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Growth Hormone Releasing Hormone Treatment in Normal Aging

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ABSTRACT

Because the aging pituitary remains responsive to stimulation by growth hormone (GH) secretagogues—GHRH, ghrelin, and their mimetics—these compounds could potentially be used instead of GH itself to increase GH secretion in aging. The factors contributing to the age-related decline in GH secretion are largely extrapituitary, and with repeated or continuous administration GHS's can significantly increase GH secretion and elevate levels of insulin-like growth factor–I (IGF-I) to the young adult normal range. Treatment with GHS's has both theoretical and practical potential advantages over GH—preserving feedback regulation by IGF-I to buffer against overtreatment, and yielding a more physiologic pulsatile pattern of GH secretion. Nonpeptide GHS's can also be administered orally. This review focuses primarily on results using GHRH; studies with ghrelin agonists are reviewed in detail in other articles from this symposium. We and others have shown that GHRH stimulates the brisk release of GH in healthy seniors, and that repeated administration of GHRH elevates IGF-I in a dose-dependent manner. In two 6-month treatment studies in healthy older women and men, subcutaneous injections of GHRH(1–29)NH_2, self-administered once nightly, chronically increased nighttime GH secretion and produced sustained elevations of IGF-I levels. IGF-I increases were greatest in men, averaging 30%. Women not taking estrogen showed somewhat lesser increases (23%), and women taking oral estrogen replacement had no significant increase despite the greatest increments in GH secretion. Lean body mass increased; body fat was reduced by an average of 5–8%, with greatest effect on abdominal visceral fat; and again this effect was blunted in estrogenized women. Effects on physical function varied by group. In nonestrogenized women, physical function deteriorated in those receiving placebo; some measures were stabilized in women receiving GHRH. These changes were not significant in estrogenized subjects. GHRH appeared to improve cognitive function, especially in domains sensitive to changes in processing speed. The formulation of GHRH used in these studies is short-acting, with effects ending within a few hours. Perhaps for this reason, late-night GH secretion decreased after the initial GHRH-stimulated surge, and sleep quality was not improved. Side effects were those of fluid retention and were generally mild. The duration of these studies do not allow inferences to be drawn on prevention of the onset of clinical features of frailty. Thus, 6-month treatment with once-daily GHRH can elevate GH secretion and IGF-I, and improve body composition in a manner similar to the effects of GH. Effects on physical function are equivocal. Effects on cognition are encouraging but preliminary. The current GHRH formulation is too short-acting to provide optimal effects.

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INTRODUCTION

MOST STUDIES OF THE EFFECTS of growth hormone (GH) in aging and in GH deficiency have been conducted using GH itself as the treating agent. Because the aging pituitary remains capable of synthesizing and secreting increased amounts of GH if appropriately stimulated, several recent studies have examined the effects of administering GH secretagogues (GHS's)—factors which stimulate GH secretion—as an alternative to GH itself. These factors include the various forms of GH-releasing hormone (GHRH), and also compounds which mimic the action of a second endogenous GHS, ghrelin. Such an approach could potentially have both theoretical and practical advantages over GH. The number of studies of GHRH and ghrelin mimetics in normal aging is still very small, however, and this use of GH secretagogues has not been approved by regulatory agencies in any country. This article primarily reviews available studies of GHRH and its agonist analogs in aging.

Muscle mass, strength, and aerobic capacity all decline progressively with aging. The loss of muscle mass (referred to as sarcopenia) and the reduction in strength increase the risk of falls and their complications. For many individuals, the loss of physical functional capacity leads to increasing difficulty and eventual inability to carry out the tasks needed to live independently, a state generally termed "frailty." Once it becomes too difficult for the individual to care for him/herself, outside assistance is required either in the home or in an institutional setting, with the extent and cost of necessary support increasing as frailty becomes more severe. As the age group >80 years now represents the most rapidly growing segment of the U.S. population, the burden of this support is increasing dramatically.

Interventions that could maintain or if possible improve functional capacity can at least theoretically prolong the capacity for independent living, and therefore interest in their potential utility is also growing rapidly. While some interventions, such as regular exercise programs and lifestyle modifications, are nonpharmacologic, there is also strong interest in a variety of trophic factors which might stabilize or reverse these age-related declines. Estrogen replacement therapy (ERT) following menopause, which is the model for these trophic factor interventions, has proven effective in the prevention of osteoporotic fractures, although its effect on muscle strength is slight, and may improve or stabilize cognition. However, these benefits are achieved at the cost of an increased risk of reproductive cancers. Estimating the relative risks and benefits of ERT for varying groups of seniors has required a large number of studies over many years of research, and debate still continues.

The two other classes of trophic factors currently undergoing the most intense scrutiny are androgens and GH. As with estrogen, levels of these hormones rise rapidly at puberty, remain high during early adulthood, and then decline progressively with aging. However, data relating to their effects in normal aging are much sparser than is the case for estrogen. Thus, the use of GHRH or other GHS's in aging is embedded in the broader question of whether increasing GH by whatever means is of net benefit to any group of older adults.

