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Potential Applications of GH Secretagogs in the Evaluation and Treatment of the Age-Related Decline in Growth Hormone Secretion

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The two classes of GH secretagogs—GH-releasing hormone (GHRH) and the GH-releasing peptides and their analogs (GHRP's)—retain their ability to endogenous GH secretion in healthy and frail elderly subjects. They have very limited utility in assessment of the state of the GH/IGF-I axis except to confirm an intact pituitary, but they are attractive potential alternatives to GH as therapeutic agents. There is wide interest in the possibility that elevating GH and IGF-I might increase muscle mass, physical strength and performance, and possibly sleep and cognition in aging. The GH secretagogs, like GH, can produce a sustained stimulation of this axis; in contrast to GH, they preserve feedback regulation at the pituitary level and stimulate a near-physiologic pulsatile pattern of GH release. GHRP's and their nonpeptide analogs are also active when given orally, a significant practical advantage. Short-term treatment studies have shown that GHRH and the GHRP's can enhance GH secretion and elevate IGF-I and IGFBP-3 levels; that GHRH may promote sleep; and that these agents are generally well tolerated. Longer-term studies assessing effects upon body composition and physical and psychological function are underway.

Key Words: Growth hormone (GH); GH-releasing hormone (GHRH); GH-releasing peptide (GHRP); insulin-like growth factor-I (IGF-I).

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Introduction

The age-related decline in GH secretion is associated with alterations in body composition, hormonal status, and functional capacity that mimic changes observed in GH deficiency. These observations have raised questions similar to those focused around the decline in sex steroids with aging or menopause. Issues under debate include whether these changes should be treated, and if so, how; who should be treated; and whether testing the functional status of the GH axis is useful in identifying those most in need of treatment. Since the aging pituitary remains responsive to GH secretagogs, including GH-releasing hormone (GHRH) *(1)* and the peptide and non-peptidyl ligands for the GHRP receptor *(2,3)*, these compounds have come under study both as potential probes for assessing the GH axis, and as potential therapeutic agents for enhancing endogenous GH as an alternative to GH administration.

It is difficult to place a review of the potential role of these compounds in diagnosis and therapy into context when the larger questions that frame these roles are still open ones. As with GH itself, it is not yet known whether reversing the age-related decline in GH secretion provides long-term net benefits; which specific populations might benefit, whether for acute or chronic treatment; and whether evaluating the functional state of the GH axis is an important part of identifying those people (if any) who would benefit the most. Given that answers for these questions are not available, at this stage of the authors' knowledge we are limited to examining the known effects of the different GH secretagogs as guides to their potential future utility.

Two general classes of GH secretagogs have been studied. GHRH, in its full sequence a 44-amino acid amidated peptide, is an endogenous hypothalamic hormone which is the final common path for many stimuli to GH secretion *(4)*. Its action is primarily on pituitary GHRH receptors. Fragments as short as GHRH *(1–29)* retain most biologic activity and are under pharmaceutical development. The

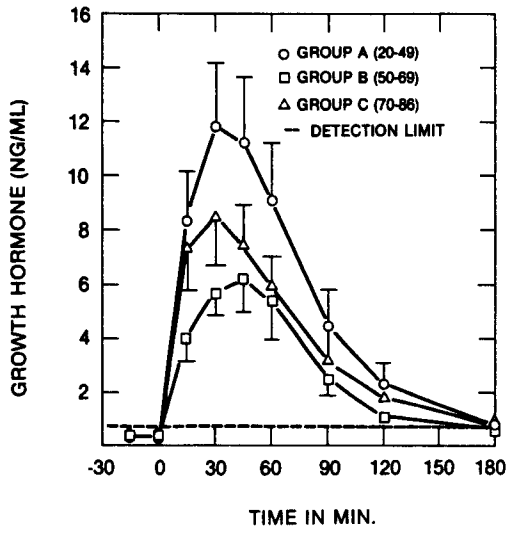

Fig. 1. GH responses to single bolus injections of GHRH (1 ug/Kg iv) in groups of healthy subjects of different ages. There is a trend toward lower responses in the two older groups, but no statistically significant differences. From ref. *(1)*.

duration of action of GHRH is short, because of proteolysis of the 2–3 bond, leading to interest in development of longer-acting or more potent analogs *(5)*.

The GHRP's are small (5–7 aa's) peptides originally derived from enkephalin *(6)*, which bind to a different receptor located in both hypothalamus and pituitary and which mimic the actions of a still-unidentified endogenous ligand. Several GHRP's have been studied in clinical settings. In addition, a group of non-peptidyl compounds, including L-163,191 (MK-0677) act via the same receptor mechanism *(7)*. Both the GHRP's and MK-677 are active when given orally. The effects of GHRH and the GHRP's (using this term to refer both to peptide and nonpeptide ligands) are synergistic in both normal and GH-deficient subjects *(8)*; the combination of GHRH and GHRP's given together is one of the most potent known stimuli to GH secretion.

