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Growth Hormone-Releasing Hormone and Growth Hormone Secretagogues in Normal Aging†

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Growth hormone (GH) secretion declines with aging, and parallels between normal aging and the signs and symptoms of adult GH deficiency have led to interest in the potential utility of replacing or stimulating GH to promote physical and psychological function and to prolong the capacity for independent living in older adults. The aging pituitary remains responsive to GH-releasing hormone (GHRH) and to ghrelin-mimetic GH secretagogues (GHS), and these agents have both theoretical and practical potential advantages as alternatives to the use of GH itself in this setting. Studies of the long duration and large scale needed to test the efficacy of GHRH or GHS on clinically important endpoints cannot be designed or conducted without first obtaining promising results in studies of smaller size focused on manageable intermediate endpoints, and all studies published to date have been of this latter type. GHRH and GHS both stimulate GH secretion, and, when given repeatedly, elevate IGF-I levels to within younger adult normal ranges. When GHRH treatment is continued for several months, these hormonal changes yield an increase in lean body (muscle) mass. GHRH, like GH, reduces body fat, but similar effects have not yet been shown with GHS. GHRH treatment has not yielded consistent improvements in physical function, although it may have a stabilizing effect. Chronic treatment with a short-acting GHRH did not improve sleep, possibly due to lack of sustained activity throughout the night. Compared to placebo, GHRH treatment improved certain tests of cognitive performance. These results, while encouraging, do not yet support the routine use of GHRH or GHS in normal aging.

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Introduction

The loss of muscle mass, or sarcopenia, which accompanies aging even in otherwise healthy older adults leads to a progressive loss of strength and aerobic capacity that can eventually result in inability to perform the tasks needed for independent living, the condition of frailty. Providing home-based or institutional support for the frail elderly is an enormous and rapidly growing expense. This has prompted the search for interventions that might slow or even reverse this decline, to extend the period of relative independence even if overall longevity is not increased, a process termed "rectangularization of morbidity" (Fig. 1). Among the interventions that have been studied are exercise conditioning, dietary supplementation, and trophic factors and hormones.

Because growth hormone (GH) secretion also declines progressively with aging, and because many of the symptoms and signs of aging, including sarcopenia, resemble those seen in younger adults with the diagnosis of GH deficiency, interventions to replace or stimulate GH secretion are among the trophic factor treatments being considered for use to delay or even reverse age-associated frailty. In this context, the differences between GH deficiency (GHD) and aging have conditioned the therapeutic approaches used as much as their similarities. Because most adults with GHD acquire this condition as the result of a pituitary tumor or its treatment, the GH response to GH secretagogues is usually reduced or absent, and GH must be replaced with GH itself. By contrast, in aging the reduction in GH secretion appears to derive primarily from suprapituitary causes, with pituitary GH responses to stimulation relatively maintained; and thus stimulating endogenous GH production with the use of GH secretagogues remains an option not usually open in GHD. This article reviews some of the studies using GH secretagogues to reverse the age-related decline in GH and suggests what further information is needed before such interventions could be considered for general use.

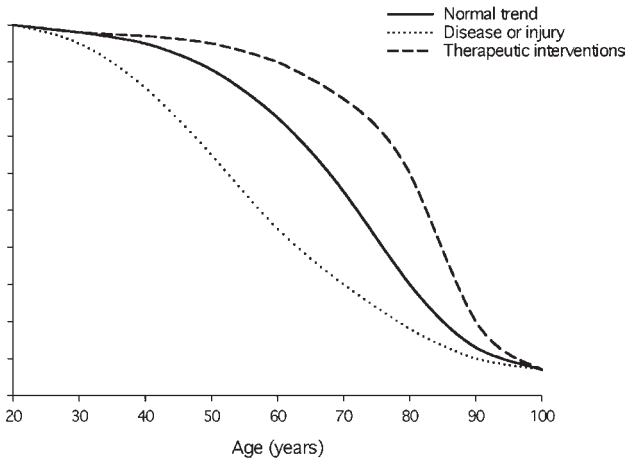

Fig. 1. Schematic (not to scale) of declining functional capacity with aging. Even if longevity is not affected, disease or injury can accelerate the loss of function (left curve). It is hoped that interventions such as exercise and possibly trophic factors could shift the normal curve to the right, allowing maintenance of adequate levels of function for a larger proportion of the lifespan. Because a sketch of the hypothetical situation in which the same level of function is maintained until just before death would look like two sides of a rectangle, this shift to the right with therapeutic interventions is called "rectangularization of morbidity."

