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GH and ageing: pitfalls and new insights

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Abstract

Interrelationships of growth hormone (GH) actions and aging are complex and incompletely understood. The very pronounced age-related decline in GH secretion together with benefits of GH therapy in individuals with congenital or adult GH deficiency (GHD) prompted interest in GH as an anti-aging agent. However, the benefits of treatment of normal elderly subjects with GH appear to be marginal and counterbalanced by worrisome side effects.

In laboratory mice, genetic GH deficiency or resistance leads to a remarkable extension of longevity accompanied by signs of delayed and/or slower aging. Mechanisms believed to contribute to extended longevity of GH-related mutants include improved anti-oxidant defenses, enhanced insulin sensitivity and reduced insulin levels, reduced inflammation and cell senescence, major shifts in mitochondrial function and energy metabolism and greater stress resistance. Negative association of the somatotrophic signaling and GH/insulin-like growth factor 1 (IGF-1)-dependent traits with longevity was also shown in other mammalian species. In humans, syndromes of GH resistance or deficiency have no consistent effect on longevity, but can provide striking protection from cancer, diabetes and atherosclerosis. More subtle variations in various steps of GH and IGF-1 signaling are associated with reduced old-age mortality, particularly in women and with improved chances of attaining extremes of lifespan. Epidemiological studies raise a possibility that the relationship of IGF-1 and perhaps also GH levels with human healthy aging and longevity may be biphasic. However, the impact of somatotrophic signaling on neoplastic disease is difficult to separate from its impact on aging and IGF-1 levels exhibit opposite associations with different chronic, age-related diseases.

Keywords

growth hormone; aging; dwarfism; insulin; longevity; IGF-1

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Introduction: A brief history of interest in growth hormone in the context of aging

Interest in the effects of aging on the endocrine system and in the rejuvenating potential of hormones dates back to the nineteenth century and predates the emergence of endocrinology as a medical discipline. The interest in growth hormone (GH) as a marker and a regulator of the aging process, and as a potential anti-aging agent is much more recent. In the early 1980s [1], employing the then new techniques of radioimmunoassays, different investigators described a progressive and often very pronounced decline in the circulating levels of GH starting in early adulthood and continuing during aging [2, 3]. This included pioneering studies of the neuroendocrinology of aging in the laboratory of Joseph Meites at Michigan State University [4]. This work clearly established age-related decline in plasma GH levels in laboratory rats [5, 6] and was followed by the elucidation of the role of declining GH releasing hormone (GHRH) stimulatory input in this process by the Sonntag group [7]. Other investigators reported age-related decline in GH levels in other species, including humans [2, 3, 8, 9]. More recently, a series of elegant studies by J. Veldhuis and his colleagues elucidated the impact of human aging on the pulsatile pattern of GH release including estimation of the mass of GH secreted [10, 11]. These findings stimulated interest in the functional implications of the age-related decline in GH secretion and led to the emergence of the term “somatopause” to describe the period of relative GH deficiency in the elderly. The normal functions of GH during adult life and the impact of progressive reduction in GH levels will be addressed later in this article.

Results of a groundbreaking study of the effects of GH administration in elderly men reported by D. Rudman and his colleagues in 1990 [12] included demonstration that GH can increase muscle mass, reduce adiposity and improve bone mineral density as well as a general sense of well-being. These findings attracted enormous clinical and media attention by suggesting that recombinant human GH (rhGH) is an effective anti-aging agent. Subsequent work raised a number of significant issues about the safety and efficacy of chronic GH treatment in the healthy (endocrinologically normal) elderly [13–15], but GH and a host of “GH-related products” continue to be aggressively advertised as anti-aging agents, and the role of GH treatment in geriatric medicine continues to be hotly debated 25 years after publication of the Rudman et al. paper [16, 17].

To add to this controversy, results obtained in transgenic mice suggested that massive, chronic elevation of GH levels accelerates rather than prevents aging [18, 19]. More importantly, H. Brown-Borg et al. reported in 1996 that hypopituitary mice that lack GH are exceptionally long-lived [20] and extension of both lifespan and healthspan in mice with GH deficiency or GH resistance has been firmly established by work conducted in several laboratories during the past 20 years [21–23]. In this article, we will discuss the functional implications of age-related decline in GH secretion and the evidence for both “anti-aging” and “pro-aging” actions of GH. We will also discuss the mechanisms believed to link suppression of GH signaling with extended longevity and the applicability of results obtained in laboratory rodents to the role of somatotrophic (GH/IGF-1) signaling in the

control of aging in other species, including humans and animals living in the natural conditions.

