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Hormonal control of aging in rodents: The somatotropic axis

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Abstract

There is a growing body of literature focusing on the somatotropic axis and regulation of aging and longevity. Many of these reports derive data from multiple endocrine mutants, those that exhibit both elevated growth hormone (GH) and insulin-like growth factor I (IGF-1) or deficiencies in one or both of these hormones. In general, both spontaneous and genetically engineered GH and IGF-1 deficiencies have lead to small body size, delayed development of sexual maturation and age-related pathology, and life span extension. In contrast, characteristics of high circulating GH included larger body sizes, early puberty and reproductive senescence, increased cancer incidence and reduced life span when compared to wild-type animals with normal plasma hormone concentrations. This information, along with that found in multiple other species, implicates this anabolic pathway as the major regulator of longevity in animals.

Keywords

Growth hormone; IGF-1; Stress resistance; Aging

1. Introduction

It has been more than 40 years since Everitt and Cavanagh (1965) removed the pituitary gland of rats and observed fewer age-related changes in tail tendon collagen fibers and a delayed onset of proteinuria compared to intact rats. Food restriction (CR) studies of rodents which predate this work showed that the secretion of most pituitary hormones was inhibited by this experimental manipulation (Mulinos and Pomerantz, 1940; Everitt and Porter, 1976). Food restriction also appeared to delay the onset of age-related disease and extend lifespan. Melding this evidence at the time, it was postulated that there were anti-aging factors produced by the pituitary gland. Everitt et al. (1980) then showed that in rats, both hypophysectomy and CR similarly retarded collagen aging and abolished proteinuria. Hypophysectomy and CR also delayed the onset of several age-related pathologies such as total tumor incidence, hindlimb paralysis, aortic wall thickening and cardiac and kidney enlargement. Based on these studies, it was believed that pituitary hormones played a significant role in lifespan regulation. More recently, hypophysectomy performed in adult mice was also shown to significantly increase lifespan (Powers et al., 2006).

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The anterior pituitary produces and secretes multiple hormones including growth hormone (GH), thyroid stimulating hormone (TSH), prolactin, follicle-stimulating hormone (FSH), luteinizing hormone (LH) and adrenocorticotropic hormone (ACTH). With regard to aging and longevity, by far the most well-studied of these hormones is GH. As such, this review will focus on the somatotropic axis in rodents as it relates to aging processes and lifespan.

The somatotropic axis consists of growth hormone, upstream hypothalamic hormones, the insulin-like growth factors (IGFs) and downstream signaling molecules. Growth hormone production and release from the anterior pituitary is controlled by two hypothalamic factors, growth hormone-releasing hormone (GHRH) and somatostatin (SS). It is the balance of these two that determines the rate of GH secretion. Plasma GH directly stimulates IGF-1 production and secretion by the liver in addition to exerting direct effects on other tissues. Local tissue production of GH or IGF-1 also occurs, suggesting the importance of autocrine and paracrine actions of these hormones. Growth hormone and IGF-1 have both somatic effects stimulating the growth of tissues and metabolic effects that play a role in protein, carbohydrate and lipid metabolism. Alterations in these interrelated pathways can thus lead to both growth retardation or tissue proliferation and a variety of metabolic disturbances.

Endocrine mutants have provided remarkable insight into the role of GH and IGF-1 in aging (Table 1). Several spontaneous mutants have been discovered and genetically engineered mice created that exhibit altered GH/IGF-1 signaling. These animals have been studied to varying degrees by investigators in the aging field, and each mutant strain has provided clues that contribute to our current understanding of the role these endocrine pathways play in lifespan regulation. These animals will be reviewed in the context of physiological actions of GH and IGF-1, including growth, metabolism, reproduction, resistance to stress and lifespan regulation.

