Chapter 18: The Pituitary Gland

OBJECTIVES

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After studying this chapter, you should be able to:

- Describe the development and structure of the pituitary gland and its relationship to the hypothalamus.
- Identify the hormones secreted by the anterior and posterior lobes of the pituitary and their target organs, and how the numbers of the various cell types in the anterior pituitary are controlled in response to physiologic demands.
- Understand the function of hormones derived from proopiomelanocortin (POMC) and how they are involved in regulating skin coloration.
- Describe how growth hormone is secreted from the anterior pituitary and circulates and activates its receptors, and the stimuli that regulate growth hormone secretion with their underlying mechanisms.
- Understand the role of growth hormone in growth and metabolic function, and how somatomedins (such as insulin-like growth factors) may mediate some of its actions in the periphery.
- Define the normal timeline of growth in humans and identify factors in addition to growth hormone that contribute to its regulation.
- Understand pituitary secretion of gonadotropins and prolactin, how these are regulated, and the actions of these hormones on reproductive tissues.
- Understand the basis of conditions where pituitary function is abnormal, and how they can be treated.

INTRODUCTION

The pituitary gland, or hypophysis, lies in a pocket of the sphenoid bone at the base of the brain and is closely related to the hypothalamus (see Figure 17–2). It is a coordinating center for control of many downstream endocrine glands, some of which are discussed in subsequent chapters. In many ways, it can be considered to consist of two separate endocrine organs that contain a plethora of hormonally active substances. The anterior lobe of the pituitary secretes **thyroid-stimulating hormone (TSH, thyrotropin), adrenocorticotropic hormone (ACTH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin,** and **growth hormone** (see Figure 17–9), and receives almost all of its blood supply from the portal hypophysial vessels that pass initially through the median eminence, a structure immediately below the hypothalamus. This vascular arrangement positions the cells of the anterior pituitary to respond efficiently to regulatory factors released from the hypothalamus. Of the listed hormones, prolactin acts on the breast. The remaining five are, at least in part, **tropic hormones;** that is, they stimulate secretion of hormonally active substances by other endocrine glands or, in the case of growth hormone, the liver and other tissues (see below). The tropic hormones for some endocrine glands are discussed in the chapter on that gland: TSH in Chapter 19 and ACTH in Chapter 20. However, the gonadotropins FSH and LH, along with prolactin, are covered here. In some species, there is a well-developed intermediate lobe of the pituitary, which contains hormonally active derivatives of the proopiomelanocortin (POMC) molecule that regulate skin pigmentation, among other functions (see below). In humans, the intermediate lobe is rudimentary, and the cells that secrete derivatives of POMC are present in the anterior pituitary.

The posterior lobe of the pituitary consists predominantly of nerves that have their cell bodies in the hypothalamus, and stores **oxytocin** and

vasopressin in the termini of these neurons, to be released into the bloodstream. The secretion of these hormones, as well as a discussion of the overall role of the hypothalamus and median eminence in regulating both the anterior and posterior pituitary, was covered in Chapter 17.

To avoid redundancy, this chapter will focus predominantly on growth hormone and its role in growth and facilitating the activity of other hormones, along with a number of general considerations about the pituitary. The melanocyte-stimulating hormones (MSHs) of the intermediate lobe of the pituitary, α-MSH and β-MSH, will also be touched upon.

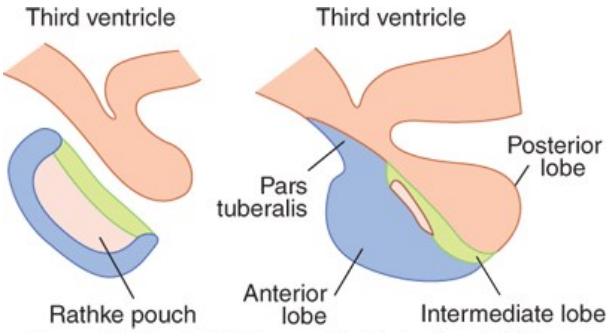
DEVELOPMENT, STRUCTURE, & CELL TYPES OF THE PITUITARY

GROSS ANATOMY

The anatomy of the pituitary gland is summarized in **Figure 18–1** and discussed in detail in Chapter 17. The posterior pituitary is made up largely of the endings of axons from the supraoptic and paraventricular nuclei of the hypothalamus and arises initially as an extension of this structure. The anterior pituitary, on the other hand, contains endocrine cells that store its characteristic hormones and arises embryologically as an invagination of the pharynx **(Rathke pouch).** In species where it is well developed, the intermediate lobe is formed in the embryo from the dorsal half of Rathke pouch, but is closely adherent to the posterior lobe in the adult. It is separated from the anterior lobe by the remains of the cavity in Rathke pouch, the **residual cleft.**

FIGURE 18–1

Diagrammatic outline of the formation of the pituitary (left) and the various parts of the organ in the adult (right).