GH Secretagogs as Diagnostic Agents

GH secretagogs continue to provoke an acute GH response in aging subjects, although the magnitude of this response may decline. In early studies the authors found that the GH response to GHRH was maintained in very healthy older subjects (Fig. 1) *(1)*, but other authors have reported a decrease in responses. This discrepancy may reflect differences in the populations studied, since many of the changes associated with aging, including an increase in adiposity, can blunt GHRH effects, perhaps by an increase in endogenous somatostatin secretion. Arginine pretreatment, which reduces somatostatin, markedly reduces age-related decreases in responses to GHRH *(9)*. There is wide variability in acute responses to GHRH, even on repeated testing of the same individual *(10)*, which also probably reflects variations in endogenous somatostatin secretion.

Because of this within-subject variability, and because pituitary GH responses to GHRH often overlap the normal range even in classical GH deficiency *(11)*, GHRH has so far proven to have very limited usefulness in diagnosing reduced GH secretion in all the settings in which it have been tested. GH responses to GHRP's may be more reproducible on repeated testing of the same individual *(12)*, but are also modulated by somatostatin tone. These responses are generally reduced in older subjects, but can be increased by arginine pretreatment *(2)*. This susceptility to external influences makes responses to both GHRH and GHRP's relatively poor reflectors of endogenous GH secretion.

If GH secretagogs are not diagnostically useful, are there other tests which help to discriminate among degrees of reduced GH secretion in aging? Ho and colleagues have examined several tests to distinguish between normal aging and true adult GH deficiency. Of the tests examined (which did not include GHRH or GHRP's), plasma levels of IGF-I or IGFBP-3 were not useful. GH responses to insulin-induced hypoglycemia provided the clearest discrimination between the two groups *(13,14)*. Because criteria for treatment have not been developed, it is not clear whether this conclusion would extend to the more general question of identifying those older individuals who would benefit from GH enhancement.

GH Secretagogs as Therapeutic Agents

Repeated doses of GH secretagogs can sustain increases in GH secretion and IGF-I levels and can accelerate growth in children with GH deficiency and growth failure *(15,16)*, and it is not surprising that many of the same effects (except growth) can be produced in normal aging individuals. The utility of such therapy is subject to many of the same unresolved questions as those concerning GH administration, but there are several physiologic and practical differences that may eventually favor the use of secretagogs over GH in those settings (if any) in which GH enhancement ultimately proves useful. The GH response to both GHRH and GHRP's is modulated by negative feedback inhibition by IGF-I and somatostatin, and these physiologic modulators may partially protect against overtreatment. In some settings, the biologic response to GH is modulated by its pattern of administration (pulsatile vs continuous) as well as the total quantity given *(17)*. In this context secretagogs may also have an advantage over GH, since GH injections produce unphysiologic sustained elevations in GH levels, while even continuously administered GH secretagogs stimulate a pulsatile pattern of GH secretion which generally mimics the normal pattern *(3,18,19)*. The oral activity of the GHRP's is a clear practical advantage. GH responses to secretagogs in aging may be blunted by obesity and

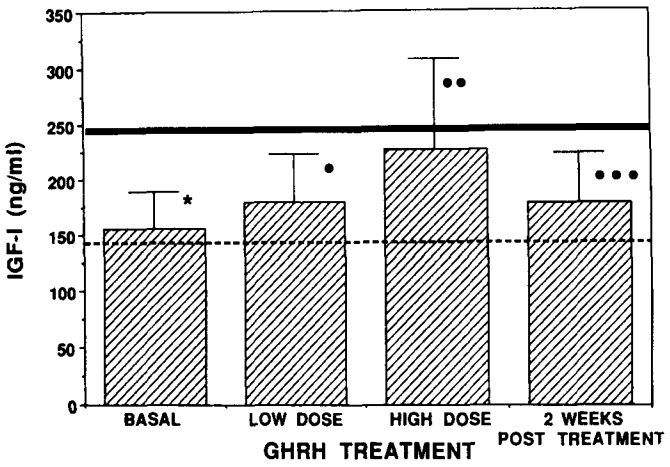

Fig. 2. IGF-I responses to two wk treatment with twice daily subcutaneous injections of either low dose (0.5 mg) or high dose (1 mg) GHRH *(1-29)* on IGF-I levels in ten healthy older men, aged 60-78 yrs. From ref. *(22)*.

increased somatostatin tone, but a variety of enhancing adjuvants, including β-adrenergic antagonists *(20)*, arginine *(2)*, and the combination of GHRH and GHRP's *(2,8)*, can boost GH responses.