2. GH and lifespan

To date, probably the best-characterized long-living rodent is the Ames dwarf mouse (reviewed in Bartke and Brown-Borg, 2004). Ames dwarf mice are diminutive in size, exhibit infantile facial features and delayed puberty (Schaible and Gowen, 1961; Bartke, 1964). A point mutation in the Prop-1 gene was identified and shown to be responsible for the inappropriate differentiation of specific pituitary gland cell types (somatotropes, lactotropes, thyrotropes; Bartke, 1979; Sornson et al., 1996). Dwarf mice thus lack circulating GH, prolactin and thyrotropin, resulting in the phenotype described above. Significantly, female Ames mice live 68% longer than wild-type females while male dwarfs live 49% longer than their wild-type counterparts (Brown-Borg et al., 1996). The lifespan data in Ames mice is derived from animals of a heterogenous background produced in a closed colony (>30 years; Bartke, personal communication). Phenotypically identical Snell dwarf mice also exhibit deficiencies in plasma GH, prolactin and thyrotropin concentrations and live longer than normal littermates (Bartke, 1964; Flurkey et al., 2001). A mutation in the Pit-1 gene (downstream of Prop-1) was identified as the causal factor in this type of dwarfism (Li et al., 1990). Lifespan data for the Snell dwarf is derived from animals where the dwarf gene mutation was studied on different backgrounds. Flurkey et al. (2001) reported no difference in lifespan of the dw/dw mutation on DW/J × C3H or DW/J ×

C3H/HeJ backgrounds (42% increase). In addition, longevity does not differ between female and male Snell dwarf mice (Flurkey et al., 2001; Vergara et al., 2004). The GH deficiency in both Ames and Snell dwarf mice results in undetectable plasma levels of IGF-1. Studies have been conducted examining hormone replacement in dwarf mice. While 11 weeks of GH and thyroxine replacement did not affect the longevity of Snell dwarfs, thyroxine administration throughout adult life did shorten lifespan significantly (Vergara et al., 2004). Moreover, hypothyroid rats (pharmacologically induced) only live a few months longer than euthyroid animals (Ooka et al., 1983). Replacing prolactin in dwarf mice shortened lifespan in one study but had no affect on longevity in another laboratory (Bartke, unpublished observations; Flurkey et al., 2001). Therefore, the deficiencies in GH and IGF-1 are proposed as the main mediators of the lifespan extension in these mice; additional evidence for this hypothesis is outlined below.

Consistent with the lack of GH and IGF-1 actions in Ames and Snell dwarf mice, the growth hormone receptor/binding protein knockout mice (GHR/BP KO; Laron dwarf) also live significantly longer than wild-type siblings (Zhou et al., 1997; Coschigano et al., 2000). The original GHR KO animals were generated on a OLA/Balb/cJ background with females living 21% longer than gender-matched wild-type mice and males living 40% longer than their counterparts (Coschigano et al., 2000). When the GHR KO mutation was expressed on a C57Bl/6 background, female and male knockout animals lived 16 and 26% longer than wild-type control mice (although the difference in females was not significant; Coschigano et al., 2003). These mice have high plasma GH but very low plasma IGF-1 levels because of the lack of GH receptor binding in target tissues. These mice are smaller than normal mice and exhibit delayed puberty. Another mutant, the ‘Little’ mouse, was first described by Eicher and Beamer (1976). These animals express a mutant GHRH receptor, resulting in low plasma GH, small body size and 23 and 25% increases in lifespan compared to female and male wild-type controls, respectively, when fed a low-fat diet (C57Bl/6 background; Flurkey et al., 2001). Studies describing attempts to knock out IGF-1 or the IGF-1 receptor report significantly reduced viability in the knockout animals along with valiant efforts to maintain live mice, therefore, no lifespan data are available (Liu et al., 1993; Powell-Braxton et al., 1996; Liu and LeRoith, 2001). However, the liver-specific IGF-1 ablated mouse (LID) exhibits serum IGF-1 deficiency (75% reduction) yet similar longevity compared to wild-type counterparts (Yakar et al., 1999). Importantly, a 50% reduction in IGF-1 receptors (IGF1R knockdown) results in 33 and 16% longer lifespans in females and males, respectively, when compared to normal littermates (difference between mutant and wild-type males was not significant; 129/Sv background; Holzenberger et al., 2003). Null animals (IGF1R knockout) were not viable. Mice that overexpress the protein Klotho on a C3H background represent yet another mouse strain with impaired IGF-1 signaling that lives longer (females 19% and males 25%) than normal mice (Kurosu et al., 2005). Finally, mice created to express a GH antagonist (GHa) that competes with endogenous GH exhibit a significant reduction in GH-induced intracellular signaling (Chen et al., 1990, 1991). These GHa animals are smaller than wild-type controls and tend to live longer than wild-type animals (especially the females) but the differences are not significant (C57Bl/6 background; Coschigano et al., 2003).