HISTOLOGY

In the posterior lobe, the endings of the supraoptic and paraventricular axons can be observed in close relation to blood vessels. **Pituicytes,** stellate cells that are modified astrocytes, are also present.

As noted above, the intermediate lobe is rudimentary in humans—most of its cells are incorporated in the anterior lobe. The anterior pituitary is made up of interlacing cell cords and an extensive network of sinusoidal capillaries. The endothelium of the capillaries is fenestrated, like that in other endocrine organs. The cells contain granules of stored hormone that are extruded from the cells by exocytosis. Their constituents then enter the capillaries to be conveyed to target tissues.

CELL TYPES IN THE ANTERIOR PITUITARY

Five types of secretory cells have been identified in the anterior pituitary by immunocytochemistry and electron microscopy. The cell types are the somatotropes, which secrete growth hormone; the lactotropes (also called mammotropes), which secrete prolactin; the corticotropes, which secrete ACTH; the thyrotropes, which secrete TSH; and the gonadotropes, which secrete FSH and LH. The characteristics of these cells are summarized in **Table 18–1.** Some cells may contain two or more hormones. It is also notable that the three pituitary glycoprotein hormones, FSH, LH, and TSH, while being made up of two subunits, all share a common α subunit that is the product of a single gene and has the same amino acid composition in each hormone, although their carbohydrate residues vary. The α subunit must be combined with a β subunit characteristic of each hormone for maximal

physiologic activity. The β subunits, which are produced by separate genes and differ in structure, confer hormonal specificity (see Chapter 16). The α subunits are remarkably interchangeable and hybrid molecules can be created.

TABLE 18–1

Hormone-secreting cells of the human anterior pituitary gland.

Cell Type	Hormones Secreted	Percentage of Total Secretory Cells
Somatotrope	Growth hormone	50
Lactotrope	Prolactin	10–30
Corticotrope	ACTH	10
Thyrotrope	TSH	5
Gonadotrope	FSH, LH	20

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

The anterior pituitary also contains folliculostellate cells that send processes between the granulated secretory cells. These cells produce paracrine factors that regulate the growth and function of the secretory cells discussed above. Indeed, the anterior pituitary can adjust the relative proportion of secretory cell types to meet varying requirements for different hormones at different life stages. This plasticity has recently been ascribed to the presence of a small number of pluripotent stem cells that persist in the adult gland.

