HHS Public Access

Author manuscript

Growth Horm IGF Res. Author manuscript; available in PMC 2017 April 01.

Published in final edited form as:

Growth Horm IGF Res. 2016 April ; 27: 41–45. doi:10.1016/j.ghir.2016.02.002.

The Somatotropic Axis and Aging: Benefits of Endocrine Defects

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Abstract

Reduced somatotropic [growth hormone (GH) and insulin-like growth factor-1 (IGF-1)] action has been associated with delayed and slower aging, reduced risk of frailty, reduced age-related disease and functional decline, and with remarkably extended longevity. Recent studies have added to the evidence that these relationships discovered in laboratory populations of mice apply to other mammalian species. However, the relationship of the somatotropic signaling to human aging is less striking, complex and controversial. In mice, targeted deletion of GH receptors (GHR) in the liver, muscle or adipose tissue affected multiple metabolic parameters but failed to reproduce the effects of global GHR deletion on longevity. Continued search for mechanisms of extended longevity in animals with GH deficiency or resistance focused attention on different pathways of mechanistic target of rapamycin (mTOR), energy metabolism, regulation of local IGF-1 levels and resistance to high-fat diet (HFD).

Keywords

growth hormone; growth hormone receptors; longevity; IGF-1; liver; muscle; adipose tissue

INTRODUCTION

Research findings reported during the last 20 years have provided numerous examples of remarkably extended longevity in mice with hereditary defects in somatotropic (GH/IGF-1) action [1–3]. Importantly, in both GH-resistant (GHRKO) and GH-deficient [hypopituitary Ames dwarf ($Prop1^{df}$) and Snell dwarf ($Pit1^{dw}$)] mice, extension of average, median and maximal longevity is associated with improved maintenance of physical and cognitive function, resistance to oxidative stress, as well as reduced incidence and/or delayed onset of neoplasms and other age-related pathologies [4–6]. Trade-offs include major decreases in

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growth rate and adult body size, delayed maturation and reduced fertility [4, 6, 5, 7] which appears to be partially offset by a delay in reproductive aging [8, 9].

Studies of the relationships among longevity, adult body size, alterations in bone characteristics and polymorphism of genes involved in GH and IGF-1 induced signaling have provided evidence that the somatotropic axis is involved in the control of aging in other mammalian species, including humans [7, 10–13]. Moreover, comparative studies of mutations that affect aging in different organisms uncovered an astonishing degree of homology [14, 15], and it is now well established that the evolutionarily conserved insulin/IGF-1 signaling (IIS) pathway has a major role in the control of aging in species ranging from unicellular yeast and microscopic worms to insects and vertebrates [16, 17]. GH has no identified homologs in yeast, worms or flies, but influences IIS as a key stimulator of IGF-1 expression and an important modulator of the secretion and actions of insulin. A recent study suggested that the remarkable differences of lifespan between various mammalian species are also related to somatotropic action [18].

The role of GH and IIS in the control of mammalian aging and the physiological characteristics of long-lived GH-related mutants were reviewed by us and others [4–7]. In this brief article we will not attempt to provide a comprehensive discussion of these topics, but instead will describe recent findings focusing on the mechanisms linking somatotropic action and aging and on the studies aimed at identifying the role of GH in different tissues in the control of longevity.