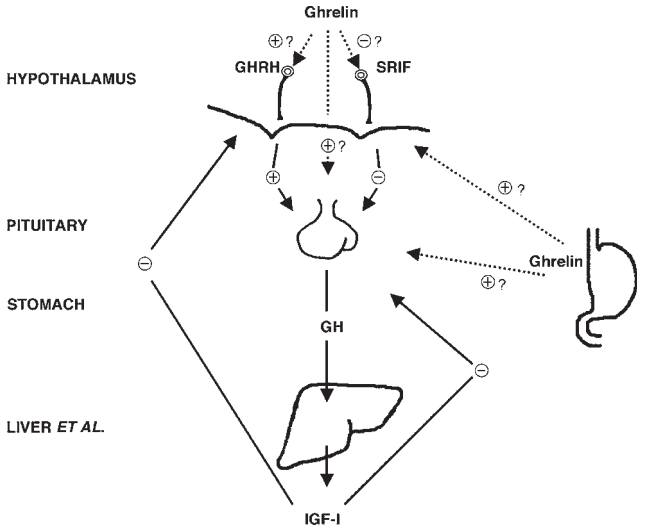

Fig. 2. Schematic of proximal factors regulating GH secretion. Central nervous system modulators integrate higher physiologic inputs responding to exercise, food, stress, sleep, and circadian and ultradian rhythms to produce changes in hypothalamic secretion of growth hormone-releasing hormone (GHRH), somatostatin (SRIF), and possibly ghrelin. Caloric balance, estrogen, and other factors modulate the response of insulin-like growth factor-I (IGF-I) to GH, and IGF-I in turn inhibits hypothalamic and pituitary responses. Ghrelin stimulates hunger and food intake, although its role in physiological GH regulation is not clearly defined. From *(49)*.

Regulation of GH Secretion

Pituitary GH secretion depends on stimulation by the hypothalamus and is regulated by tissue responses (Fig. 2). When the hypothalamic–pituitary portal circulation is interrupted, GH falls to low values. The major stimulator of GH secretion is GH-releasing hormone (GHRH), a 44-amino-acid brain–gut peptide (reviewed in ref. *1*). A second hypothalamic peptide, somatostatin, is a potent noncompetitive inhibitor of the release of GH and other hormones, and modulates the pituitary GH response to GHRH. In searching for GHRH, Bowers and other investigators defined another class of GH secretagogues, initially a group of nonphysiologic enkephalin-derived peptides, which act at a receptor distinct from that for GHRH and synergize with GHRH in stimulating GH secretion *(2,3)*. The identification of that "GH secretagogue" (GHS) receptor *(4)* led to screening procedures to identify endogenous ligands, eventually leading to the isolation and characterization of a novel octanoylated peptide, "ghrelin," by Kojima and colleagues in 1999 *(5)*. Several pharmaceutical research groups had already developed orally active non-peptide compounds that mimick the actions of ghrelin even before its chemical nature had been defined *(6)*. These compounds act at the GHS receptor to stimulate GH. Ghrelin is also a brain–gut peptide. It is abundant in oxyntic glands of the stomach and has potent appetite-stimulating effects that are separable from its effects on GH *(7)*. Ghrelin is expressed in defined populations of hypothalamic neurons that interact with appetite-regulating circuits *(8)*. Gastric ghrelin circulates at concentrations sufficient to exert effects on both GH secretion and appetite, but there is still a question as to whether either circulating or hypothalamic ghrelin is of major importance in modulating GH secretion *(9,10)*.

Although GH can exert some effects directly through binding to and dimerization of its own receptor, many of its effects are exerted secondarily through increased synthesis and secretion of insulin-like growth factor-I (IGF-I). IGF-I is produced in many GH target tissues, but IGF-I in circulation is mainly derived from the liver. IGF-I is a negative feedback regulator of GH secretion at both pituitary and hypothalamic levels, and it appears that this effect is largely due to circulating IGF-I *(11)*.