MECHANISMS OF THE SOMATOPAUSE

GH is the most abundant pituitary peptide, accounting for some 10% of pituitary dry weight. However, normal GH synthesis and secretion are dependent upon hypothalamic stimulation, and when this stimulation is removed, GH secretion falls to low levels. The observation that sectioning the pituitary stalk abolishes spontaneous GH secretion, made by Reichlin and colleagues,[1] showed that the hypothalamic control of GH is dominantly stimulatory. For technical reasons, however, the first GH-regulating hypothalamic peptide to be characterized was somatostatin (SRIF), which inhibits GH secretion. Subsequent studies have shown that hypothalamic control is exerted through at least three peptide systems, as shown in Figure 1—SRIF, which inhibits GH secretion; GH-releasing hormone (GHRH); and a second secretagogue, ghrelin, characterized in 1999.[3] The existence of this second endogenous secretagogue had been postulated after Bowers and colleagues described a series of

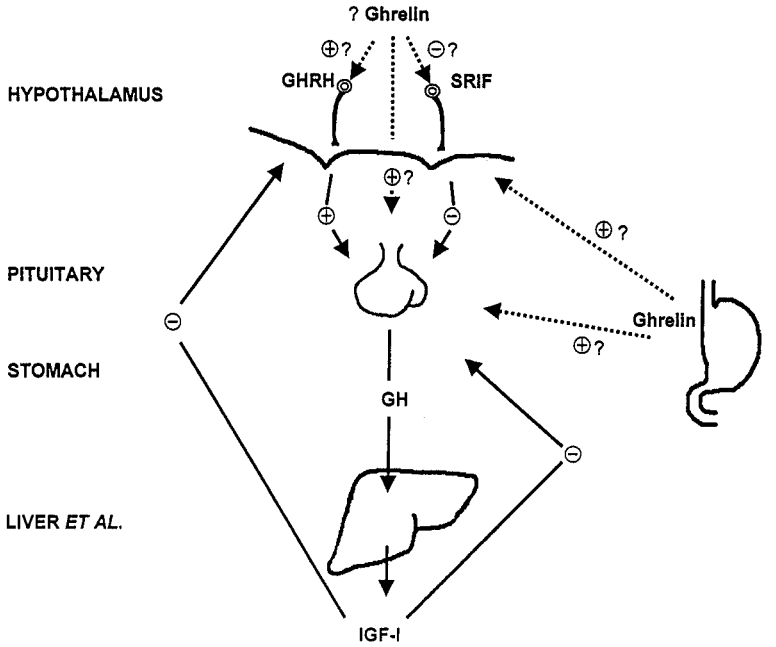

FIG. 1. Proximal regulation of GH secretion. GHRH, somatostatin, and ghrelin are all brain-gut peptides, and their circulating levels reflect primarily reflect extrahypothalamic sources. For GHRH, hypothalamic secretion is the major determinant of normal GH secretion, while for ghrelin—found in highest concentration in stomach—the relative roles of gastric versus central secretion are still uncertain. (Reproduced with permission from Anawalt and Merriam.[2])

enkephalin derivatives, GH-releasing peptides (GHRPs), which stimulated GH secretion but did not bind to the GHRH receptor and synergized with GHRH actions.[4] Smith and colleagues identified a specific receptor which bound GHRPs and their analogs,[5] but the endogenous ligand remained elusive until it was finally characterized as an acylated 28 amino acid peptide, with an octanoyl side group that is obligatory for biological activity—perhaps the reason that it so long escaped identification.[6] Bowers has speculated that some of the actions of ghrelin and GHRPs might best be explained by the intermediation of a further, still uncharacterized, U-factor, but this remains controversial. Ghrelin is found in highest concentrations in the oxyntic glands of the stomach, and gastric ghrelin appears to account for circulating ghrelin immunoreactivity. Hypothalamic ghrelin has a very low abundance and very restricted distribution, and some have questioned whether it is synthesized in hypothalamic neurons at all.

Somatostatin, GHRH, and ghrelin in turn are the final common pathway for integration of a variety of physiological controls of GH secretion. GH levels increase during sleep, particularly deep or slow-wave sleep (SWS), so that in younger adults the majority of GH secretion occurs while sleeping. (It remains unclear whether sleep stimulates GH, or vice versa, or if both are stimulated by GHRH, ghrelin, or higher regulatory factors.) GH release can also be triggered by exercise, protein intake, low blood sugar, stress, and a variety of drugs, while high glucose levels suppress GH secretion.[7] The combined influences of these systems yield a pulsatile pattern of GH secretion in peripheral blood (Fig. 2).

