**Endocrine,** *vol. 15, no. 1, 1–4, June 2001* 0969–711X/01/15:1–4/$11.00 

# Growth Hormone

## *New Ideas, Recurring Themes*

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Knowledge of basic and clinical aspects of growth hormone (GH) science, including physiology, neuroregulation, pharmacology, and a vast spectrum of clinically related issues, has unfolded over the past century. Recent decades have provided a vast and ever-growing array of information about GH. This current compendium, which touches on neuroregulation of GH secretion, GH action, therapeutic uses of GH in three different conditions, as well as on an innovative delivery system for GH, adds to this knowledge base.

The pulsatile pattern characteristic of GH secretion largely reflects interplay of two hypothalamic regulatory peptides, growth hormone–releasing hormone (GHRH) and somatostatin (SRIF), with presumed modulation by putative other GH-releasing factors *(1)*. The regulation by multiple neurotransmitters and neuropeptides of the reciprocal secretion of these hypothalamic peptides remains imperfectly understood. These factors influence GH secretion with stress, sleep, hypoglycemia, and exercise and form the basis for the many GH-stimulatory tests employed in the evaluation of GH secretory reserve. Synthetic hexapeptides capable of stimulating GH secretion are termed *GH secretagogues* (GHSs) *(2)*. These peptides stimulate GH release and enhance the GH response to GHRH but work at distinct hypothalamic and pituitary sites. Kojima et al. *(3)* recently identified ghrelin, a widely distributed, putative endogenous ligand, and a 28 amino acid peptide with the serine 3 residue *n*-octanoylated. Ghrelin strongly stimulates GH release in a dose-dependent manner in normal adult men *(4)*. Thus, multiple regulators of GH secretion are presently recognized.

The foundation for the diagnosis of insulin-like growth factor (IGF) deficiency, a term including all aspects of diminished function of the GH/IGF axis, is careful documentation of serial heights and determination of height velocity. Nonetheless, evaluation of GH production may become necessary to pinpoint the etiology of IGF deficiency. Assessment of pituitary GH production is difficult because its secretion is pulsatile, with substantial variability by gender, age, pubertal stage, and nutritional status, all of which must be factored into an evaluation. Measurement of random serum GH concentrations is virtually useless in diagnosing GH deficiency (GHD) but may help in the assessment of possible GH resistance or excess. Characterization of GH "secretory reserve," therefore, relies on physiologic or pharmacologic stimuli; such "provocative tests" have been the basis for the diagnosis of GHD for more than 30 yr. Physiologic stimuli include fasting, sleep and exercise, and pharmacologic stimuli include levodopa, clonidine, glucagon, propranolol, arginine, and insulin. Although provocative GH testing has been the "gold standard" for confirmation of GHD since GH assays first became available, there has been ample criticism *(5,6)*.

Ghigo et al. have published extensively in this field and provide further data and cogent discussion of their experience with the use of GHRH combined with arginine or GHSs for the diagnosis of GHD. They focus on adults but review their childhood experience as well. The GHRH plus arginine test mirrors GH information found through insulin-induced hypoglycemia; it may be a much safer test and appears to provide reproducible data with acceptable sensitivity and specificity, especially with appropriately chosen GH cutoff values.

Episodically released circulating GH binds to a specific tissue receptor (GHR), after which a complex cascade of post-receptor signaling occurs. GHR is a member of the class 1 hematopoietic cytokine family *(7)* and includes three domains —an extracellular, hormone-binding domain; a single membrane-spanning domain; and a cytoplasmic domain. Examination of the crystal structure of the GH-GHR complex revealed that this moiety consists of one molecule of GH bound to two GHR molecules, a GH-induced receptor dimerization necessary for GH action *(8)*. A brief summary sequence of steps in GH action include the following:

1. Binding to the membrane-associated GHR.
2. Sequential receptor dimerization through binding to each of two specific sites on GH.
3. Interaction of GHR with JAK2.
4. Tyrosine phosphorylation of both JAK2 (activation) and GHR.