Mechanisms of the Age-Related GH Decline

One can list numerous possible mechanisms contributing to the age-related decline in GH secretion, and indeed this process is likely to be multifactorial. Changes in pituitary responsivity appear to contribute relatively little to the decrease; while some investigators report that the GH

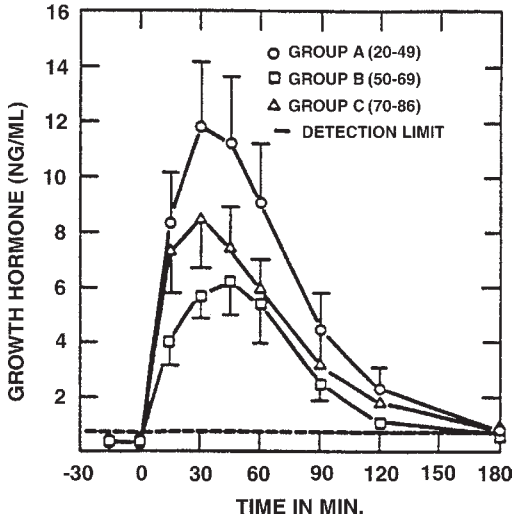

Fig. 3. GH responses to an intravenous injection of GHRH(1-44)NH_2 in healthy subjects of different ages. From *(12)*.

response to GHRH or ghrelin agonists is reduced with age, this is an inconstant finding, and in some studies healthy seniors show a brisk response *(12)* (Fig. 3). Ghigo and colleagues have shown that while the GH response to GH secretagogues is generally blunted in aging, this decrement can be reversed by coadministration of arginine or other agents that reduce somatostatin *(13)*. This result suggests that responses of the aging pituitary are intrinsically normal but that somatostatin tone may increase, perhaps in parallel with the age-related increase in central adiposity.

An increased sensitivity to negative feedback by IGF-I could also potentially reduce GH secretion in aging, but this possibility has been largely ruled out in experiments reported by Chapman and colleagues. Infusion of graded doses of synthetic IGF-I produced nearly superimposable dose–response curves in younger vs older subjects *(14)*.

Multiple frequent sampling protocols have delineated in detail the changes in the patterns of episodic GH secretion accompanying aging. The decrease largely results from a reduction in GH pulse amplitude, with little or no change in GH pulse frequency *(15)*. Most GH secretion in younger individuals occurs during deep (stages 3 or 4) sleep, stages which also decline greatly with aging; and because of this linkage, the age-related reduction in GH is most severe during the night, leading to a relative loss of the youthful diurnal rhythm of GH secretion *(16)*. At this point it is still not clear whether the reduction in deep sleep and the reduction in GH are causally related, or both reflections of a common process. But this pattern of GH decline also appears to bespeak a suprapituitary process most likely leading to reduced GHRH secretion, increased somatostatin tone, perhaps changes in ghrelin (still not defined), or some combination of these factors.

Interventions in Aging: GH Secretagogues vs GH

Because the presumed causes of the age-related decline in GH are central, in principle GH secretagogues, GHRH, and/or ghrelin agonists would provide a more physiologic intervention than GH itself, if that ultimately proves beneficial. There are other potential advantages to using GH secretagogues. When GH secretagogues are given continuously, or when long-acting preparations are administered, GH secretion is stimulated as a series of pulses in a pattern resembling the normal youthful pattern of secretion rather than as a continuous high GH level, as results from GH injections. Studies in rodents have demonstrated that some GH effects are modulated by the pattern of GH secretion, in particular, the return to low levels between pulses, as well as by the quantity of GH; and such effects would also argue for a relative advantage to GH secretagogues over GH. The GH response to secretagogues is modulated by changes in circulating IGF-I, which could potentially provide a self-regulating buffer against overtreatment, an effect bypassed when GH itself is administered. Several peptide and nonpeptide ghrelin mimetics are active by oral administration, and longer-acting GHRH analogs are under development *(17)*. Taken together, these characteristics suggest that GH secretagogues could offer both practical and theoretical advantages over the use of GH.

Despite their appeal, however, a major brake to enthusiasm in the use of GH secretagogues in aging is the lack of solid documentation of their beneficial clinical effects. While it is relatively easy to demonstrate endocrine effects, the rationale for their use in aging is largely based on the established benefits of GH replacement in bona fide GH deficiency, for which a large literature shows improvements in body composition, physical and psychological function, and self-reported quality of life; and emerging results from long-term studies point strongly toward a reduction in morbidity and mortality. Since most adult GHD derives from hypopituitarism, GH secretagogues are ineffective; and thus, except for a small number of studies of adults with hypothalamic, childhood-onset GHD, this literature is based almost exclusively upon GH rather than secretagogue treatment. GH is a profitable marketed drug produced by several manufacturers, while GHRH has only been licensed for the treatment of idiopathic hypothalamic GH deficiency in children (Geref®, Serono), and ghrelin agonists have not been licensed for therapeutic use in any country. These factors have limited the resources for the large-scale, long-term studies of GH secretagogues needed to document clinically meaningful benefits in aging.