Evidence that GH can accelerate aging

Much new information about the effects of GH was obtained from studies of GH-transgenic giant mice which were produced in several laboratories using the then new procedure of injecting gene constructs into the pronuclei of recently fertilized eggs [24–26]. Incorporation of the various numbers of copies of the injected artificial genes produced animals with very high circulating levels of human, bovine, ovine or rat GH. Because GH expression was driven by the fairly ubiquitous Metallothionein I promoter, or the gluconeogenesis-related phosphoenolpyruvate carboxykinase promoter (PEPCK), transgene-derived GH in these mice was produced throughout postnatal life in multiple tissues, primarily liver, kidneys and intestines. Moreover, the circulating levels of GH were influenced by the intake of heavy metals and by the macronutrient composition of the diet [25, 26]. Further, the rate of GH secretion was not subject to the normal IGF-1 mediated negative feedback control. The striking giant phenotype of the various GH transgenic mice attracted considerable scientific and media attention, and these curious animals have been, and continue to be, used in countless studies of GH action [reviewed in 27, 28–30]. In the course of these studies it was noticed that GH transgenic mice have reduced longevity [31–33], and we and others have reported that many physiological characteristics of these animals strikingly resemble symptoms of aging in genetically normal mice [18, 32–34]. This included kyphosis, early decline of cognitive function, turnover of hypothalamic neurotransmitters and body weight, graying of the hair and increased incidence of cancer [33–35].

It is interesting that the human syndrome of acromegaly developing as a result of excessive production of GH by anterior pituitary tumors is associated with an increased risk of hypertension, diabetes and cancer, and with reduced life expectancy [36, 37] which could collectively be viewed as signs of accelerated aging. However, it should be pointed out that acceleration of normal aging is very difficult to distinguish from various pathological processes and, thus, results obtained in transgenic animals expressing abnormally high levels of GH, and in patients with acromegaly or gigantism, are not generally accepted as evidence that GH promotes aging. However, regardless of the differences in opinions concerning the interpretation of these findings, they certainly raise a question whether action of the amounts of GH produced in the healthy normal (i.e. not genetically manipulated) individual can have any role in the control of aging and longevity. This question has been conclusively answered by the demonstration that mice lacking GH, or GH receptors, have a remarkable extension of longevity and multiple symptoms of delayed and/or slower aging (details and references later in this article).

Several mutations discovered in laboratory mice as early as 1929 [38] affect the function of the somatotrophic axis and produce hereditary dwarfism. First reports of data concerning aging and longevity of hypopituitary dwarf mice lacking somatotrophs appeared in the 1970s, but the findings were contradictory with the observed lifespans being drastically reduced [39], not reduced [40] or impressively extended [41, 42]. Subsequent studies in a different mutant with the same endocrine phenotype [20] and reexamination of the longevity

of mutants that had been studied in the 1970s [21], demonstrated that combined deficiency of GH, thyrotropin and prolactin in both Ames dwarf (Prop1^{df}) and Snell dwarf (Pit1^{dw}) mice is associated with significant, very pronounced (approximately 30 – 70%, depending on sex and diet) extension of longevity [20, reviewed in 43, 44]. Our hypothesis that the extension of longevity in these mutants is due to the absence of GH signals [20] was subsequently supported by the demonstration that mice with GH-resistance due to targeted deletion of GH receptor (GHR) and mice with isolated GH deficiency are also long-lived [21–23].

Importantly, extension of lifespan in the various GH-related mouse mutants applies to both females and males and involves not only median and average longevity, but also maximal longevity. Maximal longevity is believed to provide a better measure of aging, as opposed to premature deaths from different diseases. The conclusion that the biological process of aging is indeed slower in the absence of GH signals is supported by the evidence that the age-related changes in cognitive and musculoskeletal function, glucose homeostasis and risk of cancer are delayed and/or diminished in GH-related mutants compared to normal animals from the same strain [reviewed in 43, 44–49]. Recent analysis of survival curves of GHR^{−/−} and GHRH^{−/−} mice revealed that their mortality rate (arguably the most meaningful measure of aging) is lower in these mutants than in the normal mice, and that its age-related acceleration is correspondingly delayed [50].