One complicating factor with the lifespan studies of mutant mice is that the mutations are expressed on a variety of background mouse strains and it is known that genetic backgrounds contribute to lifespan. The C57Bl/6 background is considered one of the longerlived strains while the 129/Sv background is a much shorter living strain. With the GHR KO mutation in particular, expression of the mutant gene on a C57Bl/6 background still results in significant longevity compared to wild-type control animals (Coschigano et al., 2003). Holzenberger et al. (2003) confirmed their findings of lifespan extension when the IGF1R mutation was expressed on a hybrid 129/Sv × C57Bl/6 background.

The evidence in rodents is overwhelming and clearly demonstrates that reductions in GH/IGF-1 signaling via reductions in plasma hormone levels, or altered hormone receptor interactions, extend lifespan. Dwarf rats expressing an antisense GH transgene have moderately suppressed GH levels and live longer than normal rats (Shimokawa et al., 2002). However, dwarf rats (dw/dw) expressing specific and limited GH and IGF-1 (40% reduction) in adulthood do not exhibit lifespan extension (Sonntag et al., 2005). Problematic is that the dw/dw mutation is thought to disturb somatotroph differentiation, resulting in an increase in prolactin accompanying the GH deficiency, a highly unusual event that could alter lifespan (Tierney and Robinson, 2002). High pituitary prolactin, in this case, may compensate for the GH deficiency as it has been shown that prolactin overexpression increases body size (Greenman et al., 1998; Byatt et al., 1993). Overall, it appears that the degree of lifespan extension is associated with both the degree of hormone deficiency and background strain, among other factors.

Several other noteworthy lines of study support the evidence that the somatotropic axis regulates of lifespan. First, mice expressing GH transgenes are characterized by high plasma GH levels, increased body weights and lengths, and lifespans half that of wild-type siblings (12 months; Steger et al., 1993). Second, overexpression of IGF-2 in smooth muscle cells of mice shortens lifespan significantly, especially in males (Zaina et al., 2003). Third, high-dose GH treatment in rats has also proved to be toxic (Groesbeck et al., 1987). Although the majority of reports indicate that GH regulates lifespan, one study showed that low to moderate doses of GH in mice either slightly increased or had no effect on lifespan (Khansari and Gustad, 1991). Human GH was administered in this study, leading to the question of specificity because human GH has both lactotrophic and somatotropic activity in rodents. Finally, significant evolutionary evidence also supports the role of these pathways in lifespan regulation in yeast, worms and flies (Fabrizio et al., 2001; Kenyon et al., 1993; Tatar et al., 2001). Reductions in GH/IGF-1 signaling lead to major lifespan extensions in these diverse species.

3. GH, growth and body size

Somatic growth is driven by components of these pathways; therefore, body size differences are obvious in many of the mutants. Those mutants with reduced signaling of this pathway are significantly smaller than wild-type controls. The range of differences is most likely related to the degree of suppression of the IGF-1 pathway. IGF-1 receptor knockdown mice are slightly smaller (8% in males) than wild-type mice while Ames and Snell dwarf mice are 66% smaller (one third the size of wild-type; Holzenberger et al., 2003; Bartke, 1964). The

GHR/BP knockout mice are 40% the size of wild-type siblings as adults (Coschigano et al., 2000). Mice with a mutated GHRH receptor gene (Little) are 33% smaller than normal body size, while strains of dwarf rats are 25% (antisense GH transgenic) and 40% (dw/dw at 3 months of age) smaller than their wild-type counterparts (Eicher and Beamer, 1976; Shimokawa et al., 2002; Charlton et al., 1988). GHa mice are 61% the size of wild-type control mice (Coschigano et al., 2003). Despite a significant reduction (75–80%) in serum IGF-1 levels, LID mice do not differ in size from wild-type mice and parameters of growth and development are normal (Yakar et al., 1999). In fact, when LID mice are crossed with mice overexpressing a GH antagonist to inactivate GH, the LID × GHa mice are 44% smaller than LID mice and 30% smaller than control mice (Yakar et al., 2004). Together, these data suggest that GH is the most important mediator of postnatal growth. Moreover, the fact that small body size is significantly associated with longevity also holds true for domestic dogs and plausibly for humans (Patronek et al., 1997; Samaras et al., 2003). Further support for a relationship between small body size and longevity is derived from reports showing that mice selected for reduced body sizes live longer (Roberts, 1961). In contrast to GH or IGF-1 deficiencies, animals overexpressing GH are significantly larger (30–60%) than wild-type controls (Shea et al., 1987; Wanke et al., 1992; Rollo et al., 1999). de Magalhães et al. (2005) used Gompertz analysis to show that GH and the GH receptor statistically influence aging, while IGF1R and the insulin receptor (IR) do not. Overall, it appears that growth negatively influences lifespan in mammals (Rollo, 2002) and that GH is the major player.

