Growth hormone (GH)–releasing hormone and GH secretagogues in normal aging: Fountain of Youth or Pool of Tantalus?

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Abstract: Although growth hormone (GH) is primarily associated with linear growth in childhood, it continues to have important metabolic functions in adult life. Adult GH deficiency (AGHD) is a distinct clinical entity, and GH replacement in AGHD can improve body composition, strength, aerobic capacity, and mood, and may reduce vascular disease risk. While there are some hormone-related side effects, the balance of benefits and risks is generally favorable, and several countries have approved GH for clinical use in AGHD. GH secretion declines progressively and markedly with aging, and many age-related changes resemble those of partial AGHD. This suggests that replacing GH, or stimulating GH with GH-releasing hormone or a GH secretagogue could confer benefits in normal aging similar to those observed in AGHD – in particular, could reduce the loss of muscle mass, strength, and exercise capacity leading to frailty, thereby prolonging the ability to live independently. However, while most GH studies have shown body composition effects similar to those in AGHD, functional changes have been much less inconsistent, and older adults are more sensitive to GI1 side effects. Preliminary reports of improved cognition are encouraging, but the overall balance of benefits and risks of GH supplementation in normal aging remains uncertain.

Keywords: growth hormone, growth hormone-releasing hormone, growth hormone secretagogues, aging, sarcopenia, frailty

Introduction

Frailty in the elderly is a syndrome of progressive loss of strength and aerobic capacity that can increase the risk of falls and their complications, and leads in part to this functional decline. The result is the need for costly home-based or institutional support in the rapidly growing part of the population older than 80 years (Merriam et al 2002, 2003). Sarcopenia, or loss of muscle mass, leads to this progressive functional decline. Growth hormone (GH) also declines with age, and the findings in frail elders are similar in many ways to those signs and symptoms found in younger adults with GH deficiency (AGHD). Replacement of GH or stimulation of GH secretion with GH-releasing hormone (GHRH) or other GH secretagogues (GHS) would thus seem to be an appealing option to delay the onset of frailty in older adults and to prolong the capacity for independent living; but the balance of pros and cons is not necessarily the same as in AGHD. This review describes the components of the GH axis and their actions, compares and contrasts normal aging with AGHD; and summarizes GH replacement and the use of GHRH and GHS in these contexts.

Principal components of the growth hormone axis

GH is the most abundant pituitary hormone, accounting for 10% of pituitary dry weight (Merriam et al 2002). It plays an important metabolic role in adult life as

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per day, each lasting about 90 minutes and separated by 120 minutes. Peak GH secretory activity occurs within an hour after the onset of deep sleep (Melmed 2006). With increasing age, GH pulse amplitude is markedly reduced, and there is a loss of the nocturnal GH increase, but the number of GH pulses does not change greatly (Ho et al 1987). This secretion is modified by age and sex in addition to the stimuli mentioned above (Molitch et al 2006). GH, in turn, stimulates the synthesis of insulin-like growth factor-I (IGF-I), which mediates many of GH's effects and is a potent inhibitor of GH secretion (Merriam 2002). GH has some direct effects as well via GH receptors present on the surface of many cell types (Cummings and Merriam 2003). Circulating IGF-I is synthesized mainly in the liver, but IGF-I is also locally generated in target tissues. The inhibition of IGF-I production can create a syndrome of relative GH resistance, causing increased GH secretion with decreased GH effects. Examples include fasting, malnutrition, and oral estrogen therapy (Merriam 2002).

GH promotes lipolysis and inhibits lipogenesis, with a resultant redistribution of fat. It inhibits the conversion of cortisone to the active glucocorticoid cortisol, accelerates the conversion of l-thyroxine to the more biologically active triiodothyronine (Cummings and Merriam 2003), and exerts antinatriuretic effects by stimulating renal tubular sodium-potassium pumps and facilitating the renin-angiotensin-aldosterone system (Merriam and Cummings 2003). GH influences bone physiology after linear bone growth has ceased, and is anabolic toward bone and muscle. It contributes to an increase in overall energy expenditure by stimulating protein synthesis and fat oxidation (Cummings and Merriam 2003). GH also enhances intestinal absorption of calcium and phosphate, vitamin D activity, renal tubular phosphate reabsorption, osteoblast proliferation, and synthesis of DNA and procollagen mRNA in bone (Merriam and Cummings 2003).

