Growth Hormone, 1988

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Growth hormone (GH)[1] was isolated approximately 30 years ago and since then, major advances have been made in our understanding of the regulation and pattern of GH secretion and its actions. However, despite these achievements, our knowledge of this hormone remains in its infancy. GH is necessary for normal linear growth, but it also affects many aspects of metabolism, so that it has been described as being anabolic, lipolytic, and diabetogenic. Information on the metabolic effects of GH has been obtained from in vivo and in vitro studies of such isolated tissues as muscle and adipocytes. The recent production of human GH by recombinant DNA techniques (1), the discovery of the hypothalamic GH-stimulating hormone, growth hormone-releasing hormone (GHRH) (2–4), and the cloning of the GH receptor (5) will have a major impact on the continued study of the physiology of human GH.

The molecular biological approach to the study of GH resulted in purification, cloning, and expression of the human GH receptor and binding protein (5). Based on cloning studies, the complete amino acid sequences encoding the putative human and rabbit GH receptors have been identified. The molecular mass of these receptors is 130,000 D and they are presumably heavily glycosylated. These proteins are unique and have no similarity with other known proteins. Despite 84% identity in the amino acid sequence between the human and rabbit receptors, they are immunologically quite dissimilar (6). The GH receptor consists of three components, an extracellular portion that presumably binds GH, a transmembrane portion, and a cytoplasmic portion. The receptor does not appear to be a tyrosine kinase or to act via G proteins. It has been known for several years that cells from the IM-9 lymphocyte cell line shed a soluble GH-binding protein. It is therefore interesting that cells transfected with human GH receptor cDNA not only express a membrane-associated GH-binding protein, but also secrete a soluble GH-binding protein. This binding protein has the characteristics of the human GH receptor, in that it binds human but not bovine GH or ovine prolactin. The characteristics of rabbit GH receptor cDNA-transfected cells have the characteristics of the rabbit GH receptor, in that they bind human and bovine GH. GH-binding proteins are present in normal human blood and absent in patients who have Laron dwarfism (7, 8). These patients are believed to be deficient in the GH receptor. It is likely that these binding proteins represent the shed extracellular component of the GH receptor. An alternative possibility is that the binding protein is a separate secretory product of the cell.

GH acts both directly and via its stimulation of insulin-like growth factor I (IGF I) production to promote linear growth. However, GH continues to be secreted during adult life after growth has ceased. GH thus presumably has other important physiologic functions. In this Perspective, we will review some aspects of GH secretion and actions in man and consider important areas for further study.

GH is secreted episodically, as demonstrated by studies in which frequent blood samples are obtained. Hormone concentrations are usually below the level of assay detectability between these observed bursts. Relatively few studies have defined clearly the normal profile of GH release during development and adult life, but GH secretion apparently is low during infancy and increases but remains stable at fairly low levels during early childhood, until just before puberty (9). At puberty, GH secretion is greatly enhanced, decreases in late adolescence, and remains stable until ~ 30 yr, when a progressive decline, which endures through old age, begins (10). The reasons for the decrease in GH secretion in adults are unknown, but possible factors that influence GH secretion include caloric intake, lean body mass, and the gonadal steroid milieu. A cross-sectional study was carried out to characterize GH release in adults of different age groups. GH levels were measured every 20 min over 24 h and integrated concentrations among the groups were compared. Additionally, gonadal steroid levels, testosterone, estradiol. and free estradiol were measured. Integrated GH concentrations were lower in the older men and women (> 55 yr) than in the younger men and women (18–33 yr). Women in both age groups had more GH release than the men. The lower GH concentrations in the older subjects most strongly correlated with decreased circulating estradiol and free estradiol levels. Stepwise regression analysis was used to determine the effects of age, gender, and body mass index, independent of the effect of estradiol, on GH concentrations. When the effect of estradiol was removed, there was no significant correlation of GH secretion with age, gender, serum testosterone, or body mass index (11). It thus is likely that circulating estradiol plays either a stimulatory or permissive role in somatotrope secretion. Note that GH secretion is greatest in young women and that GH secretion is enhanced in postmenopausal women during estrogen administration (12). The effect of gonadal steroids on GH secretion is different in other species, such as the rat. GH secretion is greater in the male than in the female rat and is thought to

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1. *Abbreviations used in this paper:* GH, growth hormone; GHRH, growth hormone-releasing hormone; IGF I, insulin-like growth factor I; SRIF, somostatin.

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result from the higher testosterone concentrations in the male. Male rats have higher bursts of GH secretion and lower interpeak concentrations than do females (13). The role of androgens versus estrogens in influencing GH secretion in man thus apparently differs from that of the rat.

GH secretion is regulated by several factors including the hypothalamic hormones GHRH, which is stimulatory, and somatostatin (SRIF), which is inhibitory, and by IGF I. The hypothalamic-pituitary-peripheral axis is a closed-loop system in which episodic GH release is a result of concomitant reduction in hypothalamic SRIF secretion and an increase in GHRH secretion (14). GH stimulates the liver and other peripheral tissues to produce IGF I, which in turn feeds back on the hypothalamus and pituitary and exerts a negative influence on further GH release. Circulating IGF peptides are tightly bound to proteins. There are at least two circulating macromolecular complexes of bound IGF I that have a longer half-life than the free form and modified biological actions (15). The physiologic role of the different IGF forms remains to be determined. Since IGF is present in multiple peripheral tissues and serum, it may act as a paracrine factor and a hormone (16, 17). Circulating IGF I levels may be relatively unimportant and the tissue levels thus may be of greater physiologic and biochemical significance.