Most studies of GH secretagog treatment have been of short duration (6 wk or less), long enough to assess endocrine-metabolic responses, but not changes in body composition or physical function. Kerkhofs and colleagues reported that GHRH could acutely promote sleep in normal men; the specific effects depended upon the timing of drug administration *(21)*. Corpas et al. showed that either continous infusions *(18)* or twice-daily subcutaneous injections *(22)* of 0.5 or 1 mg GHRH (1–29) (Geref(R), Serono) could elevate plasma IGF-I levels in healthy older men, reaching normal values for young adults with the higher dose (Fig. 2). Recently Vittone et al. reported effects of 6 wk of open-label treatment in 11 healthy older men with the same total daily dose of GHRH (2 mg) as in the earlier high-dose study, but given as a single bedtime sc injection *(23)*. Two measures of muscle strength (upright row and shoulder press) improved; but in this study plasma IGF-I and IGFBP-3 levels did not rise, and the authors concluded that divided closes of GHRH may be more effective than a single higher dose. Vittone et al. recently described effects of 6 wk of open-label treatment in 11 healthy older men with the same total daily dose of GHRH (2 mg) as in the earlier high-dose study, but given as a single bedtime sc injection *(23)*. Two measures of muscle strength (upright row and shoulder press) improved; but in this study plasma IGF-I and IGFBP-3 levels did not rise, and the authors concluded that divided doses of GHRH may be more effective than a single higher dose. Very recently, Khorram et al. reported a study of 16 wk treatment with single nightly injections of a GHRH analog, reporting an increase in lean body mass in men but not in women *(24)*.

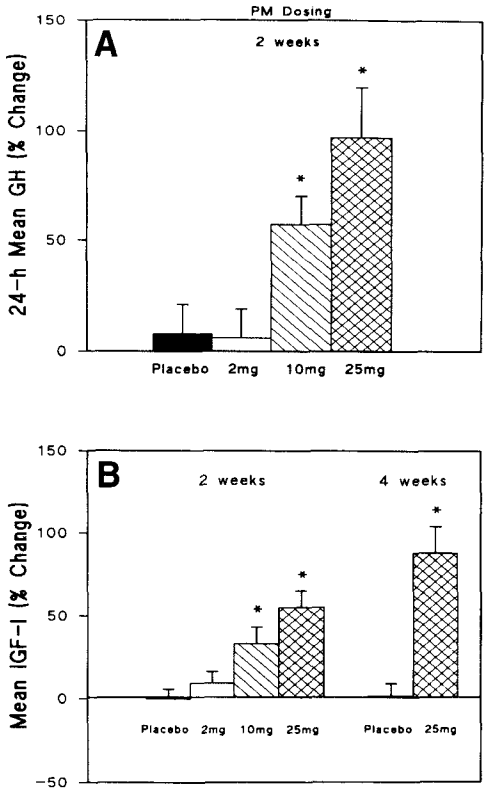

Fig. 3. Effects on mean GH and IGF-I of two or four wk treatment with different doses of the oral non-peptide GH secretagog MK-677 given once daily in the evening (*, $p < 0.05$). From ref. *(25)*.

The effects of the nonpeptide GHRP mimetics have also been studied in older adults. Even brief 24-h infusions significantly elevated IGF-I levels *(3)*. Daily oral administration of MK677 in two different doses (10 and 25 mg) to a group of healthy older men and women for 14–28 d markedly increased 24-h pulsatile GH and plasma IGF-I, with a greater effect when the drug was given in the morning than at bedtime (Fig. 3) *(25)*. A preliminary report of a recent study of the same doses in frail older men and women showed a 40–65% increase in plasma IGF-I levels *(26)*.

Side effects of these short-term treatment studies have been few compared to earlier studies of GH treatment in aging, even in the frail elderly study. Published studies of GHRH treatment have reported no effects upon fasting glucose or clinical side effects such as edema or carpal tunnel syndrome. MK677 induced a small but significant (approx 8%) increase in fasting glucose and a 24% increase in serum prolactin levels; again no clinical side effects were reported. It is still not clear whether the difference in results among these studies and in comparison to previous studies of GH treatment reflect qualitative differences or simply differences in effective potency or duration of treatment. Our study of responses to 6 mo of treatment with GHRH in healthy nonestrogenized older women, alone or in combination with strength or endurance conditioning exercise, is underway *(27)*. Assessment of the effects of

GHRH on body composition, strength, and physical and psychological function awaits completion of this study.

Given the ongoing controversy over the utility of GH replacement in adults, for which more chronic treatment results are available, these ongoing studies are likely to raise as many questions as they settle. As with GH, identifying the specific populations which may benefit from GH secretagogs, and the role of these agents as a short-term treatment to enhance recovery from illness or injury vs as a long-term replacement therapy, all remain open questions.

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