GH exerts its effects by binding to its own receptor as well as by stimulating the synthesis of insulin-like growth factor–I (IGF-I). The liver is the primary contributor to levels of IGF-I in the systemic circulation; but IGF-I is generated in many GH target tissues, and local effects may be more important than those of circulating IGF-I of hepatic origin. Indeed, two knockout mouse strains in which hepatic IGF-I synthesis was eliminated appear to grow normally.[8,9]

Although pulsatile GH secretion continues with aging, the pattern changes, with a diminished amplitude of GH pulses[10] (Fig. 2). In particular, nighttime GH secretion declines, so that

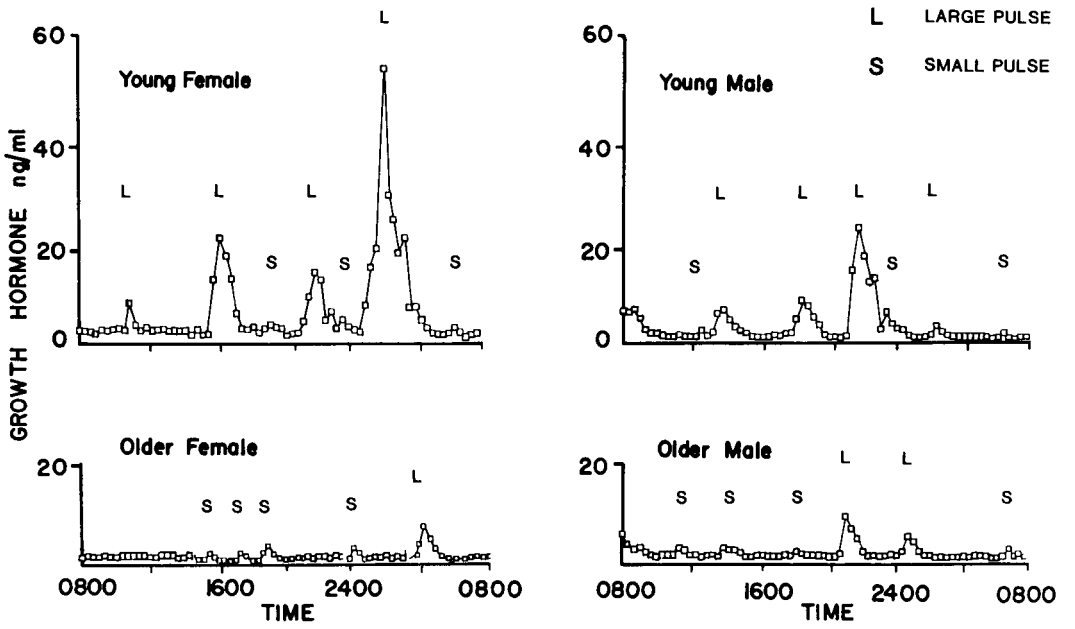

FIG. 2. Changes in the pattern of episodic GH secretion with aging in normal men and women. The decline in GH secretion is due largely to a decrease in GH pulse amplitude, especially during sleep, with little change in pulse frequency. (Reproduced with permission from Ho et al.[10])

often there is no longer a clear night–day GH rhythm. SWS also declines with aging, although it is unclear whether the GH decline is due to the reduction in SWS, whether SWS deteriorates because of the decline in GH, or whether both are decreased because of a common reduction at a higher level of regulation.[11]

A variety of mechanisms could potentially underlie this decline in GH secretion with aging. This could be the result of a reduction in GHRH, ghrelin, or both, or in putative mediators. Somatostatin secretion could be increased; and/or the pituitary could become either less responsive to stimulation or more sensitive to negative feedback suppression by IGF-I or other regulators. While a combination of factors appears to be at work, current evidence points away from the latter two possibilities. Graded infusions of IGF-I inhibit GH secretion in older subjects with approximately the same ED_{50} as in younger adults,[12] and Pavlov et al. have shown that the pituitary remains responsive to GHRH stimulation, at least in very healthy older subjects[13] (Fig. 3). By exclusion, a part of the decline in spontaneous GH secretion may thus be ascribed to a relative deficiency of endogenous GHRH and/or ghrelin. Others have shown that, in overweight or less tightly screened subjects, the GH response to GHRH does decrease with aging, and this is compatible with an increase in somatostatin tone. Simultaneous administration of the amino acid arginine, which inhibits somatostatin among other effects, enhances the GH response in older adults.[14]

Thus, current evidence suggests that in most individuals the decline in GH is multifactorial, with a decrease in GHRH and/or ghrelin activity and an increase in somatostatin, and is due to changes in pituitary stimulation and not to an intrinsic loss of pituitary capacity to secrete GH. Because of this, stimulation with GHRH or other GHS's is a potential alternative to replacement with GH itself in normal aging.