In addition to reductions in body size, changes in body composition are observed in GH mutant mice. Ames mice exhibit the expected declines in lean muscle mass and bone mineral densities (BMDs) concurrent with a lower percent body fat compared to age-matched wild-type mice (Heiman et al., 2003). Less body fat may appear paradoxical in a GH-deficient state as GH is a known lipolytic factor. However, the low insulin levels in the Ames mice may counter this effect by decreasing storage of this fuel. In contrast to Ames dwarf mice, GHR/BP KO mice showed an increased percentage of body fat, yet were similar to the Ames mice in reduced total-body bone mineral density, bone mineral content and bone area in comparison to wild-type control mice (Bonkowski et al., 2006). Body composition changes have been noted in other mutants and include an elevation in the percentage of body fat in Little mice with a significant reduction in protein in comparison to normal animals, perhaps reflecting the lack of GH and IGF-1, respectively (Donahue and Beamer, 1993). Similarly, whole body fat was increased twofold in GH antagonist transgenic and LID × GHa mice over that of controls (Yakar et al., 2004), reflecting the absence of GH lipolytic activity. In GH transgenic mice, components of body composition differ between studies. Eckstein et al. (2002) demonstrated that body composition of transgenic mice is relatively normal when normalized to body weight. However, other studies report that the overexpression of GH leads to relatively lean mice with a potential resistance to diet-induced obesity (Olsson et al., 2005; Berryman et al., 2006). Evidence in GH mutant mice suggests that this hormone plays an important role in energy utilization and regulation further contributing to differences in lifespan among mutants and their wild-type counterparts.

4. GH and metabolism

Reduced insulin secretion and enhanced insulin sensitivity are hallmarks of longevity in mutant mice. Insulin sensitivity declines with age and is related to visceral fat stores in that sensitivity increases when visceral fat decreases (Barzilai et al., 1998; Barzilai and Gupta, 1999). GH is classified as a diabetogenic factor for it opposes the actions of insulin. Maintenance of blood glucose concentrations and lipid levels represent two key systems that are modulated by GH. While insulin is the only hormone that lowers blood glucose, GH is one of several factors present that serves to increase plasma glucose concentrations. GH stimulates gluconeogenesis and glycogenolysis and inhibits glucose uptake at the tissue level. These actions are apparent in GH transgenic mice. The overexpression of GH leads to hyperglycemia, hyperinsulinemia and insulin resistance in these mice (Balbis et al., 1996; Dominici et al., 1998). In contrast, the plasma of GH-deficient (Ames and Snell) and GH-resistant (Laron dwarf) mice is low in both glucose and insulin and the animals are very insulin sensitive (Borg et al., 1995; Dominici et al., 2000a,b, 2003; Hauck et al., 2001). In addition, it was shown that the enhanced insulin sensitivity in dwarf mice, in part, results from elevated liver insulin receptors in GHR/BP KO mice and elevations in IR, IRS-1 and IRS-2 (downstream effectors of IR) in Ames mice (Dominici et al., 2000a,b, 2002). Supportive evidence is found in a recent report showing that glucose utilization, gluconeogenesis and glycogenolysis are significantly decreased in Snell dwarf mice (Brooks et al., 2007). Lower pancreatic islet numbers in Ames mice lends credence to data indicating that insulin secretion is altered via significantly reduced glucose disposal following acute glucose challenge (Parsons et al., 1995; Coschigano et al., 2000). In male IGF1R knockdown mice, glucose tolerance is reduced while insulin secretion is intact (Holzenberger et al., 2003), suggesting the existence of peripheral insulin resistance. Serum insulin levels (fasting) in the GHa mice do not differ from controls (Coschigano et al., 2003). Liver-specific IGF-1 deficient mice are hyperinsulinemic and insulin resistant despite low plasma IGF-1 and normal blood glucose levels and clearance (Yakar et al., 2001; Yu et al., 2003). This insulin resistance results from GH hypersecretion as the actions of GH are inactivated in the LID × GHa animals, and these animals are insulin sensitive (Yakar et al., 2004). The Klotho transgenic mice exhibit higher blood insulin levels with normal glucose levels, along with other data suggesting that these animals are insulin resistant (Kurosu et al., 2005). Thus, IGF-1 plays a smaller role metaboli-cally, likely fine-tuning GH and insulin activities, some of which may occur via IGF-1 binding to insulin receptors and direct effects on adipose tissue. Low plasma glucose throughout life may slow aging via decreasing the accumulation and detrimental processes associated with glycation end products, slowing metabolism and reducing the associated ROS generation (Reiser, 1998; Baynes and Monnier, 1988). The effects of GH and IGF-1 on metabolism are quite apparent in mutant rodents and provide additional clues as to the role of these hormones in aging and longevity.

