A 13-year-old boy is brought to the pediatrician by his mother because of concerns about his growth. The patient is considerably taller than all his classmates, has coarse facial features, and has a prominent jaw. Both parents are short in stature, and his growth is very abnormal for other family members. On examination, the patient is noted to be extremely tall for his age with frontal bossing, increased hand and foot size, and coarse facial features with a prominent jaw and an enlarged tongue. His skin is noted to be oily with numerous skin tags. After further workup is performed, the patient is diagnosed with gigantism.

◆ With what other pituitary hormone is growth hormone homologous?

◆ How does somatostatin inhibit growth hormone?
ANSWERS TO CASE 39: GROWTH HORMONE

Summary: A 13-year-old boy has abnormal growth and a diagnosis of gigantism.

◆ **Hormone homologous with growth hormone:** Prolactin.
◆ **Inhibition of growth hormone:** Somatomedins stimulate the production of somatostatin and act directly on the anterior pituitary.

CLINICAL CORRELATION

Growth hormone production is critical for normal adult growth. If overproduction occurs in childhood, gigantism will result. Overproduction during adolescence (after puberty) will result in acromegaly. Once a child’s growth plates have fused, responsive osteoblastic progenitor cells are stimulated in the periosteum. This results in thickening of the cranium (frontal bossing), the mandible, and the bones of the hands and feet. These patients also have thickening of the skin (increased growth of skin tags) and other soft tissue structures. Growth hormone excess can be treated with somatostatin analogues.

Failure of growth hormone secretion in childhood results in pituitary dwarfism. These children have normal growth during early infancy but have abnormal growth thereafter.

APPROACH TO GROWTH HORMONE PHYSIOLOGY

Objectives

1. Know about growth hormone (GH), including synthesis, secretion, and mode of action.
2. Understand the physiologic effects of GH.
3. Describe the regulation of GH secretion.

Definitions

**Growth hormone:** Small peptide hormone secreted by the anterior pituitary gland that binds to a plasma membrane receptor in target tissues having both direct and indirect actions to promote growth of the organism. Direct actions result in increased gluconeogenesis, and amino acid uptake in liver and muscle and lipolysis in adipose tissues. Indirect actions involve activation of specific transcription factors that generate growth factors to stimulate bone elongation.

**Growth hormone binding protein:** A circulating protein derived from the proteolytic breakdown of the GH receptor complex that binds to and stabilizes circulating GH.

**IGF-1 and IGF-2:** Insulin-like growth factors are peptide hormones that are produced and secreted mainly by the liver in GH dependent fashion that mediate indirect GH actions on growth of the organism.
DISCUSSION

Growth hormone, also known as somatotropin, is a 191-amino acid peptide hormone with a mass of approximately 22,000 Da. It is synthesized in the anterior pituitary gland in cells that are called somatotrophs and stored in dense granules in secretory vesicles. After stimulation of the cell, the secretory vesicles are translocated to the plasma membrane and undergo fusion, with release of granule content into the circulation. Although labile when free in the blood, GH is stabilized by binding to a specific binding protein. A novel aspect of the GH-binding protein was the finding that it is homologous to the extracellular domain of the GH receptor. The receptor is the source of the binding protein after proteolytic scission of its extracellular domain. The mode of action of GH is complex, with both direct and indirect actions on target cells and tissues. The GH receptor is a member of a superfamily of plasma membrane receptors known as tyrosine kinase–associated receptors that includes the prolactin receptor and several cytokine receptors. Characteristically, these receptors have an extracellular domain and a single membrane-spanning domain. Hormone binding induces the dimerization of two receptor molecules. Dimer formation forms an intracellular domain that binds to and activates the tyrosine kinase Janus kinase 2 (JAK-2). JAK-2 activation phosphorylates tyrosine residues on the receptor molecule which then serve as docking sites for other receptor-binding proteins that themselves are activated with subsequent activation of the STAT and mitogen-activated protein (MAP) kinase signaling pathways. These pathways lead to the activation of specific transcription factors.

Among the gene products are a family of peptide hormone intermediates that are required for some GH-dependent processes: the somatomedins or insulin-like growth factors (IGF-1 and IGF-2). The IGFs are structurally related to insulin, and IGF-1 has about 50% homology with the A and B chains of proinsulin. There are specific receptors for IGFs in many cell types that are structurally related to the insulin receptor and exhibit tyrosine kinase activity. IGF-1 also binds to the insulin receptor. Their mechanism of action appears to be similar to that of the insulin receptor. IGF-1 seems to be the physiologically more relevant molecule. It is synthesized and released from multiple GH target tissues and in some studies appears to have an autocrine or paracrine role in regulation. However, the IGFs do enter the circulation with an extended half-life as a result of binding with six specific insulin-like growth factor–binding proteins (IGFBP₁–₆). The primary site of synthesis is the liver, which seems to maintain the circulating level of IGFs. Many GH-dependent actions are mediated by these hormones. In the absence of GH, the hormones are not present in the circulation.