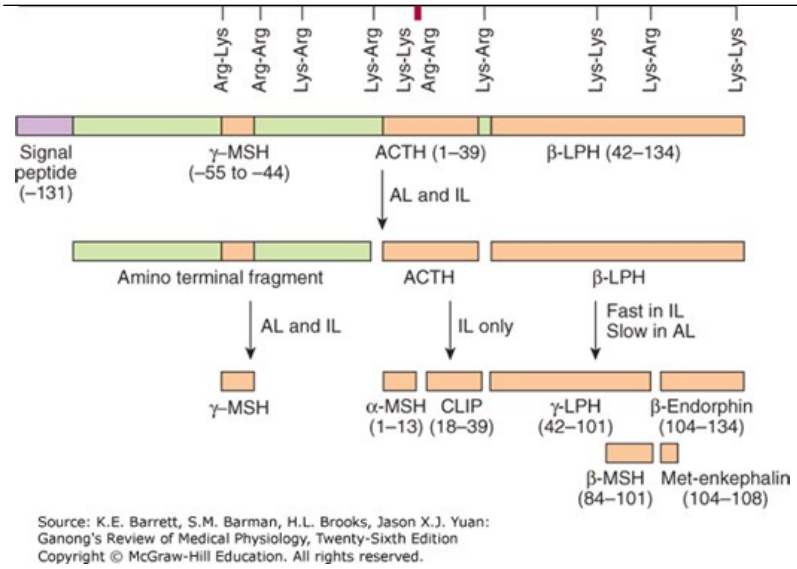
FORMATION AND FUNCTION OF PROOPIOMELANOCORTIN & DERIVATIVES

BIOSYNTHESIS

Corticotropes of the anterior lobe (or intermediate lobe cells, when present) synthesize a large precursor protein that is cleaved to form a family of hormones. Removal of the signal peptide results in the formation of the prohormone POMC. This molecule is also synthesized in the hypothalamus, the lungs, the gastrointestinal tract, and the placenta. The structure of POMC, as well as its derivatives, is shown in **Figure 18–2.** In corticotropes, it is hydrolyzed to ACTH and β-lipotropin (β-LPH), plus a small amount of β-endorphin, and these substances are secreted. Predominantly in intermediate lobe cells, POMC is further hydrolyzed to corticotropin-like intermediate-lobe peptide (CLIP), γ-LPH, and appreciable quantities of β-endorphin. The functions, if any, of CLIP and γ-LPH are unknown, whereas β-endorphin is an opioid peptide (see Chapter 7) that has the five amino acid residues of met-enkephalin at its amino terminal end. The **melanotropins** α- and β-MSH are also formed but apparently are not secreted in adult humans. In some species, however, these melanotropins have important physiologic functions, as discussed below.

FIGURE 18–2

Schematic representation of the preproopiomelanocortin molecule formed in pituitary cells, neurons, and other tissues. The numbers in parentheses identify the amino acid sequences in each of the polypeptide fragments. The locations of Lys–Arg and other pairs of basic amino acids residues are also indicated; these are the sites of proteolytic cleavage in the formation of the smaller fragments of the parent molecule. ACTH, adrenocorticotropic hormone; AL, anterior lobe; CLIP, corticotropin-like intermediate-lobe peptide; IL, intermediate lobe; LPH, lipotropin; MSH, melanocyte-stimulating hormone.



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CONTROL OF SKIN COLORATION & PIGMENT ABNORMALITIES

Fish, reptiles, and amphibia change the color of their skin for thermoregulation, camouflage, and behavioral displays. They do this in part by moving black or brown granules into or out of the periphery of pigment cells called **melanophores.** The granules are made up of **melanins,** which are synthesized from dopamine (see Chapter 7) and dopaquinone. The movement of these granules is controlled by a variety of hormones and neurotransmitters, including α- and β-MSH, melanin-concentrating hormone, melatonin, and catecholamines.

Mammals have no melanophores containing pigment granules that disperse and aggregate, but they do have **melanocytes,** which have multiple processes containing melanin granules. Melanocytes express **melanotropin-1** receptors. Treatment with MSHs accelerates melanin synthesis, causing readily detectable darkening of the skin in humans in 24 h. As noted above, α- and β-MSH do not circulate in adult humans, and their function is unknown. However, ACTH binds to melanotropin-1 receptors. Indeed, pigmentary changes in several human endocrine diseases are due to changes in circulating ACTH. For example, abnormal pallor is a hallmark of hypopituitarism. Hyperpigmentation occurs in patients with adrenal insufficiency due to primary adrenal disease. Indeed, the presence of hyperpigmentation in association with adrenal insufficiency rules out the possibility that the insufficiency is secondary to pituitary or hypothalamic disease because in these conditions, plasma ACTH is not increased (see Chapter 20). Other disorders of pigmentation result from peripheral mechanisms. Thus, **albinos** have a congenital inability to synthesize melanin resulting from a variety of different genetic defects in the pathways for melanin synthesis. **Piebaldism** is characterized by patches of skin that lack melanin as a result of congenital defects in the migration of pigment cell precursors from the neural crest during embryonic development. Not only the condition but also the precise pattern of the loss is passed from one generation to the next. **Vitiligo** involves a similar patchy loss of melanin, but the loss develops progressively after birth secondary to an autoimmune process that targets melanocytes.

GROWTH HORMONE SECRETION

BIOSYNTHESIS & CHEMISTRY

The long arm of human chromosome 17 contains the growth hormone-hCS cluster that contains five genes: one, *hGH-N*, codes for the most abundant ("normal") form of growth hormone; a second, *hGH-V,* codes for the variant form of growth hormone; two code for human chorionic somatomammotropin (hCS) (see Chapter 22); and the fifth is probably an hCS pseudogene. Only hGH-N is secreted by the pituitary; hGH-V and hCS are primarily products of the placenta, and as a consequence are only found in appreciable quantities in the circulation during pregnancy (see Chapter 22).