ADULT GROWTH HORMONE DEFICIENCY: A MODEL AND A PRECEDENT

If GH concluded its important physiological functions with the completion of skeletal maturation, then its decline with aging would not be associated with significant clinical consequences. However, it is now known that GH continues to play an important role in adult life,

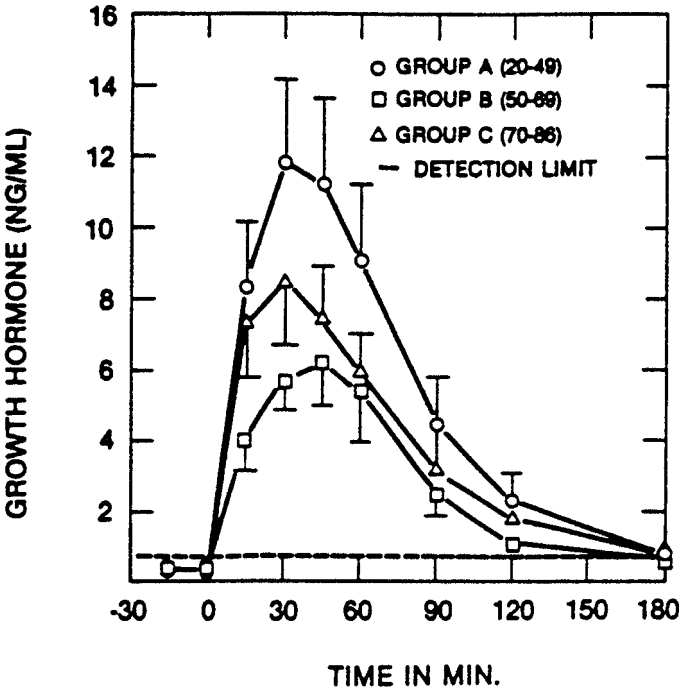

FIG. 3. GH responses to the acute intravenous administration of GHRH in subjects of different ages. In these healthy participants in the Baltimore Longitudinal Study of Aging, GH responses were sustained even in the oldest age group. (Reproduced with permission from Pavlov et al.[13])

and adults with frank GH deficiency manifest a clinical syndrome that can respond dramatically to GH replacement. The intensifying interest in GH in aging stems from parallels between normal aging and the adult GH deficiency syndrome.

GH is a partitioning hormone, supporting the growth and function of both skeletal and cardiac muscle as well as promoting lipolysis. GH-deficient adults have reduced muscle mass and increased fat, particularly abdominal visceral fat, with decreased strength and aerobic capacity. GH deficiency is also associated with an atherogenic lipid profile, with an increase in total and LDL cholesterol and a doubling of cardiovascular mortality. Bone mineral density is decreased, the skin is thinned, sweating is reduced, and lowered self-esteem and depression are often observed.[15]

The effects of GH replacement in GH-deficient adults have been documented in more than 1,000 published studies. Lean body mass, strength and aerobic capacity are increased, along with a reciprocal reduction in body fat. Cholesterol decreases, and in studies lasting more than 12 months, bone mineral density increases; an effect on fracture rates has not yet been reported. Self-reported levels of energy and vigor increase. Side effects are usually those of hormonal excess—fluid retention with peripheral edema, arthralgias, and (uncommonly) headaches due to increased intracranial pressure. These respond rapidly to a reduction in dosage. Despite speculation that as a growth factor GH might promote the growth of breast, prostate, or other cancers, no increase in cancer risk in GH-treated subjects has been observed. These clinical effects and the relative safety of GH led to its approval by the U.S. Food and Drug Administration (FDA) for continued treatment of GH-deficient patients throughout their lives.

AGING AS A PHENOCOPY OF GROWTH HORMONE DEFICIENCY: SIMILARITIES AND DIFFERENCES

Despite the similarities between aging and GH deficiency (GHD), the two states clearly differ. While GH secretion and physiological responses in older adults may resemble those

seen in younger GHD patients, they are higher than in age-matched patients with GHD.[16] Thus, aging is a milder state of relative GH deficiency than classical GHD. Also, older adults are more sensitive to GH side effects than are children or young adults. Early studies of adult GHD using pediatric doses invariably produced side effects, and currently most adults with GHD are treated with weight-related doses that are five to 10 times lower than those used for children. This suggests that even lower dosages of GH might be appropriate in normal aging.

Finally, aging is not a disease. As reasonable as the hypothesis might be, therefore, one cannot a priori conclude whether the age-related decline in GH is maladaptive and should be treated, or rather considered an appropriate adaptation to this stage of life. For example, while it seemed equally appropriate to postulate that the anabolic activity of GH should be beneficial in critical illness, in fact GH proved to have seriously detrimental effects. Thus, while results in GHD are suggestive and support further research on GH in aging, the relative benefits and disadvantages of GH replacement or stimulation in normal aging must be considered on their own merits.

GROWTH HORMONE EFFECTS IN NORMAL AGING

While the literature on adult GHD is extensive, it is unfortunate that very few controlled prospective studies have been conducted on the effects of GH and GH secretagogues in aging. In a groundbreaking study published in 1990, Rudman and colleagues treated 21 men aged 61–81 years with GH or placebo for 6 months, using doses sufficient to raise IGF-I levels to those of normal men in their twenties[17] (30 mcg/kg three times weekly). The treatment group showed a 9% increase in lean body mass, a 14% decrease in fat, 7% increase in skin thickness, and a slight (1.6%) increase in vertebral bone mineral density. A follow-up study showed that these changes persisted over one year of treatment.[18] Other investigators have generally corroborated the overall changes observed by this group, but were unable to use similar doses due to the side effects of edema and carpal tunnel syndrome.[19–22]

Neither of the Rudman group's studies examined changes in strength or physical function, and while the alterations in body composition appear desirable, they do not suffice to support lifelong treatment with a costly injectable agent. Another group examined the effect of 6 months of treatment with GH or placebo in 52 fit older men, ages 70–85 years.[23] The results confirmed increased muscle mass and a decrease in body fat, but found no changes in hand or knee strength, or in aerobic fitness. However, this negative result was rendered somewhat inconclusive by the subjects' robust baseline performance level, which was sufficiently close to the maximum readings on several tests as to make it difficult to observe further improvement. It has therefore been suggested that a less robust, pre-frail population might show a very different outcome.