Extended longevity of mice with isolated GH deficiency

Most of the evidence for the role of GH in the control of aging was derived from studies in animals with deficiencies of three adenohypophyseal hormones (GH, prolactin and thyrotropin) or disruption of GH receptors [1–7]. In contrast to findings in these animals, longevity was not affected by transgenic expression of a GH receptor antagonist [19] and the impact of isolated GH deficiency due to mutation of the GH releasing hormone (GHRH) receptor in “little” mice on longevity was relatively modest and dependent on diet composition [2]. Therefore, when Salvatori and his colleagues developed a new line of mice with isolated GH deficiency by disrupting the GHRH gene [20], it was of great interest to examine their aging-related traits and longevity. In both sexes of GHRH-KO mice the median and the maximal longevity were significantly increased [21]. The extension of median longevity was particularly striking: 43% in females and 51% in males. GHRH-KO mice share many phenotypic characteristics with GHRKO and Ames dwarf mice. This includes reductions in IGF-1 levels, body weight, blood glucose, plasma insulin, triglyceride and cholesterol levels and respiratory quotient and increases in adiposity (particularly, subcutaneous fat), plasma leptin and adiponectin levels and insulin sensitivity [21]. However, in contrast to the findings in other GH-related long-lived mutants, glucose tolerance was not altered in the GHRH-KO mice and the trend for increased oxygen consumption per gram of body weight was not significant. Analysis of hepatic gene expression profiles revealed major shifts in the expression of genes related to xenobiotic detoxification and stress resistance with many similarities to previous findings in other GH-related long-lived mutants [21].

Impact of reduced systemic and local IGF-1 signaling on longevity

Preliminary studies in mice in which circulating IGF-1 levels are reduced due to the improper insertion of a null IGF-1 construct in the native IGF-1 allele that allows expression of small amounts of IGF-1, indicated that longevity is extended in females but not in males [22]. A recent report with detailed analysis of longevity in these animals at three different locations revealed significant extension of maximal longevity and reduction of age-specific mortality rates but, surprisingly, no consistent effect on mean lifespan [23]. Phenotypically, these animals exhibited some characteristics resembling long-lived hypopituitary and GH-resistant mice including resistance to the detrimental effects of HFD [24]. However, their insulin resistance was increased rather than reduced [24].

Recent work has also provided new information on the effects of partial IGF-1 resistance on longevity. Longevity of animals heterozygous for the deletion of IGF-1 receptor [IGF-1R(+/−)] was reexamined in the Holzenberger laboratory to address the discrepancy between the major extension of female longevity and a similar trend in males in the original studies in 129/SvPas mice [25] and the very small effect strictly limited to females in C57BL/6 mice examined by Bokov et al. [26]. Results indicated that extension of female longevity in IGF-1R(+/−) animals is reproducible on both genetic backgrounds and that the difference in the magnitude of this effect is likely related to strain differences in the normal levels of activation of the IGF-1 receptor and insulin receptor substrates, IRS1 and IRS2, and in the impact of the loss of one IGF-1R allele on the activation of these IGF-1 targets [27].

Sex dimorphism in the longevity response to partial IGF-1 resistance resembles the findings in IRS-1−/− [28] and S6K1 [29] mice in which only females live longer. Differential responses of females and males to genetic or pharmacological age-delaying interventions are not uncommon [30–32] but are difficult to explain. Speculations about the possible mechanisms of these dimorphisms include the possible role of different, often opposite effects of female and male sex hormones on somatotropic signaling, metabolism and immune function, differences in the impact of diet composition on various classes of immune cells [33] and sex-specific patterns of pulsatile GH release leading to dimorphism of hepatic enzymes involved in detoxification of endogenous and exogenous toxins (xenobiotics) [34, 35].

In contrast to the relatively modest effects of reducing the levels of systemic IGF-1 or global IGF-1 receptor levels on longevity, reducing local (tissue) levels of bioavailable IGF-1 by deletion of pregnancy associated plasma protein A (PAPP-A), a protease which degrades IGF-1 binding proteins (particularly IGFBP4), produces robust extension of longevity in both sexes [36]. In addition to extended longevity, PAPP-A-KO mice have delayed incidence and occurrence of neoplasms [37] and are resistant to experimental induction of atherosclerosis and diabetic nephropathy [37] and to the detrimental effects of HFD on body composition and metabolism [37]. Interestingly, GHRKO mice, Ames dwarf mice and transgenic mice expressing GH receptor antagonist are also relatively insensitive to the detrimental impact of HFD on glucose homeostasis even though this diet further increases their enhanced adiposity [38, 39, Hill & Bartke, unpublished].