Normal aging vs adult growth hormone deficiency

GH secretion rates decline exponentially from a peak of about 150 µg/Kg/day during puberty to about 25 µg/Kg/day by age 55 (Melmed 2006). In this process there is a reduction in GH pulse amplitude, but little change in GH pulse frequency (Merriam et al 2003). There is a particularly marked decline in sleep-related GH secretion, resulting in loss of the nocturnal pulsatile GH secretion seen in younger individuals and lack of a clear night-day GH rhythm (Figure 2) (Ho et al 1987; Merriam et al 2000). It seems that the age-related decline in GH is not the cause of the decline in slow-wave sleep (SWS), however, since in most studies administering GH or GHRH does not enhance SWS in seniors (Vitiello et al 2001). The decline in GH production parallels the age-related decline in body mass index and is associated with alterations

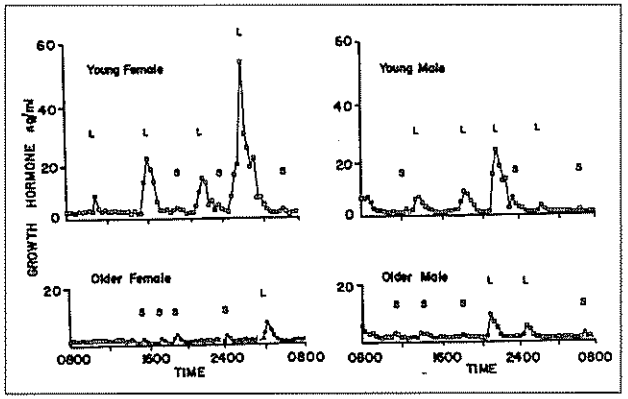

Figure 2 Patterns of GH secretion in younger and older women and men. There is a marked age-related decline in GH secretion in both sexes and a loss of the nighttime enhancement of GH secretion seen during deep (slow-wave) sleep. This decrease is primarily due to a reduction in GH pulse amplitude, with little change in pulse frequency. L = large GH pulses, S = small GH pulses. From Ho et al 1987.

with improved scores in several domains of fluid (but not crystallized) intelligence – those measures previously found correlated with circulating IGF-1 levels (Vitiello et al 2006). This intriguing preliminary finding is now being studied more systematically at the University of Washington in a new NIH-funded study (the Somatotrophics, Memory, and Aging Research Trial, or "SMART").

Thus as with GH, there is a consensus on hormonal and body composition effects but inconsistent functional effects on function; and in addition there is a very encouraging but still unconfirmed positive effect on some domains of fluid intelligence.

Ghrelin, which is produced in the stomach and increases during periods of fasting or under conditions associated with negative energy balance (such as starvation or anorexia), acts at both hypothalamic and pituitary levels via mechanisms distinct from GHRH, and thus has different effects from GHRH or GH; subjects often gain weight and do not lose, or even gain body fat) (Merriam et al 2000, 2002; Liddle 2006). The effects of ghrelin on GH secretion depend in part on the presence of GHRH; and thus if GHRH secretion declines with aging, ghrelin's effects may be blunted. While the effects of these two GHS differ clinically, they have synergistic effects on GH release, and therefore supplementation of both substances may be more effective than either alone in aging (Merriam et al 2000, 2002). Additionally, there are other substances which can enhance GH response to GHS by suppressing somatostatin secretion, including arginine and beta-adrenergic antagonists, which could potentially enhance treatment effects (Merriam et al 1997).

Several studies have shown short-term effects of GHS on GH secretion, but so far only three groups have conducted studies of their chronic effects in normal aging. Bowers and colleagues showed that chronic repeated injections or subcutaneous infusions of GH-releasing peptide-2 (GHRP-2) could stimulate and maintain increases in episodic GH secretion and IGF-1 (Bowers et al 2004). Thorner and colleagues at the University of Virginia have conducting a study of two years' oral treatment with the non-peptidyl GHS MK-677. As with previous studies, there was a sustained increase in IGF-I and episodic GH secretion, and an increase in lean body mass (Thorner et al 2006). Preliminary functional results over one year of treatment, recently reported at an abstract presentation, however, did not show significant improvements.

In cooperation with investigators at Duke University and several other sites, we conducted a trial of the Pfizer investigational oral GH capromorelin in pre-frail older men and women (Merriam et al 2006). This protocol recruited over 300 subjects and was initially planned as a two-year intervention. The study was unfortunately stopped, however, after all subjects had been treated for 6 and many for 12 months, due to failure to see an increase in per cent lean body mass, which was a pre-set non-efficacy termination criterion. Absolute lean body mass did increase significantly, but due to the appetite-stimulating effect of this ghrelin mimetic – unforeseen in early 1999 when the study was designed and ghrelin was still unknown – subjects also gained weight (about 1.5 Kg) and this washed out the effect on per cent lean body mass. However, even this truncated study is currently the largest clinical trial of chronic GHS treatment in aging. It showed the expected increases in IGF-I levels and (as noted) total lean body mass. There were also encouraging effects on physical functional performance. Of seven functional tests, one improved significantly after 6 months of treatment, and another after 12 months. Two other measures showed non-significant trends toward improvement, and the three remaining measures showed no effect. Effects on clinical endpoints such as falls could not be assessed with this relatively brief duration of treatment. Side effects were generally mild, including increases in fasting blood sugar within the normal range. Interestingly, there was a self-reported deterioration of sleep quality, though formal sleep testing was not performed. Cognition was not studied in this trial.