Intermediate vs Clinical Endpoints

The challenge posed by those needs is substantial. As summarized below, studies of relatively limited scale and duration suffice to demonstrate the endocrine effects of GHRH

or GHS on parameters such as GH secretion and IGF-I. Longer-term interventions are needed to demonstrate effects upon muscle and fat mass, and longer still upon bone mineral; and the period of time needed to show improvements in physical or psychological function may be even longer. The variability in these outcomes and the relatively low rate and perhaps delayed onset of side effects and risks require trials on a much larger, multicenter scale. But it is upon these clinical "final" outcomes, and ultimately the demonstration that frailty is deferred, falls and fractures reduced, and independence prolonged that judgment as to the clinical utility of trophic factor interventions must rest. It would not be appropriate to undertake such trials without clear indications of efficacy and safety in smaller trials of "intermediate" outcomes, and thus all studies to date have been of limited scale and duration.

Side Effects and Risks

The utility of a proposed intervention depends on its tolerability and safety as much as on its efficacy. There is an extensive literature on the side effects and risks of GH treatment in patients with GHD, for which there is now nearly 50 yr of experience. Aging is not a disease, and thus the indications for drug interventions are "softer" and the vulnerability of the population possibly greater. There are no aging studies of the duration or scale needed to provide strong safety data beyond the short-term side effects of treatment, and thus the precedent of GH for GHD is our only current source of information on the possible long-term safety of these interventions.

GH has well-defined hormonal side effects, including fluid retention (edema), noninflammatory arthralgias, and, less commonly, carpal tunnel syndrome, which have also been described with GH secretagogue treatment, although the magnitude of these has generally been less than with GH. Whether this reflects a qualitative advantage to secretagogues, or only their generally lower potency, is not yet clear. These hormonal side effects are dose-related and uniformly respond to dose reduction or drug discontinuation. Ghrelin mimetics may also have the metabolic and appetite-stimulating effects attributed to ghrelin, although the documentation for these effects in aging is still very sparse. In a small study of the effects of the ghrelin mimetic peptide GHRP-2 in GH-deficient children, 7 of 10 subjects reported increased appetite in the initial months of treatment *(18)*. While GH and GHRH generally act to reduce body fat mass, this effect was not seen in a trial of the oral ghrelin mimetic MK-677 in (younger) obese adults *(19)*. Whether or not these effects are significant and are ultimately deemed desirable or undesirable, they are hormonal effects that would also be expected to be rapidly reversible with dose reduction or disontinuation.

Long-term exposure to excessive levels of GH in patients with pituitary tumors secreting GH (acromegaly) can lead to joint deformities and long-lasting effects on the skeleton. These sorts of effects have not yet been observed with studies aiming to restore GH only to young adult normal levels. The potential risks of cancer, which might be delayed and irreversible, are a theoretical concern, but evidence of cancer risks associated with GH treatment has largely been absent. Patients with acromegaly do have an increased incidence of colonic polyps susceptible to malignant degeneration, but there is no evidence of increases in other cancers in this disorder *(20)*. Two epidemiologic studies have linked subjects with the highest levels of circulating IGF-I to increased risks for prostate or breast cancer *(21,22)*, but these cancers are not increased in acromegaly. Patients with childhood-onset GH deficiency treated with long-term pediatric (and now adult) GH replacement have been subjected to a number of surveillance programs aimed at long-term risks. In some patients the GH deficiency arises from treatment of leukemia or other malignancy, and these patients would thus be expected to have higher risks of relapse or a second malignancy whether or not they received GH. In all but one study, no excess risk attributable to GH was seen *(23)*. In one recent study, long-term followup into adulthood of patients given GH replacement as children seemed to be associated with increased risk for Hodgkin's disease *(24)*. This troubling but inconclusive finding is being subjected to further study, and its relationship to GH supplementation beginning in adult life is uncertain. The current recommendation of the Growth Hormone Research Society is that patients receiving GH replacement should be diligently placed under the level of cancer screening surveillance recommended for healthy adults of similar gender and age. This falls short of a complete assurance of safety, but suggests a consensus that the excess risk is not great.