In response to Rudman's encouraging results and the dearth of controlled trials, the National Institute on Aging (NIA) invited applications for studies of trophic factor effects in aging, which led to several trials of both GH and GHS's.[24] Most of these trials have now been completed, and results are beginning to be reported in abstract form. In one 6-month double-controlled study of combined GH and sex steroid replacement in 53 women and 72 men, ages 65–88 years, the investigators initially attempted to use the doses reported by the Rudman group, but encountered significant side effects.[20–22] When the study was continued with reduced GH dosages (20 mcg/kg three times weekly), they confirmed the findings of an increase in lean mass and decreased fat mass.[20] GH increased aerobic capacity, and combined therapy with GH and testosterone in men increased muscle strength. Other reports examined the effects of GH alone or in combination with IGF-I.[19,25] In this study, GH improved body composition but not physical performance. Glucose tolerance transiently deteriorated, an expected short-term effect of GH, but then improved again, perhaps due to promotion of insulin sensitivity by the changes in body composition. Thus, there appears to be a

consensus regarding the effects of GH on body composition in aging, but not on strength, exercise capacity, or physical or psychological functional performance.

GROWTH HORMONE VERSUS GROWTH HORMONE SECRETAGOGUES IN NORMAL AGING

As noted above, the aging pituitary remains responsive to stimulation by GHRH or ghrelin analogs, so that in principle hormonal replacement could be effected with GHS's as well as by administering exogenous GH. The literature on adult GH deficiency is of little help in assessing the relative pros and cons of this approach, since most adult cases result from pituitary causes and so cannot be treated with secretagogues. However, GHRH and other GHS's potentially offer both theoretical and practical advantages.

For one, GHRH and GHRP's produce either a brief pulse of GH secretion, or a train of pulses, rather than a prolonged rise in GH levels. Even continuous infusions of secretagogues stimulate a pattern of sequential discrete pulses, generally resembling physiological pulsatile GH secretion—presumably due to changes in endogenous somatostatin or ghrelin secretion during the GHRH infusion. In other contexts, the pattern as well as the quantity of GH delivered has been found to modulate its effects.[26] Also, when a secretagogue is used, the normal negative feedback regulation by IGF-I on pituitary GH secretion is preserved, offering at least some relative buffering against overdosing. GHRH and ghrelin are synergistic in their GH-stimulating effect, and combination therapy may be more effective than the use of either one alone. Thus, GHS's might provide a more physiologic boost to GH secretion than GH itself, which is potentially important in the more brittle senior population.

GHS's also offer potential practical advantages in administration. As smaller molecules, GHRH and ghrelin analogs can potentially be delivered transnasally or even orally, avoiding the need for daily injections. For a long-term treatment directed at primary prevention of frailty, oral administration offers compelling advantages in terms of patient acceptance.

STUDIES OF GROWTH HORMONE–RELEASING HORMONE IN NORMAL AGING: ENDOCRINE EFFECTS

The report by Pavlov and colleagues that single injections of GHRH could stimulate GH secretion in healthy seniors[13] led to several early studies of the effects of short-term GHRH treatment. Most studies have used one of two variants of human GHRH. In its complete sequence, hGHRH is a 44–amino acid amidated peptide, GHRH(1–44)NH_2. The first 29 amino acids confer full biological activity, and a formulation of GHRH(1–29)NH_2 (sermorelin acetate, produced commercially as Geref®, Serono) has received FDA approval for the treatment of pediatric GH deficiency, which like normal aging is largely a condition of suprapituitary origin in which the pituitary can respond to secretagogue stimulation. GHRH(1–40)NH_2 and GHRH(1–44)NH_2 were used in some early clinical studies, and a recombinant preparation of (1–44) GHRH has been employed in some recent trials.[27] The molar potency and pharmacokinetics of these varying preparations are very similar.

