO animals in that they do not remain small throughout their life span but progressively gain weight and often become strikingly obese (39; A. Bartke & J. Kopchick, unpublished observations).

Identifying the mechanisms that link GH deficiency and GH resistance to delayed aging is of obvious interest. The suspected mechanisms of delayed aging in Ames and Snell dwarf mice are listed in Table 1. It is most intriguing that the action of Prop1 and Pit1s mutations on aging in mice may be related to the action of longevity extending genes in the worm, *Caenorhabditis elegans* by involving the insulin signaling pathway (46).

It is of interest to point out that in spite of various similarities to calorically restricted mice and rats, delayed aging of Ames dwarf mice is apparently not due to self-imposed ("voluntary") caloric restriction. Our ongoing studies indicate that the ad libitium fed dwarfs

TABLE 1. Characteristics of dwarf mice which may be related to their prolonged survival.

Phenotypic characteristic	Mutation	Reference
improved antioxidant defenses	Ames	Brown-Borg et al. (38); Hauck et al. (40)
reduced body temperature	Ames	Hunter et al. (41)
reduced metabolic rate	Snell	Boettiger (42)
increased insulin sensitivity	Ames	Borg et al. (43); D. Pazo & A. Bartke (unpublished)
reduced number of cell divisions	Snell	Winick & Grant (44)
delayed puberty and hypogonadism	Snell & Ames	Bartke (45)
concomitant prolactin deficiency	Ames	A. Bartke, unpublished observations
differential expression of multiple genes in the liver	Ames	I. Dozmorov, A. Bartke and R. Miller, unpublished observations

TABLE 2. Life span of growth hormone receptor knock-out (-/-), heterozygous (+/-) and normal (+/+) mice (37).

Gender	Genotype	N	Lifespan (days)*
Males	+/+	7	629 ± 72
	+/-	8	668 ± 51
	-/-	7	975 ± 106[a]
Females	+/+	13	749 ± 41
	+/-	19	701 ± 36
	-/-	11	1031 ± 41[b]

The animals were group housed, not used for breeding, and maintained in a specific pathogen free environment.

* Mean ± S.E.

[a] $P < 0.01$ compared to +/+

[b] $P < 0.0002$ compared to +/+

outlive normal animals from the same line subjected to 30% caloric restriction starting at 2 months of age. Dwarf mice consume more food per gram body weight than is consumed by their normal siblings. Moreover, dwarf mice, unlike the CR animals, often become obese.

In addition to the studies summarized above, there is considerable indirect evidence that some of the actions of GH may accelerate aging. Growth hormone and GH-dependent IGF-I secretion are major determinants of postnatal growth and adult body size and there is considerable evidence that, within the species, size is negatively related to life span. Large breeds of dogs have higher IGF-I levels than small breeds (47) and are short lived (48), mice selected for small body size live longer than mice selected for large body size (49, 50), and there is recent evidence that short stature is associated with longer life span in the human (51). The mechanisms linking small body size to delayed aging (within a species) remain elusive, but several possibilities have been suggested. Thus, within the genetically determined species-specific body plan, the work load on the cardiovascular system is reduced in smaller individuals. Moreover, reduced number of cell divisions and reduced total amount of food that is consumed and processed by small individuals may produce fewer opportunities for oxidative damage, non-enzymatic glycation, somatic mutations, and cancer (51). Further research will be necessary to determine whether small body size offers protection from those lesions that typically cause death in a given species. It should also be mentioned that recently reported results of a prospective study in 864 policemen in Paris identified high normal GH levels as a risk factor for premature mortality (52).

TABLE 3. Life span of MT-bGH-Ant transgenic mice expressing antagonistic analog of bovine growth hormone (A. Bartke and J. J. Kopchick, unpublished observations)

Sex	Genotype	n	Life span (days)*
female	normal	19	744 ± 22
female	transgenic	19	802 ± 45
male	normal	21	743 ± 37
male	transgenic	33	695 ± 30

The animals were group housed, not used for breeding, and maintained in specific pathogen free environment.