5. GH and reproduction

Both growth hormone and IGF-1 exert significant control over reproductive competence in rodents. Reproductive organ development and function are impaired as well as their neuroendocrine function is dysregulated when plasma GH or IGF-1 levels are abnormally low or high (extensively reviewed in Chandrashekar and Bartke, 2003). The GHR/BP

knockout mice exhibit delays in sexual maturation but most animals are fertile. Puberty in Ames and Snell dwarf mice is significantly delayed. Female Ames and Snell dwarf mice are infertile while males are considered subfertile, although the degree of gonadal function is dependent upon background strain (Bartke, 2000). Mice that overexpress the Klotho gene resulting in IGF-1 resistance, also exhibit reduced fecundity (Kurosu et al., 2005). In contrast, the IGF-1-deficient LID mice are fertile, and females have normal litter sizes (8–10 pups) and appear to nurse pups normally (Yakar et al., 1999). The IGF1R heterozygous (knockdown) mice also do not differ from wild-type animals with regards to puberty and fertility although male mice have not been examined as thoroughly as females (Holzenberger et al., 2003). The fecundity of Little mice was reported by Chubb (1987). Female mice exhibit delayed sexual maturation and males are considered subfertile due to defects in sexual behavior. In dw/dw rats, fertility is also considered subnormal, with the males exhibiting small testes and impaired sperm motility (Gravance et al., 1997; Vickers et al., 1999). When plasma GH levels are significantly elevated as seen in GH transgenic mice, both sexual maturation and reproductive senescence occur earlier (Chandrashekar et al., 1988; Bartke et al., 1994; Cecim et al., 1993). In one line of GH transgenic mice (MT-bGH), fertility appears normal (Naar et al., 1991). However, in PEPCK-bGH mice, a line that produces very high levels of bovine GH, pregnancy failure is high, yet the ovulation rate is elevated compared to wild-type animals (Cecim et al., 1995; Danilovich et al., 2000). Excess bGH seems to have little effect on male fertility although senescence does occur earlier (Bartke et al., 1994). Most of the GH effects on the reproductive system are due to alterations in IGF-1 concentrations and actions (Chandrashekar et al., 2004), leading to the reproductive anomalies described in GH/IGF1 mutants. This idea is exemplified by findings in the IGF-1 null mouse. Males IGF-1 mutants exhibit reduced spermatogenesis, low testosterone and an absence of mating behavior, while females lack antral follicles and fail to ovulate, resulting in the sterility of both sexes (Baker et al., 1996; Wang et al., 2003).

6. GH and stress resistance

Growth hormone and IGF-1 also affect a more diffuse mechanism of lifespan extension, that of stress resistance. The components of this system are many and include heat shock proteins, cellular repair factors, metal chelators, phase II detoxification proteins, antioxidants and factors that prevent or suppress tumor growth. Resistance to oxidative stress has been evaluated in several GH/IGF-1 mutants, for it is one of the primary physiological effects that is strongly associated with longevity in multiple species. Accordingly, this topic will receive substantial coverage in this review.

It has been proposed that endogenously generated reactive oxygen species (ROS) cause aging via damage to DNA, proteins and lipids (Harman, 1988). The metabolic effects of GH and IGF-1 on the oxidative pathway and oxidative damage have been documented in numerous reports. GH is an anabolic factor that increases cellular metabolism. Increased metabolic activity (glucose oxidation and oxygen consumption) leads to increased oxidative phosphorylation and increased production of ROS as byproducts of metabolism. Growth hormone overexpression in mice increases superoxide radicals and oxidative damage to membrane lipids (Rollo et al., 1996). Tissues from mice with high plasma GH exhibit significantly reduced levels of antioxidative enzymes including manganese superoxide

dismutase (MnSOD), copper-zinc SOD, catalase and glutathione peroxidase (GPX; Brown-Borg et al., 1999; Brown-Borg and Rakoczy, 2000; Hauck and Bartke, 2001). More directly, effects of GH and IGF-1 *in vitro* strongly support the *in vivo* data showing that these two hormones downregulate catalase, GPX and MnSOD in hepatocytes from normal mice (Brown-Borg et al., 2002).