The structure of growth hormone varies considerably from one species to another. Porcine and simian growth hormones have only a transient effect in the guinea pig. In monkeys and humans, bovine and porcine growth hormones do not even have a transient effect on growth, although monkey and human growth hormones are fully active in both monkeys and humans. These facts are relevant to public health discussions surrounding the presence of bovine growth hormones (used to increase milk production) in dairy products, as well as the popularity of growth hormone supplements, marketed via the Internet, with body builders. Controversially, recombinant human growth hormone has also been given to children who are short in stature, but

otherwise healthy (ie, without growth hormone deficiency), with apparently limited results.

PLASMA LEVELS, BINDING, & METABOLISM

A portion of circulating growth hormone is bound to a plasma protein that is a large fragment of the extracellular domain of the growth hormone receptor (see below). It appears to be produced by cleavage of receptors in humans, and its concentration is an index of the number of growth hormone receptors in the tissues. Approximately 50% of the circulating pool of growth hormone activity is in the bound form, providing a reservoir of the hormone to compensate for the wide fluctuations that occur in secretion (see below).

The basal plasma growth hormone level measured by radioimmunoassay in adult humans is normally less than 3 ng/mL. This represents both the protein-bound and free forms. Growth hormone is metabolized rapidly, at least in part in the liver. The half-life of circulating growth hormone in humans is 6–20 min, and the daily growth hormone output has been calculated to be 0.2–1.0 mg/d in adults.

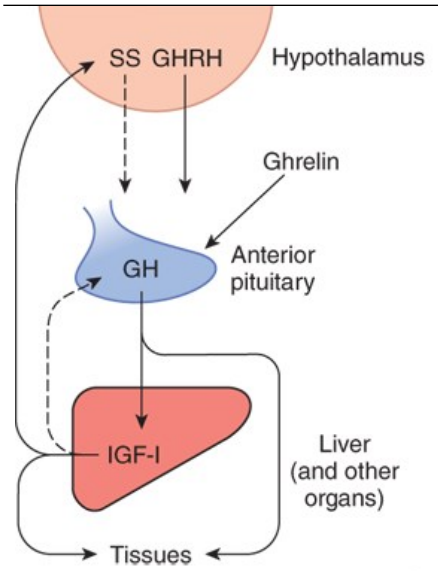
HYPOTHALAMIC & PERIPHERAL CONTROL OF GROWTH HORMONE SECRETION

The secretion of growth hormone is not stable over time. Adolescents have the highest circulating levels of growth hormone, followed by children and finally adults. Levels decline in old age, and there has been considerable interest in injecting growth hormone to counterbalance the effects of aging. There are also diurnal variations in growth hormone secretion superimposed on these developmental stages. Growth hormone is found at relatively low levels during the day, unless specific triggers for its release are present (see below). During sleep, on the other hand, large pulsatile bursts of growth hormone secretion occur. Therefore, it is not surprising that the secretion of growth hormone is under hypothalamic control. The hypothalamus controls growth hormone production by secreting **growth hormone–releasing hormone** (GHRH) as well as somatostatin, which inhibits growth hormone release (see Chapter 17). Thus, the balance between the effects of these hypothalamic factors on the pituitary will determine the level of growth hormone release. The stimuli of growth hormone secretion can therefore act by increasing hypothalamic secretion of GHRH, decreasing secretion of somatostatin, or both. A third regulator of growth hormone secretion is **ghrelin**. The main site of ghrelin synthesis and secretion is the stomach, but it is also produced in the hypothalamus and has marked growth hormone–stimulating activity. In addition, it appears to be involved in the regulation of food intake (see Chapter 26).

Growth hormone secretion is under feedback control (see Chapter 16), like the secretion of other anterior pituitary hormones. It acts on the hypothalamus to antagonize GHRH release. Growth hormone also increases circulating IGF-I, and IGF-I in turn exerts a direct inhibitory action on growth hormone secretion from the pituitary. It also stimulates somatostatin secretion **(Figure 18–3).**

FIGURE 18–3

Feedback control of growth hormone secretion. Solid arrows represent positive effects and dashed arrows represent inhibition. GH, growth hormone; GHRH, growth hormone–releasing hormone; IGF-I, insulin-like growth factor-I; SS, somatostatin.