Thus as with GH and GHRH, reports of the hormonal and body composition effects of ghrelin mimetic GHS in normal aging are relatively consistent, but there is no consensus on functional effects among these very few studies, and of course none could assess clinical final outcomes or long-term risks.

Conclusion

Sarcopenia and subsequent frailty lead to loss of independence. While aging is not a disease, it results in significant body composition and functional changes which affect the individual and the community at large. Aging represents a milder form of adult GHD, and GH replacement in GHD has met with success. Since the aging pituitary remains responsive to GH and GHS, it is reasonable to suggest that GH replacement or stimulation might be indicated in aging. However, elders are more sensitive to GH, and thus more susceptible to the side effects of replacement. Stimulating GH with GHS instead of GH replacement has the advantage of a more physiological approach to increase endogenous GH pulsatility with theoretically decreased risk for side effects (Arvat et al 2000).

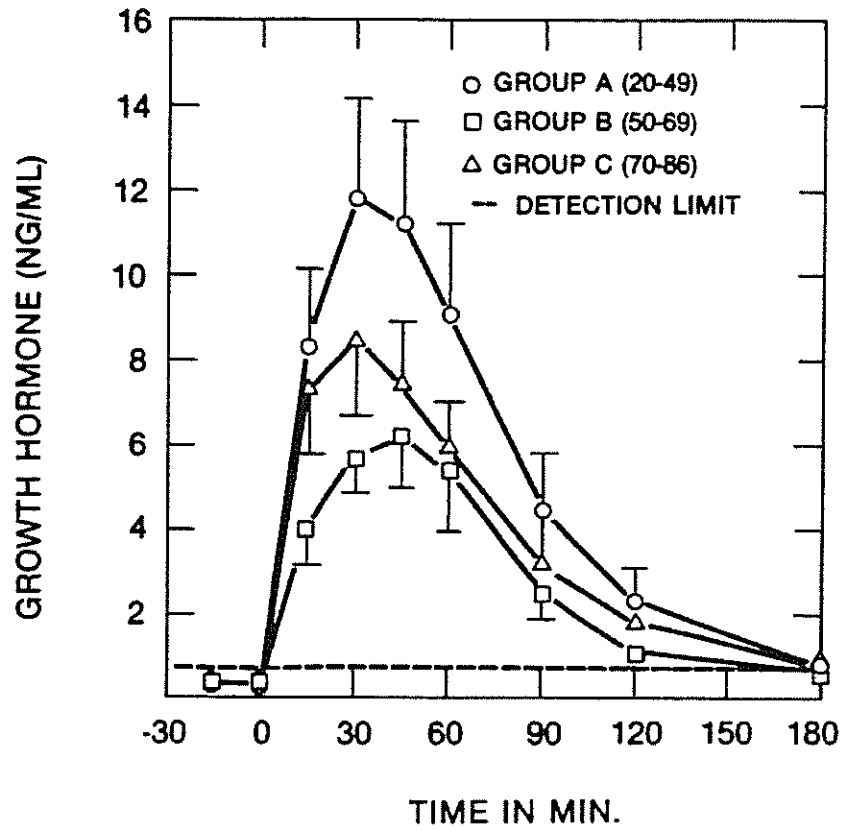

Figure 3 Effects of a single intravenous bolus of GHRH on GH secretion in healthy subjects of different ages. While the highest responses are seen in young adults, there is no significant decrease with aging, and pituitary GH responses are well preserved even in the oldest subjects. From Pavlov et al 1986.

the FDA approved the use of GH in GHD adults (Merriam and Cummings 2003; Molitch et al 2006). GH replacement in AGHD has been successful in reversing many structural and functional abnormalities in the condition (Table 2) (Merriam 2002; Molitch et al 2006). The benefits and risks of GH replacement in AGHD have been documented in more than 1000 publications (Cummings and Merriam 2003; Merriam et al 2003). While dosing was initially derived from pediatric practice, doses appropriate for growing children produced severe side effects in adults and were rapidly reduced. Over time, weight-based dosing as used in pediatrics gave way to the current adult practice of beginning with a low fixed dose unlikely to produce side effects, with subsequent dose titration until either an age- and gender-appropriate level of IGF-I or side effects are encountered. This titration must be conducted particularly carefully in older adults, who are more susceptible to adverse effects.

Since aging is a milder GH-deficient state than AGHD, GH replacement seems a potentially reasonable approach to prevention or even reversal of the frailty symptoms of aging. The first studies in non-GHD older adults took place soon after its effects in AGHD were published. In a widely cited