Nutritional state and caloric intake influence GH secretion. Chronic malnutrition, such as kwashiorkor, is associated with elevated GH levels, subnormal IGF I levels, and growth retardation (18, 19). Similarly, patients with anorexia nervosa may have increased GH levels (20). The role of nutrition on GH secretion is currently the subject of intensive study. To characterize the effect of nutrition on GH secretion, normal adult male volunteers were studied before, during, and at the end of a 5-d fast by measuring GH levels every 20 min for 24 h (21). During the first 36 h of fasting, there was a threefold increase in integrated GH concentration and an increase in the number and amplitude of the GH pulses. These increases were further enhanced on the fifth day of the fast. Serum IGF I levels were unchanged during the first day, but declined by the fifth day (21). Similar results were obtained in another study in which GH levels were measured every 5 min before and on the fifth day of fasting. The hormone concentration profiles were also subjected to analysis using a computer model that calculates both secretion and clearance functions from the measured peripheral values, which reflect both secretion and clearance. Using this deconvolution method (22), the increase in integrated GH concentrations was a result of increased hormone production and that the rate of GH clearance was unchanged. Serum IGF I levels declined progressively over the 5 d of fasting, all subjects developed ketonemia, and there was no detectable change in serum total or free estradiol levels (23). Whereas the physiologic importance of these experiments may be questioned, the results indicate that caloric deprivation has profound effects on GH secretion.

GH has been administered to domestic animals, including pigs and cattle, and resulted in increased nitrogen retention (pigs and cattle), improvement in feed efficiency (pigs), and more efficient galactopoeisis (cows) (24). GH has a marked effect on the composition of the carcass, such that the amount of fat is reduced and the protein content is increased (25). This partitioning effect may also occur in man, but the effects of GH on metabolism may only be demonstrable during times of nutritional deprivation. Since most human studies of GH effects are carried out under more than adequate nutritional conditions, the metabolic functions of this hormone may not be evident. Compared with Western man, the majority of the world's population is not overnourished and is fortunate to have one meal a day. GH may be of vital importance in optimizing use of stored fat while minimizing muscle catabolism during food deprivation. Poorly controlled diabetes mellitus is a clinical situation that may mimic this phenomenon. Hyperglycemic diabetics also have increased GH secretion, which may reflect relative intracellular starvation (glucopenia) secondary to insulin deficiency. Exercise is another potent stimulus for GH release. In general, well-trained athletes have little fat and increased muscle mass (26). Whereas precise studies of GH secretion in these subjects have not been performed, it is intriguing to speculate that the body composition of athletes may be influenced by enhanced GH secretion that results from intensive training. The current misuse of GH by some athletes with the intent of increasing muscle mass emphasizes the need to determine the metabolic role of GH.

Some preliminary studies of the role of GH in the partitioning of fat, protein, and carbohydrate metabolism in humans have been reported. In early studies, nonprimate GH was used and no effect was demonstrated (27). However, the structures of bovine and human GH differ and bovine GH does not interact with the human GH receptor. In a more recent study, placebo and pharmacologic doses of human GH were administered for 1 wk to normal men given an intravenous diet consisting of 50% of minimum caloric and normal amino acid content. Significant changes associated with GH administration compared with placebo included less weight loss, nitrogen, potassium, and phosphorous retention, hyperinsulinemia, an increase in fasting blood glucose, ketonuria, and increased calciuria. When caloric intake was reduced to 30% of the minimum requirement, the metabolic rate increased significantly during GH treatment. Serum FFA, but not glycerol, were somewhat increased during GH administration (28). In another study, obese subjects were given a pharmacologic dose of methionyl human GH every other day for 3 wk during dietary restriction. GH administration was associated with a significant decrease in the mean daily nitrogen deficit and a trend to greater fat loss when compared with the placebo treatment (29). The effects on fat metabolism were less dramatic than in the study of GH effects during more severe caloric restriction and this may reflect dietary differences. Studies have been proposed to determine whether GH is beneficial in the treatment of patients with malabsorption, extensive burn injuries, and trauma. If GH is beneficial, this may offer a new approach to the treatment of these difficult disorders.

The role of GH in the treatment of GH-deficient children is established. However, the definition of GH deficiency remains controversial for several reasons, including uncertainties about whether the GH response to a pharmacologic test or a serum IGF I concentration reflects overall GH secretion and the precise significance of GH profiles obtained by frequent sampling. The GH secretory profile in normal children of varying stature is not established. As human GH produced by recombinant DNA methodology is now widely available, the question arises: should all children with short stature be given a trial of GH therapy regardless of the results of testing? Corollary questions include: even if acceleration of growth occurs over the short term (6–12 mo), what is the effect of GH on ultimate height in GH-sufficient children? What adverse effect may arise from chronic administration of GH to GH-sufficient children? The answers are currently unknown. These questions raise serious medical, psychological, social, ethical, and

financial issues for which answers are not readily available.

Although it is exciting to speculate that GH may be useful to increase muscle mass in athletes, to increase the ultimate height of children with short stature, and to treat such diverse conditions as burns, malabsorption, and obesity, a plea must be made for well-designed and careful metabolic studies to characterize the direct effects of GH and its indirect effects via IGF I and other mediators of human metabolism. In this regard, the recent description of adipsin (30, 31), a large protein in the serine protease family that is liberated from rodent 3T3 adipocytes, offers a scientific basis for an older proposal that adipocytes dictate their own metabolic requirements (32, 33). Does adipsin exist in man and, if so, does it direct neuroendocrine function? This and many other fascinating issues await urgent study in pursuit of answers to such important clinical questions as the pathophysiology of obesity, anorexia nervosa, and type II diabetes mellitus, to mention just a few.

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