In early studies, Corpas and colleagues reported that continuous infusions or twice-daily administration of GHRH increased GH secretion and IGF-I levels, while the same total dose administered once a day was considerably less effective.[28,29] Another group reported that a norleucine-27 analog of GHRH(1–29)NH_2 also produced sustained hormonal changes.[30] Elahi et al. recently reported in abstract form that administration of 1 or 2 mg GHRH(1–44)NH_2 daily for 21 days produced sustained increases in GH secretion and IGF-I levels.[27]

Unfortunately, the duration of these studies was insufficient to yield significant conclusions regarding effects on body composition or functional status. They also leave it uncertain whether GHRH can be effective when administered once daily or must be given in divided doses, and do not define the specific dose that is required for a sustained effect. The authors'

group at the University of Washington therefore undertook a short-term dose-finding study to assess the efficacy of once-daily GHRH dosing, as well as two studies of the effects of chronic GHRH(1–29)NH_2 administration on hormonal and functional endpoints in normal older adults. One recently completed study assessed the combined effects of GHRH or placebo and an exercise intervention over 6 months of treatment. The second study focuses on the effects of GHRH or placebo on sleep and cognition over 5 months of treatment. While only preliminary results have been reported to date, a few early conclusions can be drawn.

The studies of Corpas et al. raised the question of whether GHRH could provide meaningful enhancement of GH secretion when administered as a single daily dose, or whether multiple doses of this short-acting secretagogue are needed. Therefore we conducted a short-term trial of graded doses of GHRH(1–29)NH_2 in healthy older volunteers, using subcutaneous doses of 14, 28, and 56 μg/kg—approximately 1, 2 and 4 mg—or placebo, as a single daily bedtime dose. There was a clear dose–response relationship, but even the lowest dose produced a significant elevation of IGF-I (Hirth et al., unpublished data).

These results provided a dosing strategy for the two longer-term studies in healthy older men, nonestrogenized women, and women taking oral estrogen replacement therapy. In addition to the drug intervention, the first GHRH treatment study, in nonestrogenized women, also randomized subjects to three-times weekly training sessions with strength or endurance exercise, or to control stretching/flexibility sessions. The rationale for this 2×2 design was twofold: to see whether exercise might mitigate glucose intolerance caused by increased GH, and to look for interaction effects between the exercise and drug interventions on body composition and functional performance. As an extension of this latter objective, subjects who were randomized to GHRH for the first 6 months discontinued drug treatment but continued exercise conditioning for a further 6 months.

In the second study, inclusion of men and of women on ERT allowed an examination of the effects of gender and hormone replacement status on responses to GHRH, and a more detailed examination of effects on sleep and cognition. Deterioration of restful sleep is a major problem in seniors. In younger adults, GH is secreted primarily during episodes of SWS, but both SWS and GH secretion decline progressively with aging. Conflicting results have been reported from several short-term studies examining the acute effects of GHRH or other GHS's on sleep, but there is no information on whether chronic stimulation of GH affects sleep.[11]

Emerging results from these studies show that once-nightly doses of GHRH are well tolerated and can significantly enhance GH secretion and elevate IGF-I levels. They also demonstrate differences in responses among gender/estrogen replacement groups, and limitations in current GHRH formulations.

The 1-mg dose appeared to be a good initial choice, as side effects of GH excess, mainly peripheral edema and arthralgias, were uncommon. Rarely, patients reported erythema or swelling at the injection site.

In men, subjects doubled their 24-h GH secretion (Fig. 4), and experienced a 30% rise in IGF-I levels.[31] Nonestrogenized women had similar responses, with an average 23% IGF-I increase over baseline. ERT women had the most vigorous increase in GH in response to sermorelin, but despite this they showed no statistically significant IGF-I increment. These results suggest that oral estrogen replacement induces relative GH resistance. Similar results have been reported in estrogenized versus nonestrogenized adult patients with GH deficiency receiving GH replacement. In this context, transdermal estrogen replacement had a much weaker effect on sensitivity to GH replacement,[32] and it has been suggested that switching GH-deficient women from oral to transdermal estrogen would enhance the efficacy of GH treatment. There are still no data available on the relative effects of transdermal vs. oral estrogens in subjects treated with GHRH.

While Figure 4 shows that the GH response is sustained over the 6 months of injectable therapy, it also illustrates the limitations of the

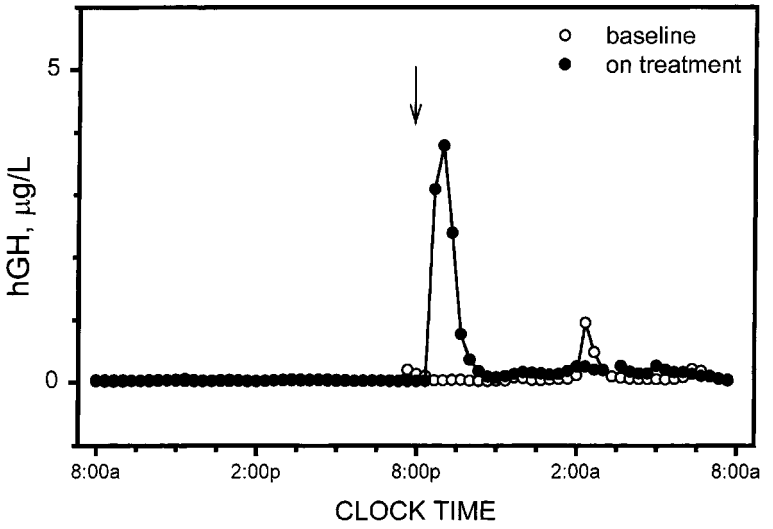

FIG. 4. Effects of chronic subcutaneous administration of 1 mg GHRH(1–29)NH_2 on the pattern of episodic GH secretion in a healthy older male. (Data from Merriam et al.[31])