Reducing circulating IGF-1 levels in adult mice by inducible disruption of the Igf1 gene in the liver induced liver inflammation, accelerated bone loss, oxidative stress in different tissues and increased incidence of hepatic tumors, thus markedly impairing healthspan [40]. This was presumably due to interference with the normal negative feedback of IGF-1 on GH release and the resulting chronic increase in GH levels [40]. In numerous studies in transgenic mice, elevated GH levels have been associated with multiple symptoms of accelerated aging, promotion of tumor development and reduced longevity [41, 42].

Selective deletion of the GH receptor in different GH target organs fails to recapitulate the effects of global GH resistance on aging and longevity

GH influences the function of multiple organs via direct and IGF-1 mediated effects as well as multiple secondary mechanisms including changes in body composition and distribution of adipose tissue, alterations in insulin levels and sensitivity and various metabolic adjustments. In an effort to identify local and systemic effects of GH signaling in its various target organs, several laboratories generated mice with targeted deletion of the GH receptor in the liver, muscle, adipose tissue, pancreatic β-cells or macrophages [43–50]. The resulting animals with organ specific GH resistance were phenotypically very different from the GHRKO mice. Thus, mice with deletion of GHR in the liver generated by Fan et al. [43] had impaired glucose homeostasis, liver steatosis and increases in fibrosis and inflammation. Presumably these characteristics represent the net result of reductions in hepatic IGF-1 expression and circulating IGF-1 levels with concomitant increase in GH release due to dampening of the IGF-1 negative feedback.

Mavalli et al. [44] and Vijayakumar et al. [45] used different promoter enhancers (Mef-2c-73k and muscle creatine kinase, MCK) to drive Cre expression specifically in the muscle in the course of producing mice with muscle-specific GHR deletion. Surprisingly, this resulted in very different, generally opposite alterations in body weight and composition, as well as insulin sensitivity as MCK mice were smaller and leaner with enhanced insulin sensitivity and Mef mice were heavier, with increased adiposity and impaired insulin sensitivity [44, 45]. Furthermore, muscle structure and strength were negatively affected in Mef mice, while lipid metabolism and inflammation markers were improved in the MCK mice [44, 45]. The reasons for these differences are unclear; however, the findings indicate that interference with GH signaling in only one of its target organs can alter phenotypic characteristics previously associated with aging as putative mechanisms or surrogate markers.

Alterations in metabolic characteristics related to aging were reported also in mice lacking GH receptors in insulin producing cells or macrophages. Disruption of GHR in pancreatic β-cell resulted in impairment of glucose-stimulated insulin secretion, failure of hyperplasia in response to HFD and glucose intolerance in HFD-fed mice [48]. Enhanced susceptibility to the detrimental effects of HFD on glucose homeostasis and inflammation was also seen in mice with deletion of GHR in macrophages [49]. This contrasts with the resistance to the diabetogenic (but, interestingly, not obesogenic) effects of HFD in GHRKO and Ames dwarf mice [39, Hill & Bartke unpublished].

To determine the role of different organs in mediating the striking effects of global GHR deletion on aging and longevity, the Kopchick laboratory produced new lines of mice with deletion of GHR limited to the adipose tissue, liver or skeletal and cardiac muscles [46, 47, 50]. Growth, body composition, glucose homeostasis and other phenotypic characteristics of animals from each of these lines were unique but none of them reproduced the phenotype of the animals with global GHR deletion (Table 1). However, mice with fat-specific GHR disruption (FaGHRKO mice) were obese similarly to the global GHRKO mice [46]. Moreover, growth and body size after 6 months of age were drastically reduced in mice with liver-specific GHR disruption (LiGHRKO mice) as expected from the suppression of hepatic IGF-1 secretion [51]. Longevity was reduced in FaGHRKO and unaltered in LiGHRKO mice [50, 52]. Normal longevity of LiGHRKO mice most likely represents a net result of the opposing effects of reducing IGF-1 and increasing GH levels. This interpretation is consistent with GH-dependent insulin resistance in mice with selective deletion of IGF-1 in the liver [51].