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Other Stimuli Affecting Growth Hormone Secretion

The basal plasma growth hormone concentration ranges from 0 to 3 ng/mL in normal adults. However, secretory rates cannot be estimated from single values because of their irregular nature. Thus, average values over 24 h (see below) and peak values may be more meaningful, albeit difficult to assess. The stimuli that increase and decrease growth hormone secretion are summarized in **Table 18–2.** The stimuli that increase secretion fall into three general categories: (1) conditions such as hypoglycemia and/or fasting in which there is an actual or threatened decrease in the substrate for energy production in cells, (2) conditions in which the amounts of certain amino acids are increased in the plasma, and (3) stressful stimuli. Growth hormone secretion is also increased in persons deprived of rapid eye movement (REM) sleep (see Chapter 14) and inhibited during normal REM sleep.

TABLE 18–2

Stimuli that affect growth hormone secretion in humans.

Stimuli that increase secretion
Hypoglycemia
2-Deoxyglucose
Exercise
Fasting
Increase in circulating levels of certain amino acids
Protein meal
Infusion of arginine and some other amino acids
Glucagon
Lysine vasopressin
Going to sleep
L-dopa and α-adrenergic agonists that penetrate the brain
Apomorphine and other dopamine receptor agonists
Estrogens and androgens
Stressful stimuli (including various psychological stresses)
Pyrogen
Stimuli that decrease secretion
REM sleep
Glucose
Cortisol
FFA
Medroxyprogesterone
Growth hormone and IGF-I

FFA, free fatty acid; IGF, insulin-like growth factor; REM, rapid eye movement.

Glucose infusions lower plasma growth hormone levels and inhibit the response to exercise. The increase produced by 2-deoxyglucose is presumably due to intracellular glucose deficiency, since this compound blocks the catabolism of glucose-6-phosphate. Sex hormones induce growth hormone secretion, increase growth hormone responses to provocative stimuli such as arginine and insulin, and also serve as permissive factors for the action of growth hormone in the periphery. This likely contributes to the relatively high levels of circulating growth hormone and associated growth spurt in puberty. Growth hormone secretion is also induced by thyroid hormones. Growth hormone secretion is inhibited, on the other hand, by cortisol, free fatty acids (FFA), and medroxyprogesterone.

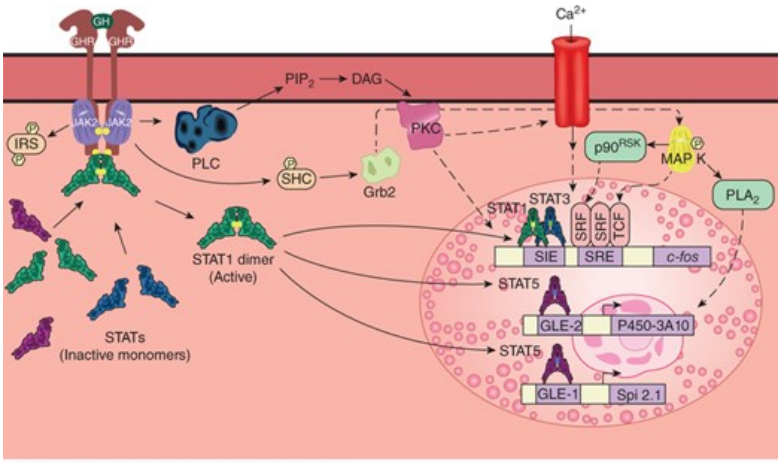
Growth hormone secretion is increased by L-dopa, which increases the release of dopamine and norepinephrine in the brain, and by the dopamine receptor agonist apomorphine.

GROWTH HORMONE RECEPTORS

The receptor that mediates the cellular effects of growth hormone has a large extracellular portion, a transmembrane domain, and a large cytoplasmic portion. It is a member of the cytokine receptor superfamily, which is discussed in Chapter 3.Growth hormone has two domains that can bind to its receptor, and when it binds to one receptor, the second binding site attracts another, producing a homodimer **(Figure 18–4).** Dimerization is essential for receptor activation.