What mechanisms link reduced somatotrophic signaling with slower aging?

Following the report of extended longevity in Ames dwarf mice [20], several laboratories directed their efforts at identifying the mechanisms responsible for slow aging of these and other GH-related mutants. Since mitochondrial generation of reactive oxygen species (ROS), and ROS-related oxidative damage to various cell components, were already well-established as important and possibly the key mechanism of aging, much work was directed at characterizing this system in Ames dwarf mice and other long-lived mutant mice. Work in the Brown-Borg laboratory provided evidence that Ames dwarf mice produce less ROS, have higher activity of antioxidant enzymes (catalase, copper-zinc and manganese superoxide dismutases) in the liver kidney, heart and hypothalamus, and incur less oxidative damage to proteins, lipids and, importantly, to nuclear and mitochondrial DNA [43, 51–54]. The biological significance of improved anti-oxidant defenses in these animals was implied by the subsequent studies of other groups showing that Ames dwarf mice have greater resistance to Paraquat, a toxic compound producing massive oxidative stress in the lungs and in other organs [55, 56]. Reduced ROS production can be viewed as evidence for improved efficiency of mitochondrial function. More recent studies described organ-specific differences between Ames dwarf and normal mice in the expression and activity of various components of the mitochondrial electron transport chain [57, 58] and in the expression and activation of PGC1 α , a key regulator of mitochondrial biogenesis [58]. The alterations in mitochondrial function in GH-related mutants provide a likely explanation of differences in whole-animal energy metabolism uncovered by indirect calorimetry [59], and may be related to the enhanced thermogenesis in these animals maintained at the “standard” animal room ambient temperature. (Later in this section, we will return to alterations in energy metabolism as another potential mechanism of extended longevity).

Association of longevity with stress resistance was firmly established in invertebrates, [60] and improved ability to withstand various environmental insults is associated with slower or delayed aging in mammals as well [56, 61, 62]. The evidence for enhanced stress resistance of long-lived dwarf mice is not limited to extended survival after receiving a sub-lethal or lethal dose of Paraquat [55, 56]. Dermal fibroblasts isolated from Ames dwarfs and other long-lived GH-related mutants, are more resistant to a variety of cytotoxic agents, glucose deprivation and inducers of oxidative damage in culture in comparison to fibroblasts obtained from genetically normal controls [61].

Growth hormone-deficient and GH-resistant mice are hypoinsulinemic with reduced or “low-normal” glucose levels and greatly improved insulin sensitivity [22, reviewed in 44, 63, 64]. Studies of the interactive effects of these “longevity genes” and calorie restriction revealed close correspondence between insulin sensitivity and longevity [65]. In GHR^{-/-} mice, alterations in the expression of genes related to transmission of insulin signals and in the activation of the insulin receptor and its downstream kinases are organ-specific [65]. Although insulin sensitivity is not uniformly associated with longevity across various mutant and transgenic mice [66–69], we believe that in the GH-related mutants it represents a consistent marker of aging and almost certainly is an important mechanism of slower and healthier aging. It is important to emphasize that improved insulin sensitivity has also been associated with human longevity, with studies of individuals from long-lived families providing a particularly clear example [70]. Moreover, modest reduction in insulin levels and marked improvement in insulin sensitivity together with a reduction in systolic blood pressure [71] represent a physiological situation directly opposite to metabolic syndrome, a condition associated with increased risk of age-related chronic diseases and reduced life expectancy [72]. While both improved insulin sensitivity and reduced secretory capacity of pancreatic β -cells in hypopituitary dwarf and GHR^{-/-} mice can be traced directly to the absence of GH signals due to the documented effects of GH on insulin target tissues and on development of pancreatic islets [73], other mechanisms are also involved. Increased levels of adiponectin, reduced levels of pro-inflammatory cytokines and reduced mechanistic target of rapamycin (mTOR; particularly mTORC1) signaling represent important reasons for improved insulin signaling in GH-deficient and GH-resistant mice [reviewed in 44, 64]. Interestingly, each of these mechanism is involved in the control of healthy aging and longevity by mechanisms not directly related to insulin sensitivity. Adiponectin has anti-inflammatory and anti-atherogenic effects [74], and it is very well documented that chronic low-grade inflammation is a key mechanism of aging and a key risk factor for multiple age-related diseases. Target of rapamycin or homologous signaling is an important regulator of aging in organisms ranging from yeast and worms to insects and mammals [75]. Treatment with rapamycin suppresses mTOR activity and extends longevity in different species, including mice [76]. In mice, rapamycin apparently acts on longevity via multiple mechanisms, including reducing the risk of cancer [77]; however, insulin sensitivity is reduced rather than improved, at least initially [78, 79]. Some of the physiological characteristics of GHR^{-/-} and Ames dwarf mice which are believed to contribute to their healthy aging and extended longevity (increased adiponectin levels and insulin sensitivity, reduced IL-6 levels, mTOR signaling and hypothalamic inflammation) resemble the phenotypes associated with leanness, calorie restriction and weight loss. Surprisingly, in the