The unexpected reduction of longevity in FaGHRKO mice is more difficult to explain. In the global GHRKO mice, plasma adiponectin levels are increased [5, 7, 53, 6], markers of inflammation in the intra-abdominal fat are reduced, and surgical removal of most of the intra-abdominal fat has a surprisingly negative impact on glucose homeostasis [54]. We hypothesized that the selective disruption of GHR in the adipose tissue would lead to similar changes and thus promote longevity. Instead, FaGHRKO mice had reduced (in males) or unaltered (in females) total adiponectin levels [46]. There was also a marked reduction in the levels of adipsin [46], a secretory product of adipose tissue that can improve β-cell function [55]. Together, these changes in the secretory activity of the adipose tissue may have contributed to the reduced longevity of FaGHRKO mice.

Mice with muscle-specific GHR deletion (MuGHRKO) tended to live somewhat longer than controls but this trend was significant only in males from one of the two cohorts used for longevity determination [50]. Apparently, disruption of GH-induced signaling in multiple organs or at a site other than adipose tissue, liver or muscle is required for the remarkable extension of longevity which is consistently observed in both sexes of global GHRKO mice. On the basis of recent findings on the impact of GH signaling on the expression of pro-inflammatory cytokines in the central nervous system [56] and on the role of hypothalamic inflammation in the control of aging [57, 58], it is tempting to speculate that hypothalamus and/or other brain regions may be involved in mediating the effects of global GHR deletion on longevity. Review of the reported beneficial and detrimental effects of IGF-1 on various aspects of brain morphology vascularity and function during aging is outside the scope of this article.

Mechanisms linking reduced somatotropic signaling and extended longevity

Previous studies in GH-deficient and GH-resistant mice indicated that the increased longevity of these mutants can be related to several interacting mechanisms [59, 5, 60, 7, 6]. These mechanisms include reduced IGF-1 levels (likely a key reason for reduced incidence of cancer), improved stress resistance, reduced mTOR signaling and a combination of

reduced insulin levels with enhanced insulin sensitivity, I.e. metabolic characteristics opposite to those of the metabolic syndrome. More recent work identified other putative mechanisms that appear to link reduced GH signaling with slower aging and these are briefly discussed below.

Studies of mTOR signaling in the GH-related mutants and other long-lived mice suggested that the previously reported suppression of mTOR signaling involves the TORC1 kinase complex, while TORC 2 signaling is increased rather than suppressed [52]. Both TORC1 and TORC2 complexes control cell growth but they are known to phosphorylate different sets of substrates [61] and to differ in their susceptibility to inhibition by Rapamycin [61]. Further studies will be needed to elucidate the role of these two complexes in the control of mammalian aging and to explain phenotypic and metabolic differences between animals in which longevity is extended by suppression of somatotropic signaling [1–7], Rapamycin treatment [62] or S6K1 deletion [29].

The numbers of pluripotent Very Small Embryonic-Like Stem Cells (VSELs) in the bone marrow are greater in long-lived GH-related mutants than in their normal siblings [63]. Results of replacement therapy with GH in Ames dwarf mice and with IGF-1 in GHRKO mice indicate that these differences in the number of VSELs stem from reduced IGF-1-dependent depletion of these cells in mutant animals [63]. We suspect that improved maintenance of stem cell populations associated with reduced somatotropic signaling may improve the potential for repair of age-related damage or cell loss in different organs and thus contribute to “healthy aging” and extended longevity.

