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The somatotrophic axis and aging: Mechanisms and persistent questions about practical implications

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Abstract

Reduced somatotrophic (GH/IGF-1) signaling delays aging and extends longevity in laboratory mice. However, it is unclear whether the physiological decrease of GH and IGF-1 levels with age represents a symptom of declining neuroendocrine function, a cause of age-related alterations in body composition and functionality or a protective mechanism against age-associated disease. Although available clinical evidence does not support the use of recombinant GH as an anti-aging therapy, many studies suggest the potential utility of GH and GH secretagogues in the treatment of sarcopenia and frailty.

Introduction; long-lived mutant mice

In laboratory populations of house mice (*Mus musculus*), mutations that reduce growth hormone (GH) and/or insulin-like growth factor 1 (IGF-1) levels or actions produce significant, often major increases in longevity (Brown-Borg et al., 1996; Flurkey et al., 2001; Coschigano et al., 2003; Holzenberger et al., 2003; Conover and Bale, 2007). In some of these long-lived mutants, there is evidence for extended maintenance of “youthful” characteristics, delayed onset of age-related disease and other indications that the biological process of aging has been postponed and/or slowed down (Flurkey et al., 2001; Silberberg, 1972; Ikeno et al., 2003; Kinney et al., 2001a, b; Vergara et al., 2004). These findings inescapably lead to a somewhat counterintuitive conclusion that the amounts and physiological actions of GH and IGF-1 normally present in these animals are not optimal for long-term survival. It could be argued that these negative effects of GH and/or IGF-1 on longevity may be unique to laboratory stocks of mice in which hundreds of generations of domestication and purposeful or inadvertent selection for growth and fecundity produced high levels of somatotrophic signaling that lead to rapid growth, early maturation and high fertility at the expense of life expectancy. Endocrine and reproductive characteristics of mice derived from animals recently caught in the wild support this possibility (Miller et al., 2002). However, the impact of GH and IGF-1 on lifespan is not limited to laboratory populations of house mice, and there is strong evidence that IGF-1 and homologous signaling is involved in the control of aging in organisms ranging from worms to mammals (details below).

GH vs. IGF-1 effects

In mice, the effects of mutations influencing GH secretion or actions on longevity are greater and more consistent than the effects of mutations that directly impact IGF-1

signaling. For example, longevity is significantly increased in both sexes of GH resistant *Ghr* ^{-/-} mice maintained in different laboratories on different genetic backgrounds and different diets (Coschigano et al., 2003; Bartke et al., 2004; Bonkowski et al., 2006) while extension of longevity in partially IGF-1-resistant *Igf1r* ^{+/-} and IGF-1 hypomorphic *Midi* mice is limited to females (Holzenberger et al., 2003; Sell and Lorenzini, 2007) and, in *Igf1r* ^{+/-} mice on a long-lived genetic background, male longevity is reduced rather than increased (Richardson, personal communication). Moreover, while complete disruption of GH signaling produces a long-lived mouse (Brown-Borg et al., 1996; Flurkey et al., 2001; Coschigano et al., 2003), complete disruption of IGF-1 signaling is lethal or detrimental (Liu et al., 1993). It must be concluded that at least some of the mechanisms by which GH influences longevity are unrelated to reduction of peripheral IGF-1 levels. Effects of GH on insulin signaling and on production of adiponectin and other secretory products by fat cells are among the most likely candidate mechanisms linking GH and aging independently of IGF-1. Further studies in animals with altered local availability of IGF-1 (Conover and Bale, 2007) or disruption of somatotrophic signaling in specific organs or cell types (as in LeRoith et al., 2008; Taguchi et al., 2007; Kappeler et al., 2008) should clarify the mechanisms by which GH and IGF-1 influence aging.

How mutant mouse data fit into the “big picture”

Extended longevity of mice with reduced activity of the somatotrophic axis complements the results of elegant studies in invertebrates showing that reduced IGF-1 /insulin-like signaling in these animals increases lifespan, often very dramatically (Tatar et al., 2003; Kenyon, 2005; Piper et al., 2008). In fact demonstration of homology of the key “longevity gene” in *Caenorhabditis elegans*, *daf-2* with mammalian IGF-1 and insulin receptor genes (Kimura et al., 1997) was followed by elucidation of conserved genetic mechanisms of aging that extend from yeast to mammals. Diminutive phenotype of most of the long-lived mouse GH/IGF-1 related mutants fits very well with the negative correlation of longevity with adult body size in genetically normal mice (Rollo, 2002; Miller et al., 2002) as well as in rats, dogs, horses and, in many comparisons, also in humans (Rollo, 2002; Patronek et al., 1997; Greer et al., 2007; Brosnahan and Paradis, 2003; Samaras, 2007).