In contrast to the suppression observed in GH excess, when a deficiency is present, enhanced antioxidative defense capacity is observed in GH/IGF-1 mutants. Numerous tissues of the Ames dwarf exhibit elevated levels of catalase, GPX and SOD (Brown-Borg et al., 1999; Brown-Borg and Rakoczy, 2000; Hauck and Bartke, 2000; Brown-Borg, unpublished data). GPX activity is preserved in muscle tissues of dwarf mice following exercise while that from wild-type mice declines with age (Romanick et al., 2004). GH replacement in dwarf mice downregulates catalase, GPX and MnSOD in both young and adult animals (Brown-Borg and Rakoczy, 2003). The thiol-containing proteins, metallothionein and glutathione (GSH) both exhibit ROS scavenging abilities, and levels of these are significantly increased in tissues of Ames dwarf mice (Meyer et al., 2003; Brown-Borg et al., 2001b). The amino acid methionine, whose metabolic pathway feeds cysteine residues into the GSH pathway, is also highly upregulated in the Ames mouse (Brown-Borg et al., 2005; Uthus and Brown-Borg, 2003, 2006). Gene expression analysis supports evidence for enhanced stress resistance in Ames dwarf mice. Several genes involved in both Phases I and II xenobiotic metabolism were found to be elevated in dwarf mice (Tsuchiya et al., 2004). These findings indicate that the Ames dwarf mouse exhibits characteristics that lead to an enhanced ability to counter genotoxic and metabolic insults.

Snell dwarf mice follow similarly with regard to antioxidative defense although the means of demonstration have been somewhat different. Skin-derived fibroblasts from Snell mice are more resistant to multiple forms of cellular stress including percent increases in LD_{50} values following exposure to UV light (45%), H_2O_2 (147%), paraquat (53%), cadmium (180%) and heat (102%) (Murakami et al., 2003). These studies indicate an overall increase in stress resistance to both oxidative and non-oxidative challenges. Further studies in Snell mice showed that enhanced antioxidative defense was not solely responsible for the resistance observed (Salmon et al., 2005). Madsen et al. (2004) challenged dwarf mice with an inhibitor of succinate dehydrogenase (mitochondrial complex II), which causes free radical generation in tissues (Coles et al., 1979; Fu et al., 1995) and presented evidence suggesting altered management of oxidative stress in the long-lived dwarfs compared to the wild-type control mice. Although antioxidative defense enzymes have not been systematically evaluated in the Snell dwarf, an overall enhancement of this system is likely responsible for increased resistance to oxidative insult as found in phenotypically identical Ames dwarf mice. Ames mice showed similar resistance to these cellular stressors (UV: 43%; H_2O_2: 79%; cadmium: 95%) as did GHR/BP knockout mice (UV: 194%; H_2O_2: 108%; paraquat: 47%; Salmon et al., 2005). The IGF1R knockdown mice are also resistant to oxidative stress (Holzenberger et al., 2003) as are mice that overexpress the protein, Klotho (Kurosu et al., 2005).

The GHR/BP knockout animals differ from Ames mice with regard to antioxidative defense. Hauck et al. (2002) showed that these dwarf animals had higher GPX activity levels in

kidney tissues but levels of GPX and catalase were lower in liver tissue compared to wild-type mice. Preliminary data on tissue metallothionein levels indicates an overall increase compared to wild-type animals (similar to Ames mice; Swinscoe et al., 2006). Studies are underway in our laboratory to discern whether glutathione metabolism is similar. Minimal differences in hepatic gene expression were observed between GHR/BP knockouts and wild-type mice with the exception of a 50% increase in SOD2 in the knockouts (Al-Regaiey et al., 2005).