Recent evidence for reduced number of senescent cells in the intra-abdominal adipose tissue of GHRKO, Snell and Ames dwarf mice [64] suggests yet another mechanism of extended longevity. Senescent cells are an important source of pro-inflammatory cytokines, and chronic inflammation is a consistent feature and likely an important mechanism of aging. In support of the causal nature of the relationship between the number of senescent cells and longevity, experimental depletion of senescent cells was shown to reduce progression of aging in progeric mice [65].

Both GH-deficient and GH-resistant mice have increased expression of adiponectin, a key anti-inflammatory cytokine, and reduced expression of pro-inflammatory cytokines in the adipose tissues [53, 54, 66, 67] with corresponding changes in the levels of circulating adiponectin and interleukin-6 (IL-6) [66, 67]. Recent studies indicate that expression of proinflammatory cytokines, primarily IL-1β is reduced in various brain regions of these animals, including the hypothalamus and the hippocampus [56, 57]. These findings may denote reduced chronic inflammation in the central nervous system and thus may represent yet another reason for the delayed and slower aging of these animals. Experimental reduction of hypothalamic inflammation was shown to have anti-aging effects [58].

Measurements of oxygen consumption and respiratory exchange ratio (RER, often referred to as respiratory quotient, RQ) in long-lived GH-related mutants [57, 68] provided evidence for increased metabolic rate and alterations in mitochondrial function, including increased reliance on fatty acids rather than carbohydrates as an energy source. Current studies in our

laboratory are aimed at relating these metabolic characteristics to thermogenesis in different adipose tissue depots, liver and muscle and to the control of aging.

Somatotropic axis and human aging

In epidemiological studies, Laron dwarfism (hereditary GH-resistance) was associated with protection from cancer and diabetes [69, 70], with no apparent differences between men and women (V. Longo, personal communication]. Congenital GH-deficiency was shown to provide unexpected protection from atherosclerosis [71] and reduced GH/IGF-1 action was associated with reduced old-age mortality in women [12, 13, 72]. Comparisons of offspring of long-lived families to their spouses (or partners) demonstrated that individuals genetically predisposed to longevity have lower fasting insulin levels and enhanced insulin sensitivity [73, 74]. Intriguingly, these characteristics mimic the phenotype of long-lived mice with GH-related mutations [5, 7].

Samaras and his colleagues described numerous examples of a negative association of height (a GH/IGF-1-realted trait) with longevity [75, 76]. In a recent study by a different group of investigators, smaller height was associated with reduced mortality in American men of Japanese ancestry [77]. This latter effect was particularly evident in the oldest members of the studied cohort and, interestingly, was associated with reduced insulin levels and polymorphism of the FOXO3 gene that was related to human longevity in numerous studies [78, 79, 7]. These findings provide yet another indication that GH and IIS are involved in the control of human aging and longevity.

Concluding remarks

As described above, GH action influences mammalian aging and several molecular mechanisms have been proposed to mediate the effects of the somatotropic axis on longevity. We anxiously await future results in which the relationship between these mechanisms and their effect on aging/longevity are resolved.

Acknowledgments

Studies in the authors' laboratories and the preparation of this article were supported by NIA P01AG031736 and by NIA R01AG019899 We wish to apologize to those whose work relevant to this topic was not cited or discussed due to limitations of space or inadvertent omission.

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Table 1

Effects of organ-specific (Mu-Muscle, Li-Liver Fa-Fat) vs. global dysruption of GH receptors. Arrows pointing up and down denote statistically significant increases and decreases respectively. Double arrows denote numerically large effects. Horizontal lines denote lack of significant change. [Based on data in references 7, 43, 44, 48]

	GHRKO	MuGHRKO	LiGHRKO	FaGHRKO
Body weight	↓↓	—	↓	↑
GH	↑	—	↑	—
IGF-1	↓↓	—	↓↓	↑ male
IGFBP-2	↑	—	—	—
Insulin	↓	↓	↑	—
Insulin sensitivity	↑	↑male	↓	—
Adiposity	↑	—	↓	↑
Adiponectin	↑	↓	↑	↓male
Longevity	↑↑	↑male	—	↓