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5. Changes in cytoplasmic and nuclear protein phosphorylation and dephosphorylation.
6. Stimulation of target gene transcription.

Activated JAK2 appears to phosphorylate the GHR on multiple tyrosine sites. GH- and JAK2-dependent phosphorylation and activation have been demonstrated for STAT1, -3, and -5, cytoplasmic proteins that, after forming homodimers or heterodimers, translocate into the nucleus, bind DNA, and activate transcription *(9–11)*. Other GH-activated signaling molecules provide redundant pathways that presumably interact to mediate the various anabolic and metabolic actions of GH. The nature of the GH exposure, i.e., pulsatile or continuous, affects the degree and duration of activation of the STAT5b protein by modulating dephosphorylation *(12,13)*. Espanel et al. reviewed the modulation of receptor signaling by a group of protein tyrosine phosphatases (PTPs), specifically those that hydrolyze receptor tyrosine phosphates. PTP inhibitors may therefore act as hormone mimetics. The cascade of events that follow GH binding to its receptor include substantial amounts of tyrosine phosphorylation. Thus, the potential for modulating GH expression by altering the degree of phosphorylation is potentially a new way of addressing the need to affect GH-mediated IGF production and consequent growth or alteration of other metabolic parameters.

Because untreated patients with IGF deficiency syndrome owing to GH deficiency have profound short stature (averaging nearly −5 standard deviation score [SDS]), the clinical urgency to utilize GH therapy was and is apparent *(14)*. Patients treated largely with biosynthetic GH have improved actual or near-final adult height SDS, with the average final height now approximating −1.3 SDS below the mean. Bercu et al. report successful and safe long-term (as long as 11 yr) data showing that children with GHD reached −1.5 SDS at 7 yr of treatment with an increment of 1.8 SDS during this period, with continuing longer-term growth potential. This protocol had used a lower GH dose than is now commonly utilized (0.2 vs 0.3 mg/[kg·wk]) and did include some patients who received thrice-weekly treatments. As in too many GH treatment studies, the median age at starting treatment was later than one would desire (9.7 yr). Despite the availability of GH therapy, long-term studies still show that most patients fail to achieve their genetic target heights. Even in a cohort of closely followed patients in whom mean adult height reached −0.7 SDS, with 80% being within 2 SDS for normal adult Americans *(15)*, there was still a −0.4 to −0.6 SDS difference from midparental targeted height. By multiple regression analysis, factors found to correlate with enhanced adult height were baseline height, younger age at onset of treatment, longer treatment duration, and greater growth velocity during the first year of treatment *(16)*. Although the development of recombinant GH solved the supply problem experienced in the pituitary GH era, delays in diagnosis and initiation of therapy still compromise adult height outcomes.

Non-GH-treated patients with Turner syndrome have mean final heights about 20 cm lower than those of normal women *(17)*, averaging about 143 cm in the United States *(18,19)*. In 1983, a randomized, controlled North American study of GH (at a dose of 0.375 mg/[kg·wk]) with or without added oxandrolone was initiated. Analysis at near final height showed mean statural gain of 8.4–10.3 cm compared with Lyon height predictions *(19)*. In a reassessment of North American treatment data, early initiation of GH treatment was shown to allow the administration of estrogen at a physiologic age without loss of adult height *(20)*. Several other recent studies *(21,22)*, using higher doses of GH have shown even greater gains in adult height outcomes, achieving as much as a mean increment of 16 cm over Lyon predictions *(21)*. Bramswig reviewed the multiple and diverse studies of GH therapy of Turner syndrome. The substantial variations in the GH-induced growth increments relate to GH dose, duration of estrogen-free GH treatment years, age of initiation of GH and estrogen administration, as well as population and parental adult heights. Some lingering uncertainty still exists because none of the studies were placebo-controlled to adult height and a few have yielded rather poor height outcomes *(23)*. Nonetheless, in light of historical data on natural growth in Turner syndrome, the available treatment results do provide powerful and convincing support for the belief that appropriately dosed GH therapy can both accelerate growth and increase adult height. The diagnosis of Turner syndrome should be sought at any age in a short girl and GH therapy initiated at that young age (i.e., at diagnosis).