The role of GH is to regulate growth of the organism. The physiologic actions of GH are primarily anabolic, characterized by an increase in RNA and protein synthesis. GH tends to favor lipolysis in adipose tissue but promote gluconeogenesis, amino acid uptake, protein synthesis in the liver and muscle, and IGFs and IGFBPs in the liver and target tissues. Most of
the effects on other tissues (eg, bone, heart, lung) are indirect and are mediated by IGFs produced in the liver or the target tissue. Administration of GH to GH-deficient individuals causes an immediate nitrogen retention and decrease in urinary urea and phosphate excretion, signaling an increase in protein synthesis and structural remodeling.

**GH stimulates skeletal elongation** and growth through its action on the bone epiphyseal plates. GH targets chondrocytes, which are a major cell type populating the epiphyseal growth plate. Chondrocytes are cartilage-forming cells that generate a cartilage matrix that subsequently becomes calcified. Osteoblasts migrate into the calcified matrix, resulting in bone formation. Thus, bone elongation occurs by continual generation of chondrocytes in the epiphyseal growth plate and production of the cartilage matrix. GH stimulates amino acid uptake, protein synthesis, collagen synthesis, chondroitin sulfate production, and cartilage formation. There is an increase in cell number and cell size with a continual elongation of columns of chondrocytes. In the absence of GH, the epiphyseal growth plate atrophies and chondrocyte growth diminishes.

GH is secreted in a pulsatile fashion with an irregular frequency. Characteristically, GH secretion follows a pattern of frequent bursts of secretory activity throughout the day, with a maximal prolonged burst in the early morning hours. GH secretion occurs throughout life but is maximal during the years with the highest growth rate, peaking during early puberty and adolescence. Secretion is controlled by the hypothalamus through the two neuropeptides growth hormone–releasing hormone (GHRH) and somatostatin. The regulated release of these two hormones acts in concert to control the secretion of GH. GHRH stimulates the synthesis and secretion of GH, and somatostatin interferes with the pituitary response to GHRH. A third control is exerted through a negative feedback by IGF-1 to inhibit GH secretion. For each of these controls, there are specific receptors on the GH-secreting cells.

**COMPREHENSION QUESTIONS**

[39.1] The actions of GH are mediated in part by which of the following?
   A. Insulin
   B. Somatomedins
   C. Thyroid hormone
   D. Estrogen

[39.2] A 45-year-old woman has a cerebrovascular accident that causes necrosis of the posterior pituitary. Which of the following effects is most likely to be seen?
   A. Inability to lactate
   B. Hypothyroidism
   C. Hypoglycemia
   D. Hypernatremia
GH acts on which of the following cells to cause long bone growth?

A. Chondrocytes  
B. Osteocytes  
C. Intracellular matrix  
D. Lymphocytes

**Answers**

**[39.1]**  
B. Somatomedins, also known as IGFs, are produced in response to GH by the liver and locally by GH target cells. Those produced by the liver enter the circulation and act in an endocrine fashion, whereas those produced locally act in a paracrine or autocrine fashion by binding to specific IGF receptors. Many GH actions are mediated by IGFs.

**[39.2]**  
D. The anterior pituitary secretes thyroid-stimulating hormone, GH, adrenocorticotropic hormone, prolactin, follicle-stimulating hormone, and luteinizing hormone, whereas the posterior pituitary secretes oxytocin and antidiuretic hormone (ADH). Lack of ADH would lead to the inability to resorb free water, leading to hyponatremia.

**[39.3]**  
A. Chondrocytes are the primary target for GH in the epiphyseal plate.

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**PHYSIOLOGY PEARLS**

- GH is secreted in a pulsatile fashion and follows a circadian pattern. The two main regulators are GHRH and somatostatin, with bursts of GH secretion occurring when somatostatin secretion is lowest.
- GH actions are mediated by IGFs produced by the liver and locally by the target tissues. There are specific receptors on target cells for the IGFs, which can act in an endocrine, paracrine, or autocrine fashion.
- GH stimulates the growth of long bones, and its absence during early puberty and adolescence prevents development into full adult stature.
- GH stimulates bone growth through the production of IGF-1, which stimulates chondrocyte growth and cartilage synthesis in the epiphyseal plates.
- GH acts on other tissues involved in energy metabolism and promotes lipolysis by adipose tissue and fatty acid utilization to reduce body fat. At the same time, GH promotes protein synthesis and muscle development. The combined effects result in an increase in the lean body mass with increased GH secretion.
- At puberty, there is an increase in the frequency and amplitude of the GH secretory pulses that are dependent on increased levels of gonadal hormones, driving the growth spurt through puberty and into adolescence.
REFERENCE