Hypophyseal Growth Hormone: I. Control of Secretion

M. Saeed Zafar
Raymond C. Mellinger
Lewis B. Morrow

Follow this and additional works at: https://scholarlycommons.henryford.com/hfhmedjournal

Part of the Life Sciences Commons, Medical Specialties Commons, and the Public Health Commons

Recommended Citation
Available at: https://scholarlycommons.henryford.com/hfhmedjournal/vol18/iss2/9

This Article is brought to you for free and open access by Henry Ford Health System Scholarly Commons. It has been accepted for inclusion in Henry Ford Hospital Medical Journal by an authorized editor of Henry Ford Health System Scholarly Commons.
Growth hormone (GH) is a major hormone of the anterior pituitary gland. Once established, its secretion continues throughout life. GH was first recognized in 1866 as a factor controlling growth. More recently, it has been demonstrated as a vital regulator of fat, carbohydrate and protein metabolism. In fact, GH influence on the intermediary metabolism is the major mechanism by which growth and development are regulated. Numerous hormonal and nonhormonal factors have been shown to modify the basic pattern of GH synthesis and secretion. In this article we have reviewed some of these nonhormonal factors.

Human growth hormone (GH), a polypeptide of 188 amino acids with a molecular weight of 21,500, shares with melanocyte-stimulating hormone the distinction of being an anterior pituitary factor having no target endocrine gland. An association between the pituitary and growth was first recognized in 1866 by Marie, who observed pathologic changes in the hypophysis of patients with acromegaly. Subsequently, Aschner demonstrated that hypophysectomy of young animals resulted in dwarfism, and in 1921 Long and Evans made the first successful attempt to influence growth with hormones when they produced giant rats by prolonged daily injections of ox pituitary extract.

Synthesis and release of growth hormone is controlled by a hypothalamic secretion called growth hormone releasing factor (GHRF). Produced in or around the ventro-medial nucleus, GHRF travels via the hypothalamo-hypophyseal portal system to the anterior pituitary. Existence of this hypothalamic factor was demonstrated when Deuben and Meites showed that rat hypothalamic extract caused the secretion of GH in a tissue culture of rat anterior pituitaries. Shortly thereafter, similar activity was demonstrated in bovine and porcine hypothalamic extracts incubated with rat pituitaries. Pecile et al. first studied the effects of hypothalamic GHRF in vivo and the factor has been identified in the hypothalami of various species including man.

Localization of GHRF in the ventro-medial nucleus of the hypothalamus is documented by experiments in which monkeys with isolated lesions of this
region fail to release GH in response to hypoglycemia.\textsuperscript{11} In man also, an intact hypothalamo-hypophyseal system is essential for release of GH; patients with pituitary stalk section have no GH response to hypoglycemia.\textsuperscript{12} Experimental evidence in rats indicates that GHRF acts directly on the pituitary to promote GH synthesis as well as its release.\textsuperscript{4,13-15}

Many factors, both hormonal and non-hormonal, influence the secretion of growth hormone. The plasma GH level fluctuates rapidly and widely under the influence of various known stimuli and at times without any known stimulus. Accordingly, growth hormone must be studied under controlled conditions and initial plasma levels determined with the subject in the basal state. Thereafter, GH response to modifying conditions may be evaluated.

Non-Hormonal Factors Affecting GH Secretion

\textit{Age}. Basal growth hormone values vary little with age. In the newborn, umbilical vein blood levels are high\textsuperscript{16} but by the age of four years, the lower adult levels have been reached and no consistent change in basal values is evident thereafter.\textsuperscript{17-22} Although no increase in basal GH levels has been demonstrated during the adolescent growth spurt, both estrogens\textsuperscript{23} and androgens\textsuperscript{24} can be shown to cause an increased GH response to other stimuli.

\textit{Glucose}. In normal subjects, a 50\% fall in blood sugar can cause a fivefold or greater elevation in plasma GH.\textsuperscript{12} The increase occurs 15 to 30 minutes after the nadir in blood glucose concentration and persists for several hours. Since the plasma half-life of GH is no more than 30 minutes\textsuperscript{22,25} the persistence of high concentrations for several hours during prolonged hypoglycemia suggests sustained GH hypersecretion. This pattern of response differs from that of the catecholamines\textsuperscript{26} and corticosteroids\textsuperscript{27} whose blood levels also increase with acute hypoglycemia but are not sustained, despite persistent low blood sugar.\textsuperscript{22}

A fall in blood glucose is a powerful stimulus for GH release whether induced by insulin, tolbutamide or fructose.\textsuperscript{18,22,28} Actual hypoglycemia is not essential to the reaction inasmuch as a rise in GH may occur after the third hour of a glucose tolerance test when the elevated sugar is falling to control values.\textsuperscript{22} On the other hand, ethanol-induced hypoglycemia may not provoke a rise in GH, possibly because there is associated central suppression of the GH releasing mechanism.\textsuperscript{29} Overnight fasting is accompanied by a continued GH rise but the levels do not reach the height induced by acutely lowered glucose concentration.\textsuperscript{22}

The mechanism by which hypoglycemia provokes release of GH is not entirely established but a fall in intracellular glucose utilization is considered the essential stimulus. The rise in plasma GH can be prevented by the simultaneous administration of glucose with insulin or even by the administration of glucose 20 minutes after the insulin injection, hypoglycemia having already ensued.\textsuperscript{22} Furthermore, the administration of 2-deoxy-D glucose, an inhibitor of intracellular glucose utilization, causes a rise in plasma GH even in the presence of elevated blood sugar.\textsuperscript{30}

It may be concluded, therefore, that a decrease in glucose available for utilization at a critical intracellular site in
Hypophyseal Growth Hormone

the median eminence of the hypothalamus provokes release of GHRF. This factor is carried through the hypothalamic-hypophyseal portal system to the acidophilic cells of the anterior hypophysis where it stimulates GH synthesis and secretion.