GHRH Treatment in Aging

The observation that GHRH continues to stimulate GH release in normal older men and women led to a series of short-term studies of the effects of repeated GHRH administration. Corpas and colleagues showed that both continuous subcutaneous (sc) GHRH infusions and once or twice daily injections of GHRH elevated IGF-I levels *(25,26)*, a result also seen with administration of a GHRH analog *(27)*. We have conducted two placebo-controlled treatment studies of intermediate term (5–6 mo) using GHRH(1-29) NH_2 (Geref®, Serono), self-administered as sc injections once daily in the evening, in healthy older men and women. The first protocol studied a combined intervention with GHRH or placebo with or without exercise conditioning in non-estrogen-replaced (NERT) older women, and concentrated on changes in body composition and physical function *(28–30)*. Physical function was assessed both by conventional measures of aerobic capacity and strength in isolated muscle groups, and by a continuous-scale physical performance test developed at the University of Washington that assesses

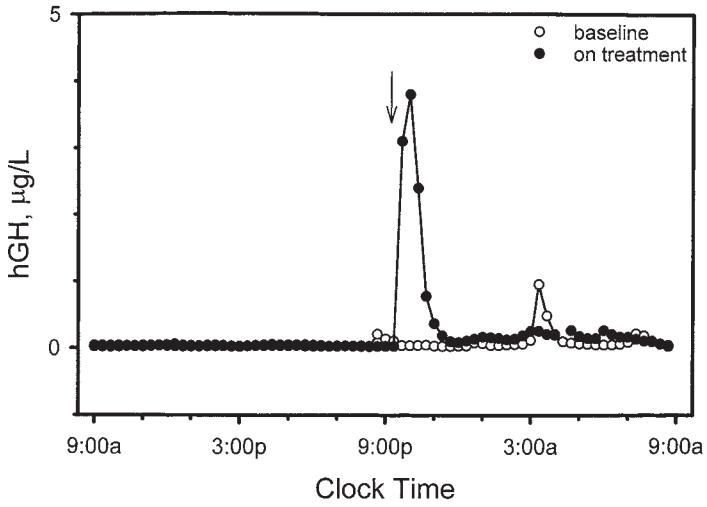

Fig. 4. Effects of a single self-administered nightly subcutaneous injection of 1 mg GHRH(1-29)NH_2 on GH secretion in a healthy older man. The arrow marks the time of the injection. There is a large immediate GH response, but late-night GH secretion is not increased compared to the pretreatment baseline assessment.

upper and lower body strength, balance, and coordination in tests patterned after activities of daily living *(31)*. A second GHRH treatment protocol expanded the treatment groups to include men and estrogen-replaced (ERT) women. This protocol did not have an exercise conditioning arm, but included 24-h sampling for GH, polysomnography/sleep EEG, and a battery of cognitive tests, as well as body composition and physical functional performance *(16,32–34)*.

As compared to placebo, daily GHRH approximately doubled integrated GH secretion. Given the relatively short duration of the GHRH formulation used, this effect resulted from a single large evening burst of GH secretion *(35)* (Fig. 4). Late-night GH was not stimulated; indeed, there was a trend toward inhibition of endogenous late-night GH secretion. IGF-I levels rose, but this effect differed among the three treatment groups, with the largest increase in men, and the lowest in ERT women *(36)*. These results are consistent with the known effect of estrogen, especially when given orally, to block GH actions, and resemble those seen in GH treatment of GH-deficient men, NERT, and ERT women *(37,38)*. In NERT women, exercise conditioning had no effect on IGF-I levels, and when GHRH treatment was discontinued, IGF-I levels returned to baseline even if subjects continued to exercise *(39)*. This result is consistent with earlier studies reporting no effect of exercise on IGF-I even with intensive conditioning regimens *(40)*.

Over 5–6 mo of treatment, GHRH increased lean body mass and reduced fat, especially abdominal visceral fat, an effect also markedly blunted in ERT women *(29,33,41)*. Exercise conditioning increased muscle strength and physical functional performance, consistent with previous studies *(31)*. GHRH did not significantly improve either of these parameters but appeared to mitigate a declining trend in physical functional scores seen in nonexercising women taking placebo. Whether this is a true stabilizing effect of GHRH requires further confirmation. Deep sleep was not improved by GHRH, a negative result possibly due to the short duration of action of the GHRH formulation used *(42)*. In a preliminary study, GHRH improved several measures of cognitive function, particularly those sensitive to changes in processing speed, compared with placebo treatment *(34)*.