Mitochondrial oxidant production (liver H_2O_2) is significantly lower in dwarf mice, possibly indicating decreased metabolic activity in the absence of GH and thyroid hormone (Brown-Borg et al., 2001a). Isoprostanes are thought to reflect the level of oxidative stress due to lipid peroxidation (Roberts and Morrow, 2000). A recent report by Choksi et al. (2007) showed that Ames mice have lower levels of isoprostanes in both serum and liver at multiple ages, suggestive of lower oxidative stress. The reduced ROS and elevated antioxidative capacity of dwarf mice leads to lower nuclear DNA, mitochondrial DNA, and protein oxidative damage in several tissues (Brown-Borg et al., 2001a,b; Sanz et al., 2002). Functionally, Ames mice out-survive their GH sufficient counterparts following paraquat administration (systemic oxidative stressor; Bartke et al., 2000). The IGF-1 receptor knockdown mice challenged with paraquat also lived longer than mice with normal levels of IGF-1 receptors (wild-type; Holzenberger et al., 2003). In addition, mean survival following paraquat challenge was significantly reduced in the GHR/BP knockout males while female knockout and wild-type mice did not differ. Taken together, these studies suggest that low to normal plasma GH is consistent with resistance but that high levels suppress mechanisms that counter oxidative stress.

Overall, the reported studies provide significant support for the concept that GH and IGF-1 signaling pathways are intimately involved in the modulation of oxidative stress. The suppressive effect of GH on multiple components of the antioxidant system and consequent oxidative damage may be a mechanistic reason that levels of this hormone decline with aging.

GH and IGF-1 are anabolic hormones that support cell proliferation and prevent apoptosis and as such, deficiencies lead to a decreased propensity to develop tumors. Dwarf mice and rats have been shown to resist cancer development following administration of chemical carcinogen (Bielschowsky and Bielschowsky, 1961; Ramsey et al., 2002) and exhibit a reduction in growth of transplanted tumors (Rennels et al., 1965). Spontaneous tumor incidence is delayed and the severity reduced in the dwarf mice (Flurkey et al., 2001; Ikeno et al., 2003). Additionally, in IGF-1-deficient mice, tumor growth is reduced relative to control mice (Yang et al., 1996). Ames mice also exhibit greater heat shock protein levels and elevated levels of methionine sulfoxide reductase, an enzyme involved in protein repair (Brown-Borg, 2005). It has been proposed that stress resistance is coordinately upregulated (heat shock proteins, antioxidants, detoxification systems, metal chelators and repair systems) and this increase results in multi-stress resistance to different stressors (Rollo, 2002; Jazwinski, 1996; Martin et al., 1996). Indeed, studies by Murakami et al. (2003) and Salmon et al. (2005) show that cells from long-living mice are resistant to multiple forms of cellular stress.

7. Delayed and premature aging

Growth hormone and IGF-1 exert significant control over physiological processes that, in turn, affect aging. High circulating GH levels in rodents are strongly associated with signs of both premature and accelerated aging. An early onset of age-related kidney pathology is found in the form of glomerulonephritis and glomerulosclerosis in GH transgenic mice (Doi et al., 1988; Quaife et al., 1989; Wanke et al., 1992). The increased severity of this pathology along with the earlier expression in comparison to normal mice likely leads to the earlier demise of the transgenic animals. In addition, these mice develop significant mammary (those expressing human GH) and liver tumors earlier in their life in comparison to wild-type animals (Cecim et al., 1994; Bartke and Ikeno, unpublished). Relatively young mice (6–8 months of age) begin to show physical signs of aging including weight loss, scoliosis and coat deterioration. Other characteristics of aged normal animals are also found at much younger ages in GH transgenic mice including reduced hypothalamic neurotransmitter turnover, astrogliosis and an increase in age-related plasma corticosterone levels (Steger et al., 1993; Miller et al., 1995). In addition, stress-induced elevations in plasma corticosterone levels persist longer in animals with high plasma GH than in normal mice (Bartke, 2003). As mentioned previously, reproductive senescence occurs earlier in transgenic mice with infertility appearing at 5–7 months of age (Bartke et al., 1994). Declines in cognitive function have also been observed at much younger ages in GH transgenic mice (Meliska et al., 1997; Rollo et al., 1999). Finally, evidence that cells from GH transgenic mice exhibit a reduced capacity to replicate is also consistent with accelerated aging (Pendergrass et al., 1993). These data suggest that pharmacological levels of circulating GH lead to early onset of age-related pathologies in rodents. Some of the pathology observed may also be related to the overactivation of the somatotropic axis and its effects on insulin release and action as GH-transgenic mice are hyperinsulinemic and severely insulin-resistant (Quaife et al., 1989; Dominici et al., 1999a,b). The metabolic effects of high GH and insulin are costly; these include increased ROS, reduced antioxidative defense and increased oxidative damage. In addition, animals with high GH levels have been shown to partition energy differently, favoring rapid growth at the expense of reproduction and defense and repair processes (Kajiura and Rollo, 1994; Brown-Borg and Rakoczy, 2000; Hauck and Bartke, 2001). IGF-1 transgenic mice do not experience such severe pathological changes as GH transgenic mice (Doi et al., 1988), suggesting that the main effector is GH.