Although current (2001) indications for GH treatment in childhood and adolescence approved by the Food and Drug Administration are GHD, Prader-Willi syndrome, chronic renal failure, and Turner syndrome (GH insufficiency need not be documented in the latter three conditions of poor growth), the availability of GH permits consideration of its use for treatment of other short-stature syndromes. Indeed, children with growth failure owing to multiple different disorders have received GH and have grown substantially *(24,25)*. Although these data arise from large uncontrolled databases, certain trends do emerge. On purely auxologic grounds, it is difficult to discriminate among responses to GH, over at least 4 yr, in children diagnosed as GH deficient by current criteria or in Turner syndrome and those in many children with other conditions *(24)*. Such data suggest that responsiveness to GH, rather than an arbitrary diagnosis of GHD, should determine appropriateness of GH therapy *(26)*.

Prospective evaluations of GH treatment of short stature associated with intrauterine growth retardation (IUGR) exemplify such a clinical circumstance. Short post-IUGR children comprise a substantial portion of growth-retarded patients seen in pediatric endocrine practices *(27,28)*. Since these children may have heights in the range seen in IGF deficiency syndrome, GH treatment certainly seems appro-

priate assuming that the insulin resistance noted in these children *(29)* does not become a relevant clinical issue. Czernichow treated a group of short children with IUGR for a 3-yr period with a relatively high dose of GH (0.067 mg/[kg·d]) and found a dramatic increase in linear growth velocity with a 2 SDS gain in height to −1.3 SDS over the treatment period. Subsequently, however, with discontinuation of treatment for an additional 3 yr, growth velocity fell markedly and height SDS dropped back to −2.0 SDS. The importance of prolonged therapy is emphasized by these findings. Long-term responses to GH treatment reported by Sas et al. *(30)* and de Zegher et al. *(31,32)* showed mean increments of 12–14 cm over predicted adult height after 5–7 yr of GH treatment, using several different dosing regimens. GH therapy for this group of patients, which accounts for about 20% of short-statured children, could become a quantitatively important use of GH.

Multiple systems are now available for administering GH. Either reconstituted or liquid GH is administered in insulin syringes with ultrafine needles that are almost pain-free in skilled hands. Pen devices with internal reconstitution of the GH are frequently used because of ease, accuracy, and hidden needles. Autoinjectors that automatically insert the needle and inject GH are reducing stress and pain of daily injections. Sustained-release GH is administered through a short, larger bored needle, and the injection pain is balanced against the low frequency of treatments. Needle-free, jet injector systems are available and yield a normal serum immunoreactive and bioactive GH profile *(33)*. Silverstein et al. describe an experience with such a delivery system. A group of young children with type 1 diabetes reported that they had minimal pain, stinging, and nervousness relating to using the needle-free device, with 74% preferring it to their standard insulin syringes and fine-gage needles. Their data certainly support the use of this technologic advance in GH treatment.

These reports raise the possibilities and expectations for different therapeutic modalities for patients needing GH and stress the importance of early and appropriate diagnosis, treatment with adequate doses of GH, and adherence to a continuous regimen. That daily GH administered for an adequate duration is necessary for the best outcomes is reaffirmed in several of the studies. The recognition that changes must be undertaken in patients who are not responding appropriately is stressed in the study of Saenger et al. In that series, patients who did not grow optimally during treatment with growth hormone-releasing factor (GRF) achieved better growth velocity with GH. This serves as another reminder of the need to closely monitor patients to ensure adequate growth, perhaps to use sophisticated modeling to recognize the individual child who does not have the expected response, and then to change the therapeutic regimen.

The diversity of studies reported in this issue of *Endocrine* affirms that interest in GH is not waning. The search for new treatment modalities that specifically address the individual needs of our patients remains the goal and encourages performance of innovative basic and clinical research in this discipline.

## Acknowledgment

The publication of these articles and the journal supplement was supported by Serono International S.A.

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