current GHRH formulation. A single large burst of GH secretion was observed immediately following the evening injection. Not only was there not a full reconstitution of overnight pulsatile GH secretion, but on average late-night GH secretion was reduced compared to baseline GH profiles. This could represent temporary exhaustion of releasable GH stores following the acute supraphysiological effect, or negative feedback suppression by the increased circulating levels of IGF-I. Daytime GH secretion, while still low, was not suppressed, favoring the former explanation. The net effect of GHRH treatment is the observed near-doubling of overall GH secretion and increased IGF-I. This may suffice for peripheral effects mediated through IGF-I, but it is far from a restoration of nighttime pulsatile GH secretion, which may be required to support any possible beneficial effects on sleep quality. For this, a sustained-release formulation or analog with a duration of action of at least 8 hours will be needed.

Although exercise acutely stimulates GH secretion in younger subjects, chronic exercise did not induce or sustain the hormonal effects of GHRH. Subjects receiving placebo had no increase in IGF-I levels whether or not they exercised, and subjects receiving GHRH showed similar increments in IGF-I regardless of their exercise conditioning status. In subjects who received GHRH for the first 6 months and continued to exercise after the treatment was withdrawn, IGF-I levels rose during GHRH therapy and then returned to baseline values when it was discontinued. These observations are similar to those previously reported in studies of exercise without drug intervention—even very intensive 5 days/week regimens effected no change in circulating IGF-I.[33]

In placebo-treated subjects, IGF-I levels measured during the baseline and exit admissions were closely (±4%) reproducible, but varied much more widely (±14%) when measured monthly on an outpatient basis between the two admissions in both placebo- and sermorelin-treated groups.[34] While several factors, including activity and intercurrent illness, may contribute to this variability, the influence of dietary variation—a known modulator of IGF-I levels—likely plays a major role. Subjects were maintained on an isocaloric (weight-stabilization) diet during the two admissions at baseline and the end of treatment, but ate *ad lib* between those times. The magnitude of this variability is easily large enough to obscure significant drug-related changes in IGF-I levels in studies where diet is not controlled.

GROWTH HORMONE–RELEASING HORMONE EFFECTS ON BODY COMPOSITION AND FUNCTIONAL CAPACITY

These endocrine changes indicate that once-daily GHRH injections can stimulate significant increases in GH and IGF-I. By themselves, however, they do not support an indication for treatment unless these increases induce meaningful changes in muscle mass and functional capacity. Final results are not yet available for all these measures, but some preliminary observations can be made at this time.

Body composition measured by whole-body DEXA scans showed an approximately 8% decrease in percentage body fat in men and nonestrogenized women, with a reciprocal 4% increase in lean body mass.[31,35] As the body composition effect is also blunted in ERT women, it appears that oral estrogen induces a resistance to GH action beyond its effects on circulating IGF-I.[36] This blockade is qualitatively similar to the effect seen in ERT GH-deficient women being replaced with growth hormone.[32]

In these studies, physical function was assessed by both standard measures of strength and a continuous-scale physical functional performance (PFP) test developed at the University of Washington.[37] In contrast to functional measures aimed at nursing-home residents, this test was designed to assess the higher capabilities of subjects living independently. It measures lower and upper body strength, balance and coordination through a series of timed tasks that resemble those of daily life—such as carrying shopping bags, or getting on and off a bus—which subjects are asked to perform as quickly as they can safely do so. Longitudinal assessment over periods as short as 6 months shows a progressive deterioration in PFP which is not clinically apparent.

PFP results remain very preliminary. In nonestrogenized women, the effects of GHRH appear to vary by specific task, some showing improvement in the actively treated group and no change in those receiving placebo, while others show no change with GHRH and deterioration with placebo.[35] In estrogenized women, there appears to be no drug effect.[36]

Measures of sleep and cognitive function are also tentative at this time, with no clinically apparent improvement in sleep quality or delta sleep energy. This may relate to the short duration of action of the GHRH formulation used, as any direct effects may have dissipated with a few hours of the evening injections. However, there are strong suggestions of improvement in certain cognitive measures in the GHRH-treated group compared to placebo. Subjects showed significant improvement compared to placebo in WAIS digit symbol substitution (5%, $p < 0.05$), finding A's (7%, $p < 0.05$), and the single-dual task (7%, $p = 0.04$).[38] These are tasks involving perceptual and psychomotor processing speed, which is known to decline with age.[11] Earlier studies have pointed to a correlation between cognitive function and circulating levels of IGF-I,[39,40] but there are many possible reasons for such a correlation, including nutritional status and general health. These preliminary observations suggest that a specific intervention which elevates IGF-I can also alter cognitive function in normal aging.