An abundance of evidence suggests that GH deficiency is consistent with delayed or decelerated aging in rodents. GH/IGF-1 mutant mice exhibit delays in sexual maturation, delayed tumor development, reduced tumor incidence and resistance to tumor growth. In addition, dwarf mice develop significantly less osteoarthritis than wild-type mice (Silberberg, 1972). Enhanced antioxidative defenses, lower ROS generation and less oxidative damage also contribute to delays in age-related pathology. Significant delays in the occurrence of both age-dependent collagen cross-linking and multiple indices of age-sensitive immune system status have been reported in dwarf mice (Flurkey et al., 2001). Age-dependent splenomegaly is also prevented in GH deficiency (Flurkey and Harrison, 1990). Low GH and IGF-1 signaling results in low circulating glucose and insulin levels as

well as significantly enhanced insulin sensitivity. Finally, there is compelling evidence suggesting that GH deficiency is associated with maintenance of cognitive function. Ames dwarf mice do not exhibit the age-related decline in cognitive function (including memory) and behavior that is observed in wild-type control mice (Kinney et al., 2001a). Similarly, GHR/BP knockout mice show no decline in cognitive function when age-matched wild-type littermates are significantly impaired (Kinney et al., 2001b), suggesting that the absence of GH action enhances memory retention. Other than hypophysectomy, which decreases brain IGF-1 mRNA, direct evidence of brain dysfunction in GH/IGF-1-deficient animal models is lacking (Hynes et al., 1987). Correlative data are available and show that deficits in the IGF-1 axis occur in aged brain and that IGF-1 levels are associated with cognitive function (Sonntag et al., 2000; van Dam and Aleman, 2004). Enhanced neurogenesis and elevated hippocampal IGF-1 may explain the maintenance of cognitive activity in GH-deficient dwarf mice (Sun et al., 2005).

8. Conclusion

The natural age-related decline in plasma GH levels and the concomitant decrease in IGF-1 that occurs in mammals is likely a protective mechanism to decrease metabolic activity and cellular division. Elevated levels of either of these hormones throughout life contribute to the pathological changes associated with aging such as increased collagen cross-linking, osteoarthritis, immune system dysfunction, insulin resistance, oxidative damage, sensitivity to stress and cancer. There is a wealth of literature on hormones and aging in other species including nematodes and flies, with most, if not all, directly supporting that found in mammals. It has been proposed that during evolution, the common GH/IGF/insulin pathway diverged into two: one to regulate cell division and growth and the other to control metabolism and partitioning of energy resources (Guarente and Kenyon, 2000; Finch and Ruvkun, 2001). In nematodes, flies and mammals, these metabolic pathways regulate energy, reproductive activity, and stress responses so that when food is abundant, growth, sexual maturation and reproduction dominate. When food is scarce, resources are used to favor survival and directed away from growth and reproduction to increase stress resistance and repair processes leading to delayed aging and longevity. Overall, there is clearly very strong evolutionary evidence implicating the endocrine system and the somatotropic axis in particular, as a major regulator of aging and lifespan.

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Table 1

Phenotypic characteristics of GH/IGF-1 long-living mutant mice

Phenotype	AMES (prop-1)	SNELL (*pit-1*)	GHR/BP KO	IGF-1R +/-	LID (Liver IGF1 mutant)	Little (GHRHR mutant)	Klotho
GH/IGF1/ Insulin signaling	↓	↓	↓	↓	↓	↓	↓
Body size	↓	↓	↓	↓	↔	↓	↔
Reproduction	↓	↓	↓	↔	↔	↓	↓
Insulin sensitivity	↑	↑	↑	Partially IGF1 resistant	Insulin resistant	NK	Insulin & IGF1 resistant
Stress resistance	↑	↑	↑	↑	NK	NK	↑
Longevity	49-68% ↑	42% ↑	21-40% ↑	33% females ↑	↔	23-25% ↑	18-30% ↑

NK: not known.