Contrary to the provocative action of hypoglycemia, hyperglycemia suppresses GH release. For unknown reasons the GH level is variable during the first half hour after glucose administration but declines thereafter to a nadir at three hours, followed by a rise between the 4th and 6th hour. Normally, glucose-induced suppression does not occur in acromegaly, in some patients with intracranial tumor and in infants.

Protein. Consistent elevation of plasma GH following ingestion of beef has been reported in female subjects. The extent and time of the response is variable but elevation occurs most frequently three hours after oral feeding. Knopf et al proved that infusion of various L-amino acids also simulates GH release and arginine was found to have the most potent action. Inexplicably, the GH rise to amino acid stimulus was inconsistent in males but after pre-treatment with stilbestrol, unresponsive male subjects reacted sensitively. Amino acid infusion also causes changes in blood glucose and stimulates secretion of insulin but the extent and time relationship of these changes are such that GH release is not considered to be a secondary phenomenon. In fact, even during hyperglycemia, arginine infusion can induce a rise in plasma GH.

Parker et al analyzed the response of 49 persons age 4 to 65 to arginine infusion. In the 28 males and 21 females, maximum GH level was reached by 40 minutes to an hour and the mean peak was 21 m\(\mu\)g/ml. In a control group studied during insulin testing the mean peak was 17 m\(\mu\)g/ml. The response to arginine was higher in post-pubertal individuals than in children. In the study of growth retarded children, both insulin and arginine stimulation is advocated because of the occasional failure of normal subjects to respond to either test situation.

Fat. Ingestion of fat has not been shown to affect plasma GH. No rise in plasma GH occurs with increased plasma free fatty acids (FFA) and GH levels of human subjects do not change following administration of 50 gm of olive oil. Moreover, heparin-induced elevation of FFA does not alter plasma GH levels. On the other hand, Blackard et al demonstrated that lipid infusion in monkeys completely inhibits the anticipated rise in GH following insulin-induced hypoglycemia. Infusions of soybean oil emulsion or sodium octanoate were equally effective although the large doses used produced plasma FFA levels far above the physiologic range.

Sleep. Serial determinations of plasma GH levels indicate that secretion occurs in intermittent bursts. Such fluctuations are more prominent at night. A marked elevation which occurs with the onset of deep sleep soon subsides and is followed by additional GH peaks of decreased magnitude. When a state of full wakefulness is maintained at night, plasma GH does not fluctuate. The secretion pattern is closely related to the depth and course of sleep. Honda et al believe that activation of the neocortex inhibits GH secretion whereas slow-wave sleep is associated with re-
lease of GHRF and consequently, with growth hormone.\textsuperscript{45}

\textit{Exercise}. Roth et al\textsuperscript{30} observed that moderate exercise stimulates GH secretion. Thirty minutes of walking at moderate speed is regularly followed by an elevation of plasma GH although this rise can be blunted by ingestion of glucose prior to the exercise.\textsuperscript{22}

\textit{Surgery}. An increase in GH parallel to the rise of cortisol occurs during surgical stress.\textsuperscript{47,48} Recently, Charters studied anterior pituitary function in 13 patients during surgery and convalescence.\textsuperscript{49} Plasma GH concentration rose from a control of 2.0 to a mean peak of 16 m\textsuperscript{\mu}g/ml during the first hour of the operation, but decreased toward control levels at two hours despite continued surgical stress. In contrast, corticosteroid concentration increased concomitantly with the GH rise but remained elevated throughout the operation. During convalescence, plasma GH varied greatly on the first postoperative day and stabilized in the normal range subsequently.

\textbf{Summary}

Regulation of growth is the primary but not the only function of growth hormone. GH levels in the premature infant and in the cord blood of newborns are very high, and the widely held concept that GH is not essential for growth in the first year of life has recently been challenged.\textsuperscript{50} During the time of accelerated pubertal growth, basal GH levels are not elevated but the overall secretion may be augmented, consistent with the increased GH response to various stimuli which follows administration of sex steroids.

Because somatic growth requires protein synthesis, nitrogen storage is considered the fundamental biologic GH effect. This anabolic activity is accomplished by complex alterations of the intermediary metabolism of fats and carbohydrates, sparing protein for tissue synthesis. GH secretion, functioning as a metabolic regulator, persists even after potential growth is attained. Just as growth hormone regulates metabolism of proteins, fat, and carbohydrates, the available concentrations of these factors in turn regulate GH secretion. This relationship suggests the "negative feedback" which exists between pituitary tropic hormones and their target gland secretions. In the presence of high glucose concentration (meals) GH secretion is inhibited; during relative glucose deficiency (fasting and exercise) GH secretion is stimulated. The increased hormone reduces glucose utilization, tending to maintain the blood sugar level. Concomitantly, GH-induced lipolysis provides fatty acids to be utilized for energy and gluconeogenesis, while catabolism of proteins is proportionately diminished. Increased concentration of amino acids also stimulates GH release, the increased hormonal levels serving to enhance amino acid transport and protein synthesis.

The physiologic significance and possible utility of the alterations induced by deep sleep are speculative, but the biologic value of increased growth hormone during exercise and physical stress is readily appreciated.

In this article we have reviewed some of the effects of nonhormonal factors regulating GH secretion. Subsequently, we will discuss the significance to the body economy of the interplay between GH and other hormones.
Hypophyseal Growth Hormone

REFERENCES