GH-related mutants, these characteristics coexist with increased adiposity [80, 81]. This paradox was addressed in studies involving surgical removal of intra-abdominal (visceral) fat depots [82, 83]. The results indicated that compared to normal animals, visceral adipose tissue of mutants produces less TNF α and IL-6 and more adiponectin and thus acts to promote insulin sensitivity rather than insulin resistance [82].

The impact of congenital, life-long deficiency of GH signals on inflammation and immune function deserves special emphasis. Although actions of GH are often described as anti-inflammatory [84], GH-deficient and GH-resistant mice are characterized by reduced expression of pro-inflammatory cytokines in the adipose tissue, in the hypothalamus and in other brain regions [82, 85–87], reduced NLRP3 inflammasome activation [88], reduced hypothalamic astrogliosis [86] and increased adiponectin levels [80, 89]. This shift from a pro- to an anti-inflammatory profile almost certainly contributes to healthy aging and the extended longevity of these mutants. The causative role of “inflammaging” in the control of disease risk and life expectancy is well-supported, and recent studies in the D. Cai laboratory provided strong evidence that hypothalamic inflammation promotes mouse aging [90, 91].

Various parameters of immune function are suppressed in Ames and Snell dwarf mice [39, 92, 93], thus resembling the situation of normal animals subjected to calorie restriction. This likely represents a shift in the distribution of food-derived energy toward other energetically costly processes and in particular, thermogenesis [94]. However, these animals exhibit normal antibody production in response to a strong challenge [95] and exhibit a delay in immunosenescence [21, 88].

Other mechanisms believed to link reduced GH signaling with slow aging include adjustments in energy metabolism to increase oxidation of fatty acids and mitochondrial efficiency [59, 94], increased levels of humanin, a mitochondrial product that regulates cellular stress responses [96], improved maintenance of stem cell populations [97], reduced mutation frequency implying improved genome maintenance [98] and major alterations in the profiles of gene expression [99–102] including expression of microRNAs [103, 104]. Please refer to Table 1 for a summary of mechanisms linking reduced somatotrophic signaling with slower aging.

What is the relevance of findings in mutant mice to our understanding of the control of aging in genetically normal animals and in other mammalian species?

Studies reviewed in the preceding section of this article provided clear evidence that in laboratory mice, elimination of GH or its receptors promotes stress resistance, healthy aging and a remarkable extension of longevity. Although well supported by independent studies, these findings are counterintuitive by implying that the normal actions of GH somehow promote age-related functional decline and greatly reduce life expectancy. The evidence that massive, clearly unphysiological increase in circulating GH levels in transgenic mice and in patients with GH-secreting tumors is associated with reduced longevity [18, 31–33, 36, 37] is of obvious interest in this context but does not resolve the conundrum of normal hormonal

signaling being apparently detrimental. Thus, extended longevity of GH-deficient and GH resistant mice leads to many questions:

- Are findings in these mutants relevant to the control of aging in genetically normal animals?
- Could reduced somatotrophic signaling offer any advantages to animals living under natural conditions?
- Can findings in laboratory mice be extrapolated to other species, including humans?

Available evidence suggests that the answer to the first of these questions is affirmative. Negative correlation of adult body size, a GH-dependent trait to longevity, has been demonstrated in numerous comparisons of normal mice from different strains [105, 106]. Importantly, this relationship was also shown in individual mice from a genetically heterogeneous population produced by crossing inbred animals [107]. Furthermore, in a study of multiple mouse strains, longevity was negatively related to circulating IGF-1 levels [108]. The same study provided evidence that female sexual maturation is occurring later in mice from longer living strains, thus resembling the findings in long-lived GH-related mutants [109, 110].