GHS Treatment Studies

A few groups have pursued treatment with ghrelin mimetics in normal aging. These studies began with GHRPs and oral nonpeptide GHS even before the identity of ghrelin was defined. Bowers and colleagues administered GHRP-2 for periods of up to 90 d, showing persistent increases in episodic GH secretion, synergy with the effects of GHRH, and increases in IGF-I levels *(43)* (Fig. 5). Thorner and colleagues and other groups have examined the effects of the orally active nonpeptide GHS MK-677 in protocols of increasing duration. Given as short-term treatment, MK-677 stimulates episodic GH secretion and increases the levels of IGF-I *(44)* (Fig. 6). When treatment is continued for two months, circulating markers of bone turnover are increased *(45)*. A 2-yr intervention with MK-677 examining changes in body composition and function is still in progress *(46)*. A large multicenter study of another investigational oral GH secretagogue (CP-424,391, Pfizer) has concluded. This trial, originally planned to continue for 2 yr, was discontinued after 12 mo because preliminary analysis of the results of 6 mo of treatment reportedly showed only a modest body composition effect compared to placebo. These results have been summarized in press reports but not formally presented

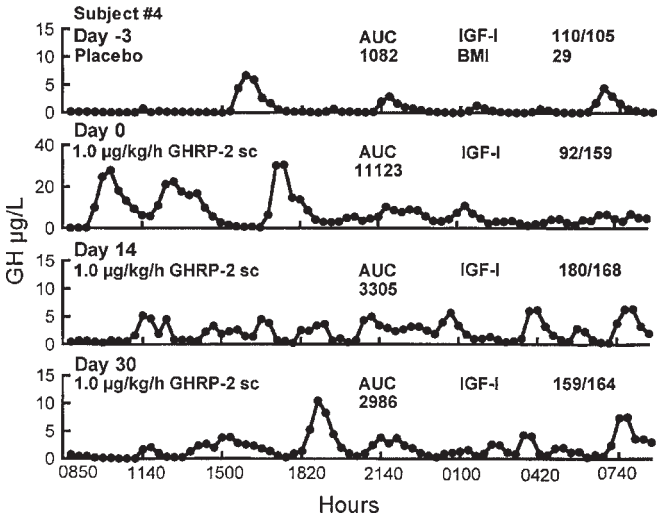

Fig. 5. Effects of sustained subcutaneous infusions of GH-releasing peptide-2 (GHRP-2) in a healthy 49-yr-old woman. There is a marked increase in GH secretion the first day of the infusion, which diminishes over time as IGF-I levels rise. Even after 30 d, GH secretion remains pulsatile, integrated GH secretion is approximately three times greater, and IGF-I levels are 50% higher than during placebo infusion. AUC, area under the curve of GH levels; BMI, body mass index; IGF-I levels (ng/mL) measured at two times during each profile. From *(43)*.

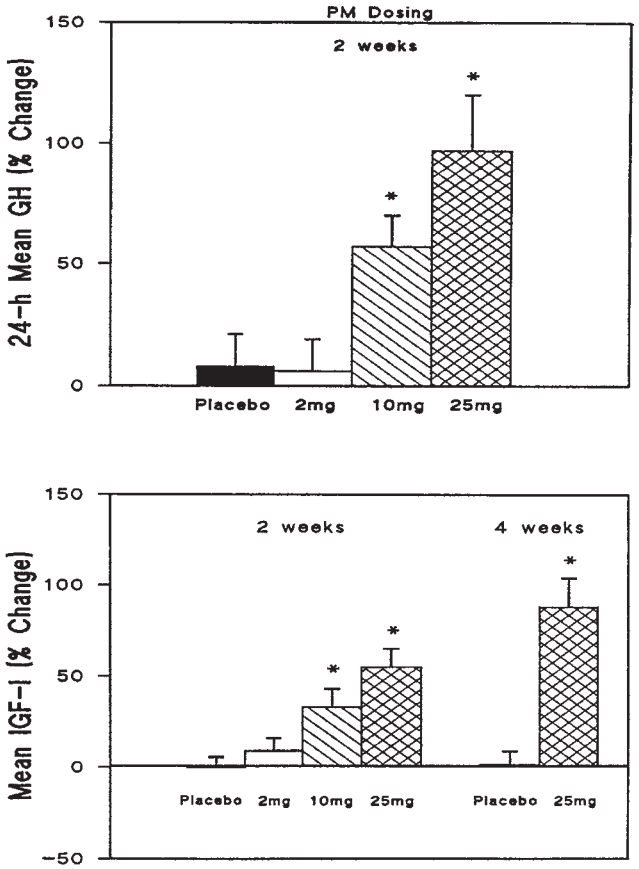

Fig. 6. Effects of graded doses of the oral GH secretagogue MK-677 on 24-h mean GH and IGF-I levels in normal older men and women. From *(44)*.