* Mean ± SE

DISCUSSION AND CONCLUSIONS.

Results described earlier in this article could be summarized by stating that GH was reported to both promote and prevent aging. How can these contradictory conclusions be reconciled? There is evidence that the dose-response relationships for many GH actions may be biphasic (inverted "U"-shaped) (53), and thus, effects of GH excess may not be representative of its physiological actions. In support of this reasoning, cardiovascular function is adversely affected by both GH deficiency and GH excess and the affected patients benefit from normalization of GH levels, i.e. GH replacement and suppression of GH release, respectively (54). These peculiar dose response characteristics of GH action could explain how GH therapy in relatively GH deficient elderly patients may be beneficial while GH excess in acromegaly is detrimental, but provide no clue as to the possible reasons for prolonged survival of GH deficient individuals.

We would like to suggest that the actions of GH on growth and development have important implications for determining the rate of aging and the life span. Thus, the normal and otherwise highly desirable stimulatory effects of GH on growth, metabolism, thermogenesis, sexual maturation, and reproductive fitness may incur certain "costs" in terms of longevity. This concept is consistent with the evolution of reproductive strategies, i.e. early maturation and intensive reproductive effort in many short-living species, and slow development, late maturation, and low rate of reproduction in those species that are long living. We believe that somatotropic axis (GH and IGF-I) affects aging by multiple mechanisms which reflect altered pattern of gene expression at different stages of the life span. We are hoping to identify these alterations using DNA microrarray technology (Dozmorov, Miller & Bartke, unpublished observations).

The consequences of the relative GH and IGF-I deficiency in old age and the rationale for GH replacement in elderly humans may represent a different biological

issue. Thus, there is considerable evidence that some of the changes in physical appearance and body composition, as well as development of various deficits in physical and cognitive function that normally accompany aging can be traced to age-related changes in endocrine function. A decline in GH release and signaling, sometimes referred to as "somatopause" is among these changes and thus GH replacement or supplementation emerge as potential preventive means or therapeutic interventions in the aging process. What is currently known about the benefits of GH administration to the elderly and the side effects of such treatment provides strong rationale for extensive multi-center long-term studies of the risks and benefits of GH therapy in endocrinologically normal middle aged and elderly subjects. Similar studies are needed to evaluate the potential utility of natural and synthetic GH-releasing compounds for stimulating the endogenous GH release. Some of these compounds offer hope for mimicking the normal pulsatile, diurnal, and sleep-related pattern of GH release, and also for reducing the cost of therapy.[2] As a result of these studies, GH or GH-releasing compounds may well find a place in the armamentarium of the emerging field of anti-aging medicine.

However, it is important to realize that supraphysiological levels of GH and, consequently, IGF-I can exert a variety of untoward effects and the normal physiological role of this hormone in the determination of life span may be to limit rather than to prolong survival. The latter point is rather dramatically illustrated by the findings in mice with mutations at the Prop1 or the Pit1 locus which are dwarfed, seemingly frail and somewhat infantile, but live much longer than their normal siblings. Intriguingly, undersized, hypothyroid, and sexually infantile humans with mutations at the same locus also appear to have increased life expectancy. Recent findings of prolonged life span in GH-R-KO mice with an isolated, well defined defect in GH signaling, further focus attention on the role of GH in aging. Finally, it should be pointed out that currently available data do not allow any predictions as to the possible relationship of the changes in body composition induced by GH treatment in elderly individuals to life expectancy.

On the basis of information reviewed in this article, we would like to venture a prediction that future research will provide conclusive evidence for negative correlation of activity of the somatotropic axis and longevity within a species. We will further predict that GH signaling early in life, before attainment of the final (adult) body size, will prove to be particularly important in this regard.

[2] Cost of the usual doses of recombinant GH is currently a rather staggering $10,000-$15,000 per year.

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