The second of the questions posed above is difficult to answer. There is very little information about aging “in the wild,” particularly for species which, like mice, are targets of numerous predators. It is also difficult to know how findings obtained in animals living in the protected, carefully controlled and clearly artificial environment of a modern laboratory animal facility can be related to animals exposed to pathogens, parasites, wide fluctuations in temperature and other environmental challenges of natural conditions. The contrast between the dependence on the foraging in a seasonally changing environment in nature and the constant availability of high-energy food in the laboratory is another important factor in such comparisons. In spite of these limitations, we hypothesize that a range of variation in the strength of the GH signals and the corresponding variation in various GH-dependent phenotypic traits may facilitate survival of rodent populations, and thus may have been preserved in the course of evolutionary adaptations to a somewhat unpredictable environment. Under this scenario, the individuals with a less active somatotrophic axis (i.e. lower levels of GH and IGF-1) would exhibit phenotypic characteristics resembling the GH-related mutants, but being less extreme. Thus they would grow more slowly, mature later and produce smaller litters during the reproductive season following their birth, but due to improved stress resistance [55, 56, 61] and a delay in reproductive aging [111–113], would be more likely to survive winter and reproduce during the next spring and summer. In this manner, the obvious reduction of their evolutionary fitness (i.e. probability of leaving offspring) during their first breeding season would be offset by slower aging. Presence of such slow aging individuals in the population would facilitate its long-term survival by adaptation to fluctuations in the environmental temperature and food availability from year to year. These speculations indirectly address yet another question arising from the surprising characteristics of GH-related mutants, namely why genes that accelerate the process of aging have not been eliminated from the population thousands of years ago? Presumably, evolutionary advantage of fast growth, large adult body size, early maturation

and high fecundity counterbalance the negative impact of the same genes and their products on long-term survival and the ability to maintain reproductive competence. Thus, under natural conditions, the population would benefit from the variation in growth, maturation and reproductive strategies among its members.

The third question posed earlier in this section concerns applicability of data concerning the role of GH in aging that have been derived from studies in mice to other species. There is very strong evidence that adult body size, a GH- and IGF-1-dependent trait, is negatively related to longevity in domestic dogs, a species in which selective breeding produced an astounding (greater than 100 fold) range of difference in body size [114, 115]. A similar relationship of body size and longevity was also reported in laboratory rats [33], domestic cats [116] and horses [117]. The relationship of body size to longevity in our own species is less obvious and often described as controversial. However, there are numerous examples of shorter people living longer than taller people from the same population or the same study cohort [118]. A recent report on longevity of American men of Japanese ancestry showed significantly greater longevity of shorter individuals [119]. Importantly, this was related to insulin levels, which have been previously related to familial longevity [70] and to heterogeneity of *FOXO3*, a gene with well-documented association with survival to extremely old age in different human populations [120, 121]. Moreover, extreme human survival was related to circulating IGF-1 levels [122] and to polymorphism in the gene coding for IGF-1 receptors [123].

Actions of GH are not limited to the regulation of growth and adult stature

As discussed in detail in other articles in this special issue of *Best Practice & Research Clinical Endocrinology & Metabolism*, mutations affecting development of the anterior pituitary, GH secretion or function of GHR can result in syndromes of hypopituitarism, isolated GHD or GH-resistance. Much of what we know about the physiological actions of GH has been learned from the study of individuals affected by these syndromes. This included realization that in addition to the expected major impact on linear growth and adult stature, congenital lack of GH-action leads to profound changes in body composition. Appreciation of the importance of GH in the regulation of body composition and adult physiology also emerged from the studies of experimental animals and individuals with adult GHD.

