

GROWTH

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Growth Hormone Physiology and Pathophysiology: A Review

The complex system that encompasses the release and action of growth hormone (GH) includes many neurotransmitters, hormones, and organs. Among these are biogenic amines such as dopamine and serotonin in the brain; somatotropin-releasing hormone (SRH) and somatostatin or somatotropin-release-inhibiting hormone (SRIH) in the hypothalamus; somatotropin or GH in the pituitary; and insulin-like growth factors I (IGF-I) and II (IGF-II) in the liver and possibly in other organs. The mechanisms by which this complex system generates growth as a result of GH production and release from the pituitary are rapidly being elucidated.

One purpose of this article is to review the current concepts regarding these mechanisms, thus facilitating interpretation of the abstracts that are highlighted in this newsletter. The second goal is to briefly emphasize that more is known about the mechanisms involved in the secretion of GH and IGF than about the indications for treatment with GH.

A number of phasic changes in GH secretion are mediated by brain centers under the stimulus of bioamines. For example, dopamine is a stimulus to GH secretion. The arcuate nucleus, in particular, and possibly the ventromedial nucleus as well, respond by releasing SRH and SRIH. Both are transported from the hypothalamus via the portal system to the pituitary, where they attach to their respective receptors on the somatotrophs. Interestingly, SRIH, also referred to as somatotropin-release-inhibiting factor (SRIF) or somatostatin, is present in organ systems other than the

brain (ie, the pancreas and gut). However, SRH has not been shown to be present normally in structures other than the hypothalamus. Three forms of SRH have been identified—one with 44, one with 40, and one with 37 amino acids. These forms are approximately equipotent. The first two have been identified in the hypothalamus.

The synthesis and release of GH in the somatotrophs are under the control of the cAMP system. Both synthesis and release are sensitive to calcium ion fluxes and diacylglycerol. Protein kinase-C, the putative phorbol ester receptor, also plays an important role in the stimulated secretory pathway for GH, as indicated by marked increases in GH release by anterior pituitary cells of rats following stimulation with the phorbol ester, phorbol-12-myristate-13-acetate. SRH, cholera toxin, and forskolin lead to cAMP accumulation in somatotrophs and stimulate growth hormone release; SRIH inhibits both actions of these secretagogues, and thus its action is also closely related to the cAMP system. As the pituitary portal blood concentrations of SRH and SRIH change, the serum levels of GH rise

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and fall in an intermittent pulsatile fashion.

The feedback mechanisms to control GH release are multiple and complex. For example, SRH can diminish its own secretion in the rat, as shown by Tannenbaum, who injected SRH in graded doses into the cerebral ventricles of rats. Increasing doses given in this manner led to a dose-dependent inhibition of GH secretion. This profound effect was not due to SRIF secretion, as shown by the inability of the antiserum to SRIF to reverse the suppression of GH release. Thus, SRH can affect its own secretion by means of an ultra-short negative feedback loop mechanism.

In addition, SRH produces negative feedback at the somatotroph when there is lengthy exposure to the peptide. Pretreatment of anterior pituitary cell cultures from rats with SRH resulted in decreased cAMP and GH concentrations in these cells when the cells were reexposed to SRH.

Insulin-like growth factors also are involved in the feedback control of GH secretion. When placed in the cerebral ventricles, IGF-I causes a profound decrease in the spontaneous intermittent secretion of GH in rats. This action may occur through the release of SRIF; Berelowitz et al demonstrated that IGF-I directly stimulates the acute release of SRIF from rat hypothalamic fragments in culture.

Growth hormone also plays a feedback role in GH secretion. Berelowitz et al noted that GH acts at the hypothalamus to stimulate both the synthesis and release of SRIF. Abrams, Grumbach, and Kaplan demonstrated in humans that GH injections given every six hours for six days diminished GH release by the pituitary when insulin was given eight hours after the last GH injection. It was not ascertained whether this was a direct effect of GH or an indirect effect through somatomedin generation. In summary, there is a complex series of negative feedback loops that control the tonic and phasic secretion of GH.

After GH is released into the circulation, it travels to the liver and other

tissues, including chondrocytes in growing cartilage. In the liver, and possibly in cells of other tissues, GH stimulates the production of IGF-I and IGF-II. These growth factors, homologues of the proinsulin molecule, have biologic effects that are qualitatively similar to those of insulin. Although IGF-II possesses more insulin-like activity than IGF-I, neither factor reacts with anti-insulin antibodies. The molecular weight of each is about 7,500 daltons, and the factors resemble proinsulin in that about 50% of the amino acid residues in the A and B chains are identical with the corresponding sequences in human proinsulin. Radioimmunoassays specific for each of these have been developed, and a radio-receptor assay for IGF-II is performed in several laboratories.

Both IGF-I and IGF-II are under GH control, since concentrations of both have been reported to fall with GH deficiency. There is no question that IGF-I uniformly falls with GH deficiency; however, Bucher et al reported that IGF-II levels were normal in most patients with GH deficiency. Only IGF-I rises above adult values with GH excess. Moreover, the concentration of IGF-I rises slowly throughout childhood and peaks during adolescence at values that are two to three times higher than preadolescent and postadolescent values. IGF-II increases sharply after birth and normally remains constant throughout life. The insulin-like growth factors also differ in their growth-promoting activity: IGF-I is a potent sulfation factor, but IGF-II is weak in this regard.

IGF-I itself is probably essential to growth, although the possibility that GH may act directly on chondrocytes has not been totally excluded. Recent studies have suggested a direct effect on the longitudinal bone growth process by GH to the epiphyseal cartilage growth plate of hypophysectomized rats. Even the generation of IGF-I, however, does not guarantee normal growth. In certain humans with a GH-deficient-like phenotype, GH and IGF-I concentrations are normal or elevated, but growth does not occur normally. Therefore, the cell must be

able to accept IGF-I and translate its presence into action with synthesis of DNA, leading to cell multiplication (see page 12, Bierich et al: *Eur J Pediatr* 1984;142:186).

It is apparent that many steps are required for the synthesis and secretion of GH, and in the synthesis and action of insulin-like growth factors. Consequently, the physician evaluating a child with short stature, delayed bone age, and the clinical appearance of GH deficiency may be perplexed by the results of tests for GH secretion. Growth hormone deficiency may be complete, partial, or even transient as in children with psychosocial short stature. The child being evaluated may even secrete normal or increased amounts of GH but not generate IGF-I normally.

Therefore, IGF-I (somatomedin-C) determinations become important adjuncts in the evaluation of such patients. However, as mentioned previously, there are some patients who secrete GH and IGF-I normally, but who are unable to translate the presence of IGF-I into action on cell growth and multiplication. Consequently, consultation and sharing of knowledge among physicians interested in growth problems is an essential component of appropriate diagnosis and treatment.

Treatment of patients with obvious GH deficiency is straightforward. However, treatment of patients who have a GH-deficient-like phenotype—but who generate GH in at least certain testing situations—is not straightforward. Growth hormone may be effective in some such children, but not in others. Appropriate controlled studies need to be done to determine which children with a GH-deficient-like phenotype will increase their growth rates and, possibly, their ultimate heights.

Until such time as these studies have been done and we know as much about the therapeutic aspects of GH as we know about the physiologic aspects as outlined above, cautious prescribing of GH is judicious.

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References supplied upon request to authors.