FIGURE 18–4

Some of the principal signaling pathways activated by the dimerized growth hormone receptor (GHR). Solid arrows indicate established pathways; dashed arrows indicate probable pathways. The details of the PLC pathway and the pathway from Grb2 to MAP K are discussed in Chapter 2. The small uppercase letter Ps in yellow hexagons represent phosphorylation of the factor indicated. GLE-1 and GLE-2, interferon γ-activated response elements; IRS, insulin receptor substrate; $p90^{RSK}$, an S6 kinase; PLA_2, phospholipase A_2; SIE, Sis-induced element; SRE, serum response element; SRF, serum response factor; TCF, ternary complex factor.



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Growth hormone has widespread effects in the body (see below), so even though it is not yet possible precisely to correlate intracellular and whole body effects, it is not surprising that, like insulin, growth hormone activates many different intracellular signaling cascades (Figure 18–4). Of particular note is its activation of the JAK2–STAT pathway. JAK2 is a member of the Janus family of cytoplasmic tyrosine kinases. STATs (for signal transducers and activators of transcription) are a family of cytoplasmic transcription factors that, upon phosphorylation by JAK kinases, migrate to the nucleus where they activate various genes. JAK–STAT pathways are known also to mediate the effects of prolactin and various other growth factors.

EFFECTS OF GROWTH HORMONE ON GROWTH

In young animals in which the epiphyses have not yet fused to the long bones (see Chapter 21), growth is inhibited by hypophysectomy and stimulated by growth hormone. Chondrogenesis is accelerated, and as the cartilaginous epiphysial plates widen, they lay down more bone matrix at the ends of long bones. In this way, stature is increased. Prolonged treatment of animals with growth hormone leads to gigantism.

When the epiphyses are closed, linear growth is no longer possible. In this case, an overabundance of growth hormone produces the pattern of bone and soft tissue deformities known in humans as **acromegaly.** The sizes of most of the viscera are increased. The protein content of the body is increased, and the fat content is decreased **(Clinical Box 18–1)**.

CLINICAL BOX 18–1

Gigantism & Acromegaly

Tumors of the somatotropes of the anterior pituitary (pituitary adenomas) secrete large amounts of growth hormone, leading to **gigantism** in children and to **acromegaly** in adults. If the tumor arises before puberty, the individual may grow to an extraordinary height. After linear growth is no longer possible, on the other hand, the characteristic features of acromegaly arise, including greatly enlarged hands and feet, vertebral changes attributable to osteoarthritis, soft tissue swelling, hirsutism, and protrusion of the brow and jaw. Abnormal growth of internal organs may eventually impair their function such that the condition, which has an insidious onset, can prove fatal if left untreated. Hypersecretion of growth hormone is accompanied by hypersecretion of prolactin in 20–40% of patients with acromegaly. About 25% of patients have abnormal glucose tolerance tests, and 4% develop lactation in the absence of pregnancy. Acromegaly can be caused by extra-pituitary as well as intrapituitary growth hormone–secreting tumors and by hypothalamic tumors that secrete GHRH, but the latter are rare.

THERAPEUTIC HIGHLIGHTS

The mainstay of therapy for acromegaly remains the use of somatostatin analogues that inhibit the secretion of growth hormone. A growth hormone receptor antagonist has become available and has been found to produce clinical improvement in cases of acromegaly that do not respond to other treatments. Surgical removal of the pituitary tumor is also helpful in both acromegaly and gigantism, but sometimes challenging to perform due to the tumor's often invasive nature. In any case, adjuvant pharmacologic therapy must often be continued after surgery to control ongoing symptoms.

EFFECTS FOR GROWTH HORMONE ON PROTEIN & ELECTROLYTE HOMEOSTASIS

Growth hormone is a protein anabolic hormone and produces a positive nitrogen and phosphorus balance, a rise in plasma phosphorus, and a fall in blood urea nitrogen and amino acid levels. In adults with growth hormone deficiency, recombinant human growth hormone produces an increase in lean body mass and a decrease in body fat, along with an increase in metabolic rate and a fall in plasma cholesterol. Gastrointestinal absorption of Ca^{2+} is increased. Na^{+} and K^{+} excretion is reduced by an action independent of the adrenal glands, probably because these electrolytes are diverted from the kidneys to the growing tissues. On the other hand, excretion of the amino acid 4-hydroxyproline is increased during this growth, reflective of the ability of growth hormone to stimulate the synthesis of soluble collagen.