or published, and so details are few *(47)*. The relatively weak effects on lean body mass in this study are at variance with the relatively consistent effects of GH or GHRH in similar groups of healthy aging subjects. One earlier study with MK-677 in a different population—younger adults with obesity—also noted a lack of decrease in body fat *(19)*. It is not clear, however, whether the reportedly negative result of the Pfizer GHS study represents a problem with the specific compound tested, or a general effect common to ghrelin mimetics as contrasted with GHRH—for example, a blunted reduction in body fat resulting from increased appetite *(18)*.

GH Secretagogues vs GH in Aging

With the exception of possible differences in effects on body fat, the results of these studies of GHRH and ghrelin agonist GHS parallel those of studies of GH itself in normal aging. Hormonal effects, particularly an increase in IGF-I, are clear, with greater effects in men than in women. There is an increase in muscle mass and (with GHRH) a reduction in body fat, especially in the abdominal visceral compartment. But functional effects on strength and aerobic capacity have been inconsistent, with many studies, including one large study of GH and sex steroid replacement in men and women, reporting negative results *(48)*. Does this mean that GH and GH secretagogues have no functional effects? Our positive results with exercise conditioning show that the functional testing methods used can detect changes in the populations studied, e.g., that there is no "ceiling effect" of the sort that clouded the interpretation of some GH studies. Within the framework of these protocols, however, clear functional improvements have not been demonstrated. These generally negative results admit of several possible interpretations. It may be that effects are truly minimal or lacking. It may be that trophic factors in this category are more effective in stabilization than in reversal of age-related changes. Or it may be that after decades of senescence, interventions need to be continued for periods of time much longer than 6 mo in order to demonstrate improvement. Side effects of GHRH and of GHS have so far been milder than those after GH treatment, but it is not clear whether this represents a true qualitative difference due to preservation of endogenous feedback regulation, or simply a dosing effect due to reduced potency of GHRH and GHS vs the GH doses that have been employed.

Summary

Similarities in the hormonal changes and the signs and symptoms of normal aging and adult GH deficiency make the GH axis an appealing target for trophic factor interventions in aging. Preservation of pituitary responsiveness and both theoretical and practical arguments suggest that GHRH

and GHS could be as effective as GH, and perhaps more physiological and more practical agents. The studies reported so far show that these compounds can stimulate GH, although reconstituting true pulsatile GH secretion requires agents of sufficiently long duration of action, and these agents can elevate circulating levels of IGF-I to within the youthful normal range. Given over several months of treatment, they can increase lean body mass, and GHRH can reduce body fat. So far there is not enough published data on ghrelin mimetics to document the effects of GHS on body fat in aging. As with GH, effects on strength, aerobic capacity, and physical functional performance have been equivocal. It remains an open question whether GH secretagogues can enhance the effects of exercise, which appear to be exerted by non-IGF-I related mechanisms, or even have a stabilizing effect upon function. The lack of beneficial effects of GHRH on sleep may be related to the short duration of action of the formulation used. The suggestion of improvement in certain cognitive measures during GHRH treatment is an exciting and potentially important but still very preliminary finding requiring further confirmation.

All published reports in normal aging have been of modest scale and duration, and have examined intermediate rather than "final" clinical endpoints. No study so far has demonstrated the ability of GH secretagogues or GH to promote quality of life, prevent falls or fractures, or prolong the capacity for independent living in healthy seniors. These are the sorts of results that would be needed to justify widespread use of these agents in clinical practice. But because the studies capable of demonstrating these results are of large scale, long duration, and very high cost, funding to undertake such trials is unlikely to be forthcoming without clearer demonstration of improvement or stabilization in physical or psychological function. This suggests that clinical studies of GH secretagogues are likely to remain of moderate scale and focused on intermediate endpoints for the next several years.

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