Adult GHD can have different etiologies, but most often develops as a result of anterior pituitary tumors and their treatment or traumatic brain injury (TBI). Numerous studies provided evidence that adult GHD is associated with increased adiposity, reduction of muscle mass and bone mineral density and reduced general well-being and quality of life as measured by the various questionnaires, number of doctor's visits and number of days missed at work [124], implying a causal relationship to reduced levels of GH in the circulation. On this basis, adult GHD is among the FDA approved conditions for rhGH therapy. Intriguingly, symptoms of adult GHD resemble changes in body composition, psychological well-being and sexual function that generally accompany aging. This resemblance together with the evidence that GH levels progressively decline during adult life led to interest in using GH to reduce or reverse the unwelcome effects of aging. As was

mentioned earlier, the 1990 paper by Rudman and his colleagues [12] provided widely quoted support for this concept. However, results of subsequent studies [13–15] led to significant concerns about side effects of GH therapy resulted in the general (although not universal) rejection of the idea that endocrinologically normal elderly individuals will benefit from treatment with exogenous GH [17]. We will return to this topic later in this article.

Insulin-like growth factor 1 (IGF-1) and aging

Many of the physiological actions of GH are mediated by IGF-1, which also plays a key role in the negative feedback control of GH expression. Circulating IGF-1 levels provide a very useful measure of GH secretion and activity. Not surprisingly, the age-related decline in GH secretion is associated with a general parallel (although less pronounced) reduction of plasma IGF-1 levels [125]. Evaluating the functional and pathological implications of the concomitant decrease in GH and IGF-1 levels is complicated by the fact that while some actions of GH are mediated by IGF-1, some are not. Moreover, effects of GH and IGF-1 on the same process, or target tissue, can be different and in some cases even opposite. For example, GH is lipolytic while IGF-1 is not, GH promotes insulin resistance while IGF-1 reduces it and mimics various insulin effects [reviewed in 44, 126].

Yet another complication in interpreting the effects of altered GH-action in terms of the resulting changes in IGF-1 levels stems from differences in the regulation of IGF-1 expression in various organs. While the expression of IGF-1 in the liver (the main source of circulating IGF-1) is clearly GH-dependent, IGF-1 expression in other tissues is not. In mice with deletion of GH receptors in all tissues, there is very little if any expression of IGF-1 in the liver, but in the kidney IGF-1 expression is only partially reduced, and in the heart and brain it is not affected [127]. As a result, in both GH-deficient and GH-resistant mutants, dramatic suppression of plasma IGF-1 levels co-exists with maintenance of normal or elevated expression of IGF-1 in different brain regions [128]. Analysis of local, tissue-specific IGF-1 expression and activity is important in deciphering the phenotypic consequences of altered GH signaling, including its effects on healthspan and lifespan. Studies in animals with deletion of pregnancy associated plasma A (PAPP-A), a protease that degrades IGF-1 binding proteins, provided important evidence for the role of local (tissue) availability of biologically active IGF-1 in the control of aging and longevity [129, 130].

Similarly to the age-related decline of GH, the decrease in IGF-1 levels is believed to cause or contribute to functional deficits that develop during aging. Research in experimental animals and in cell cultures provided very strong evidence for neuroprotective [131, 132] and cardioprotective [133] effects of IGF-1. Moreover, epidemiological studies indicate that while higher IGF-1 levels increase the risk of cancer development and progression, they reduce the risk of cognitive decline, dementia [134] and cardiovascular disease [135]. Recent studies provided new evidence for the role of IGF-1 in maintaining brain microcirculation during aging [136, 137].

However, work in this area is also not free of controversy. Results of tissue-specific deletion of IGF-1 receptors in the heart and in the central nervous system were reported to prevent, rather than accelerate, various age related changes [138–141]. Reducing the insulin/IGF-1 signaling (IIS) or homologous signaling pathways delays aging and extends longevity in organisms ranging from yeast to mice [142, 143] likely via suppressing mTOR activity and reducing the inhibitory cytoplasmic sequestration of the FOXO family transcription factors [121]. Evidence for the existence of a “biphasic” relationship between the levels of IGF-1 and longevity [144] is likely to prove important for reconciling some of the seemingly conflicting findings in this area.

Emerging conclusions: how can the seemingly contradictory findings be reconciled?