EFFECTS OF GROWTH HORMONE ON CARBOHYDRATE & FAT METABOLISM

The actions of growth hormone on carbohydrate metabolism are discussed in Chapter 24. At least some forms of growth hormone are diabetogenic because they increase hepatic glucose output and exert an anti-insulin effect in muscle. Growth hormone is also ketogenic and increases circulating FFA levels. The increase in plasma FFA, which takes several hours to develop, provides a ready source of energy for the tissues during hypoglycemia, fasting, and stressful stimuli. Growth hormone does not stimulate β cells of the pancreas directly, but it increases the ability of the pancreas to respond to insulinogenic stimuli such as arginine and glucose. This is an additional way growth hormone promotes growth, since insulin has a protein anabolic effect (see Chapter 24).

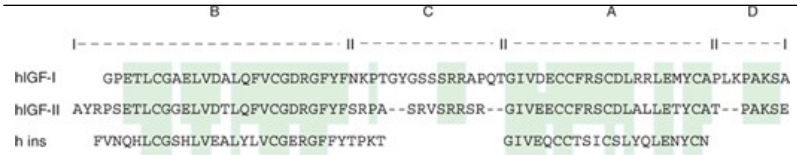
ROLE OF SOMATOMEDINS IN RESPONSE TO GROWTH HORMONE

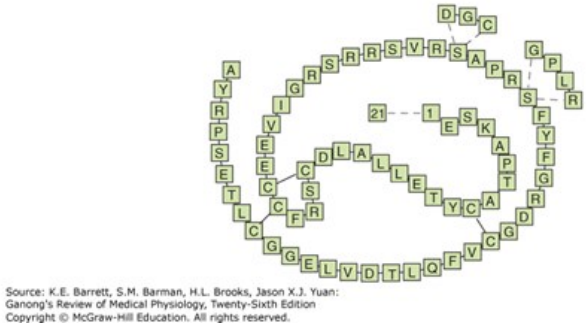
The effects of growth hormone on growth, cartilage, and protein metabolism depend on an interaction between growth hormone and **somatomedins,** which are polypeptide growth factors secreted by the liver and other tissues. The first of these factors isolated was called sulfation factor because it stimulated the incorporation of sulfate into cartilage. However, it also stimulated collagen formation, and its name was changed to somatomedin. It then became clear that there are a variety of different somatomedins and that they are members of an increasingly large family of growth factors that affect many different tissues and organs.

In humans probably the only circulating somatomedins are **insulin-like growth factor I (IGF-I, somatomedin C)** and **IGF-II.** These factors are closely related to insulin, except that their C chains are not separated **(Figure 18–5)** and they have an extension of the A chain called the D domain. The hormone relaxin (see Chapter 22) is also a member of this family. Humans have two related relaxin isoforms, and both resemble IGF-II.

FIGURE 18–5

Structure of human IGF-I, IGF-II, and insulin (ins) (top). The lower panel shows the structure of human IGF-II with its disulfide bonds, as well as three variant structures: a 21-aa extension of the C-terminus, a tetrapeptide substitution at Ser-29, and a tripeptide substitution of Ser-33.





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The properties of insulin, IGF-I, and IGF-II are compared in **Table 18–3.** Both IGF-I and IGF-II are tightly bound to proteins in the plasma, prolonging their half-life in the circulation. The contribution of the IGFs to the insulin-like activity in blood is discussed in Chapter 24. The IGF-I receptor is very similar to the insulin receptor and probably uses similar or identical intracellular signaling pathways. The IGF-II receptor has a distinct structure (see Figure 24–5) and is involved in the targeting of acid hydrolases and other proteins to intracellular organelles. Secretion of IGF-I is independent of growth hormone before birth but is stimulated by growth hormone after birth, and it has pronounced growth-stimulating activity. Its concentration in plasma rises during childhood and peaks at the time of puberty, then declines to low levels in old age. IGF-II is largely independent of growth hormone and plays a role in the growth of the fetus before birth. In human fetuses in which it is overexpressed, several organs, especially the tongue, other muscles, kidneys, heart, and liver, develop out of proportion to the rest of the body. In adults, the gene for IGF-II is expressed only in the choroid plexus and meninges.

TABLE 18–3

Comparison of insulin and the insulin-like growth factors (IGFs).