However, these findings are difficult to reconcile with the thoroughly documented age-related decline in GH and IGF-1 levels in all mammals studied to date (Sonntag et al., 1980; Crew et al., 1987; Müller et al., 1993; Veldhuis et al., 1997) and with numerous reports of reversal of age related changes in body composition and various functional parameters by therapy with GH, GH secretagogues or IGF-1 (Rudman et al., 1990; Welle et al., 1996; Khan et al., 2001; Sonntag et al., 2005; Roy et al., 2007). Although species differences may contribute to or perhaps even account for some of these discrepancies, more likely explanations are related to the divergent physiological roles of GH during different stages of life history and its relationship to longevity within the framework of the concept of antagonistic pleiotropy. Long-term survival presumably confers little or no reproductive and thus evolutionary advantage. Therefore, robust somatotrophic signaling early in life may have been selected for as a promoter of sexual maturation and reproductive fitness, regardless of the “costs” in terms of longevity and age-related disease.

Will growth hormone find legitimate use in anti-aging medicine?

Similarly to other alterations of endocrine function during aging, it is difficult to decide whether reduced activity of the somatotrophic axis should be viewed primarily as a symptom or a mechanism of aging. It could also be argued that the age-related decline in GH secretion constitutes a natural protection from insulin resistance and cancer or perhaps activation of survival mechanisms (Bartke, 2003; Shechter et al., 2008) rather than simply reflecting a progressive failure of the hypothalamus-somatotrope axis.

Congenital GH deficiency and resistance lead to obesity and have been traditionally considered as serious risk factors for cardiovascular disease, but recent studies uncovered unexpected protection from atherosclerosis (Schumacher et al., 2008; Oliveira et al., 2007) and the impact of these endocrine syndromes on longevity remains controversial (Krzisnik et al., 1999; Besson et al., 2003; Laron, 2005). Studies of anti-aging interventions further fuel these controversies. While suppression of somatotrophic signaling and circulating IGF-1 levels have long been considered among likely mechanisms by which calorie restriction (CR) delays aging and extends life, recent studies indicate that both short- and long-term CR in humans improves numerous aging-related risk factors without reducing either GH or IGF-1 levels (Redman et al., 2008; Fontana et al., 2008).

When viewed against this background, it is not surprising that opinions about the potential use of GH or GH secretagogues as anti-aging agents differ widely and are highly controversial. Data from well designed clinical studies reported to date indicate unfavorable risk:benefit ratio for treatment of endocrinologically normal elderly subjects with GH (Blackman et al., 2002; Liu et al., 2007). Prescribing GH to individuals who are not GH deficient in an attempt to slow aging is not supported by the available evidence, is not included among its approved uses and, in the US, is specifically disallowed. Increasing IGF-1 levels is believed to be risky, and inhibitors of IGF-1 signaling are presently undergoing clinical trials as therapy for different types of cancer.

Nevertheless, the use of GH as an anti-aging medication continues to be commercially promoted, and it is believed to be widespread in many countries. Numerous clinical and animal studies support the ability of GH to increase muscle mass (although strength is not affected), reduce adiposity and improve various aspects of cardiac function and brain blood supply (Rudman et al., 1990; Welle et al., 1996; Khan et al., 2001; Sonntag et al., 2005; Papadakis et al., 1996; Le Corvoisier et al., 2007; Giovannini et al., 2008), but more data are needed to develop a well-informed consensus on the potential utility of GH in geriatrics. Some of the available information supports a very intriguing possibility that judicious use of low doses of GH, ghrelin analogs or other GH-releasing agents may find its place in legitimate medical practice as a treatment of sarcopenia or for other age-associated indications (Giovannini et al., 2008; Mekala and Tritos, 2009; White et al., in press; Nass et al., in press OR Thorner et al., in press).

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