Understanding the role of the somatotrophic (GH/IGF-1) signaling in the control of mammalian aging is far from complete; interpretation of many research findings is controversial, and clinical practice guidelines concerning GH-treatment of elderly subjects are not universally accepted. This is in spite of the fact that the bulk of information gathered from studies in various animal species (including humans) is in general agreement. To reiterate some of the key findings discussed earlier in this article:

- In laboratory mice, GH-deficiency or resistance is associated with extension of healthspan, delayed onset and reduced incidence of age-related disease and a remarkable extension of longevity [20, 21, 43, 44];
- In humans, the same endocrine syndromes are associated with protection from some of the age-related diseases [44, 145], and from insulin resistance [146];
- In endocrinologically normal humans, genetic polymorphisms in genes related to the somatotrophic axis and its downstream target FOXO3, and variation in the level of IGF-1 are associated with differences in the “risk” of achieving exceptional longevity [119, 121–123];
- Adult body size, a GH/IGF-1 dependent trait, is associated with extended longevity in laboratory rodents (including both normal and genetically altered animals) [44, 105–108], in various domestic animals (carnivores and ungulates) [114–117], and also, albeit less consistently, in the human [118, 119].

It should not be particularly surprising that quantitative (if not qualitative) differences should exist between regulation of any age-related characteristics in a short-lived species such as a mouse and long-lived species such as a human, particularly when the impact of hundreds of generations of domestication and selection of the laboratory mice in a carefully controlled and completely artificial conditions is also considered. Indeed, we believe that it is the convergence of many findings in mice and men that is striking and deserving of emphasis. However, the contrast between the markedly extended longevity of GH-related dwarf mouse mutants and the unaltered [147], or reduced [148] longevity of humans with various hereditary dwarfing syndromes remains to be explained.

Future studies will likely determine whether mild or transient reduction of the somatotrophic axis activity by nutritional or pharmacological means could have beneficial effects on human longevity and risk of age-related disease. Considering the multiplicity of the physiological functions of GH and IGF-1, it is also likely that selective manipulation of only a few (or perhaps a single) of the targets of the somatotrophic axis may be more desirable than reducing GH secretion or signaling. Ongoing and future clinical studies will undoubtedly determine whether treatment with GH can help individuals affected by sarcopenia or other aspects of frailty and what criteria may allow identifying candidates for such treatment.

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Practice points

- There is a clear age-related decline in both growth hormone (GH) and IGF-1, sometimes referred to as somatopause.
- Somatopause, and benefits of GH treatment in adult GH deficiency, led to GH and GH-related products being marketed as “anti-aging.”
- While GH is marketed as “anti-aging,” the general consensus among biogerontologists is that GH accelerates aging.
- While many studies involving GH and aging are in laboratory animals, there is evidence that altered GH, IGF-1 and insulin signaling affect human longevity.

Research agenda

- Elucidating if alterations in somatotrophic signaling only during early, middle or late life affect longevity.
- Elucidating what interventions to lower somatotropic signaling may be beneficial in humans.
- Examining the trade-offs of decreased somatotropic signaling in people (e.g. shorter stature vs extended longevity).

Table 1**Proposed Mechanisms of Extended Longevity in GH Deficient and Resistant Mice**

<u>Insulin and Glucose Homeostasis</u>	
Hypoinsulinemia and mild hypoglycemia (22, 48, 63, 64)	
Increased insulin sensitivity (48, 65, 70)	
Decreased pancreatic β cell secretory function (73)	
<u>Stress Resistance and Oxidative Damage</u>	
Increased antioxidant enzyme activity; decreased ROS production (51 – 54)	
Decreased oxidative damage to macromolecules (47)	
Resistance to cytotoxic, metabolic and oxidative stressors (55, 56, 61, 62)	
Increased levels of humanin (96)	
<u>Energy Metabolism</u>	
Improved mitochondrial function (57, 58)	
Increased fatty acid oxidation, food consumption and oxygen consumption (59, 94)	
Lower core body temperature; alterations in thermogenesis (94)	
Shift in energy expenditure from growth to repair (39, 92, 93)	
<u>Inflammation, Immune Function and Cancer Risk Factors</u>	
Shift from pro-inflammatory (TNF- α , IL-6) to anti-inflammatory (adiponectin) cytokines (80, 82, 83, 89)	
Decreased chronic, low-grade inflammation (86)	
Delayed immunosenescence (21, 88)	
Decreased NLRP3 inflammasome activation (88)	
Decreased circulating IGF-1 and mTOR signaling (specifically mTORC1 and S6K) (35, 44, 47 – 49)	
<u>Other</u>	
Maintenance of protective, local IGF-1 levels (specifically heart and brain) (127, 128)	
Improved genome maintenance (98)	
Altered expression of numerous genes and miRNA (99 – 104)	
Increased number of stem cells (97)	