USE OF GHRELIN AGONISTS IN AGING

While this review focuses on the effects of GHRH and its analogs, in principle it appears likely that some of the same results could be produced with chronic administration of ghrelin or its mimetics. Two classes of ghrelin agonists were developed before the natural ligand was clearly identified—small peptides called GH-releasing peptides (GHRP's), the GH-releasing activity of which led to the search for the receptor and then the endogenous ligand; and non-peptide GHSs which are orally active. Several studies have shown that GHRPs acutely stimulate GH secretion, and when administered chronically can increase IGF-I.[4,41] Oral administration of the non-peptide GHS's yields longer-lasting effects which can induce pulsatile GH secretion for several hours after being administered, and also increases IGF-I.[42] Most reported GHS studies have been conducted with the analog MK-0677, commercial development of which has been suspended. A study of 2-year administration of MK-0677 remains in progress at the University of Virginia.[41a] Other peptide nonpeptide GHS's are currently in early clinical trials, and several recent re-

views provide a more detailed discussion of these ghrelin analogs.[43,44]

It should not be assumed, however, that the clinical effects of using ghrelin or analogs would be precisely homologous to those of GHRH or its analogs, even if titrated to equivalent amounts and patterns of GH stimulation. While this may be true for those effects that are strictly GH-mediated, ghrelin is also active in separate hypothalamic pathways which may modulate very different effects upon appetite and metabolism. Animals given repeated doses of ghrelin, or the ghrelin mimetic ipamorelin, for example, gain weight and body fat,[45,46] a very different effect from that of GH or GHRH, where fat mass is decreased. GH-deficient children given the ghrelin agonist GHRP-2 for 1 year reported marked increases in appetite.[47] Thus, the overall clinical effects of GHRH and ghrelin-mimetic GHS's may differ significantly.

The effects of ghrelin on GH secretion also appear to depend in part on the presence of GHRH, and the effects of two classes of GHS on GH release are synergistic. If secretion of both endogenous ligands decreases with aging, full reconstitution of GH secretion may be best accomplished with dual therapy, and the synergy may allow maximal effectiveness of each class of ligand. In the context of childhood GH deficiency, we have shown that the synergy between GHRH and GHRP is maintained during chronic treatment.[48]

CONCLUSION

These studies show that once-daily evening subcutaneous injections of GHRH(1–29)NH_2 are generally well tolerated and can increase 24-h GH secretion, boost circulating levels of IGF-I, and improve body composition in older patients. Preliminary analyses also suggest beneficial effects on cognitive performance. Effects on physical function are equivocal; and with the formulation and dosing schedule used there appears to be no significant benefit on sleep. While they encourage further study, these results are far short of those needed to support regulatory approval for formal drug registration. As aging is not a disease, drug therapy cannot be broadly encouraged until meaningful functional benefits are shown either in treatment or in the prevention of sarcopenia.

In contrast to prevention studies, treatment trials can be accomplished with smaller numbers of subjects, to assess whether GH or GHS therapy improves recovery from catabolic illness, surgery, or a fracture. A report that high-dose pharmacologic GH treatment—designed to overcome GH resistance rather than replace GH deficiency—increases mortality in critically ill patients raises appropriate cautions.[49] However, no similar deleterious effects have been seen in more chronic wasting illnesses such as AIDS, or with lower GH doses. A recent preliminary report of a multicenter European study showed that GH could accelerate recovery from hip fracture,[50] a finding that will surely lead to further treatment trials of GH and GH secretagogues.

Prevention studies will have to be much larger in scale, and definition of a meaningful but attainable endpoint is a major challenge. While endocrine changes and improved scores on functional tests must first be observed for such studies to proceed, they do not constitute a sufficient outcome. Personal and economic benefits must be demonstrated with clinical outcomes such as a reduction in falls or fractures, or prolongation of the capacity for independent living, and the safety of chronic preventive therapy will have to be shown on this larger scale before it can be widely recommended.

If treatment or preventive therapy proves beneficial, what type of agent should be used? Earlier, we alluded to several potential advantages of using a GH secretagogue rather than GH itself, and to date GHRH appears to be associated with fewer side effects than GH in the few studies which have reported results. Nonetheless, it remains unclear whether this represents a qualitative or simply a quantitative difference: GHRH produces less elevation in IGF-I than that seen in most GH interventions in aging, and it may be that the lower incidence of side effects results from this lesser potency. A good theoretical argument can be made regarding the benefits of mild, near-physiological intervention for prevention, but at present the actual relative advantages and disadvantages of the two approaches are unknown. It may well be that GH will become the preferred intervention for those treatment indications where a more supraphysiological therapy is desired.

From a practical perspective, orally active agents—currently only the nonpeptide ghrelin mimetics—have a compelling advantage, especially for prevention, and it seems unlikely that GHRH can become a practicable therapy in aging until a longer-acting preparation or an orally active nonpeptide analog is developed. Thus, one can anticipate research proceeding on two tracks: better definition of the clinical benefits of increasing GH, and development of new GHRH and ghrelin agonists to make these benefits accessible to seniors who currently represent the fastest growing segment of the population.

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