	Insulin	IGF-I	IGF-II
Other names	—	Somatomedin C	Multiplication-stimulating activity (MSA)
Number of amino acids	51	70	67
Source	Pancreatic β cells	Liver and other tissues	Diverse tissues
Level regulated by	Glucose	Growth hormone after birth, nutritional status	Unknown
Plasma levels	0.3–2 ng/mL	10–700 ng/mL; peaks at puberty	300–800 ng/mL
Plasma-binding proteins	No	Yes	Yes
Major physiologic role	Control of metabolism	Skeletal and cartilage growth	Growth during fetal development

DIRECT & INDIRECT ACTIONS OF GROWTH HORMONE

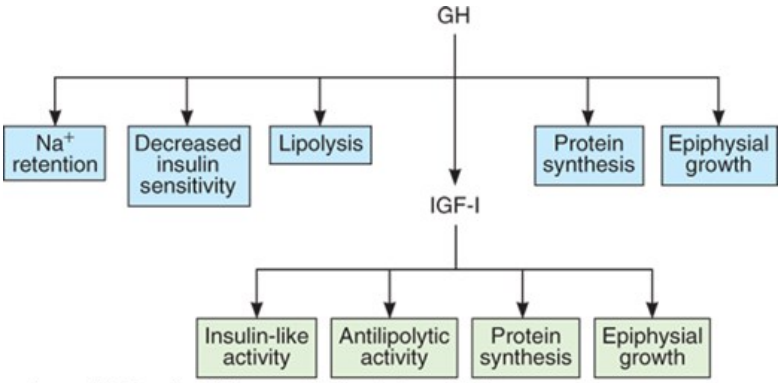
The understanding of the mechanism of action of growth hormone has evolved. It was originally thought to produce growth by a direct action on tissues, and then later was believed to act solely through its ability to induce somatomedins. However, if growth hormone is injected into one proximal

tibial epiphysis, a unilateral increase in cartilage width is produced, and cartilage, like other tissues, makes IGF-I. A current hypothesis to explain these results holds that growth hormone acts on cartilage to convert stem cells into cells that respond to IGF-I. Locally produced as well as circulating IGF-I then makes the cartilage grow. However, the independent role of circulating IGF-I remains important, since infusion of IGF-I in hypophysectomized rats restores bone and body growth. Overall, it seems that growth hormone and somatomedins can act both in cooperation and independently to stimulate pathways that lead to growth.

Figure 18–6 is a summary of current views of the actions of growth hormone and IGF-I. However, growth hormone probably combines with circulating and locally produced IGF-I in various proportions to produce at least some of the latter effects.

FIGURE 18–6

Direct and indirect actions of growth hormone (GH). The latter are mediated by the ability of GH to induce production of insulin-like growth factor-I (IGF-I). (Used with permission of R. Clark and N. Gesundheit.)



TIMELINE OF GROWTH & OTHER REGULATORS

Growth hormone, while being essentially unimportant for fetal development, is the most important hormone for postnatal growth. However, growth overall is a complex phenomenon that is affected not only by growth hormone and somatomedins but also by thyroid hormones, androgens, estrogens, glucocorticoids, and insulin. It is also affected, of course, by genetic factors, and it depends on adequate nutrition. It is normally accompanied by an orderly sequence of maturational changes, and it involves accretion of protein and an increase in length and size, not just an increase in weight (which could reflect the formation of fat or retention of salt and water rather than growth per se).

ROLE OF NUTRITION

The food supply is the most important extrinsic factor affecting growth. The diet must be adequate not only in protein content but also in essential vitamins and minerals (see Chapter 26) and in calories, so that ingested protein is not burned for energy. However, the age at which a dietary deficiency occurs appears to be an important consideration. For example, once the pubertal growth spurt has commenced, considerable linear growth continues even if caloric intake is reduced. Injury and disease, on the other hand, stunt growth because they increase protein catabolism.

GROWTH PERIODS

In humans, two periods of rapid growth occur (**Figure 18–7**): the first in infancy and the second in late puberty just before growth stops. The first period of accelerated growth is partly a continuation of the fetal growth period. The second growth spurt, at the time of puberty, is due to growth hormone, androgens, and estrogens. Because girls mature earlier than boys, this growth spurt appears earlier in girls. Of course, in both sexes the rate of growth of individual tissues varies (**Figure 18–8**). The eventual cessation of growth is due in large part to closure of the epiphyses in the long bones by estrogens (see Chapter 21). After this time, further increases in height are not possible.

FIGURE 18–7

Rate of growth in boys and girls from birth to age 20.

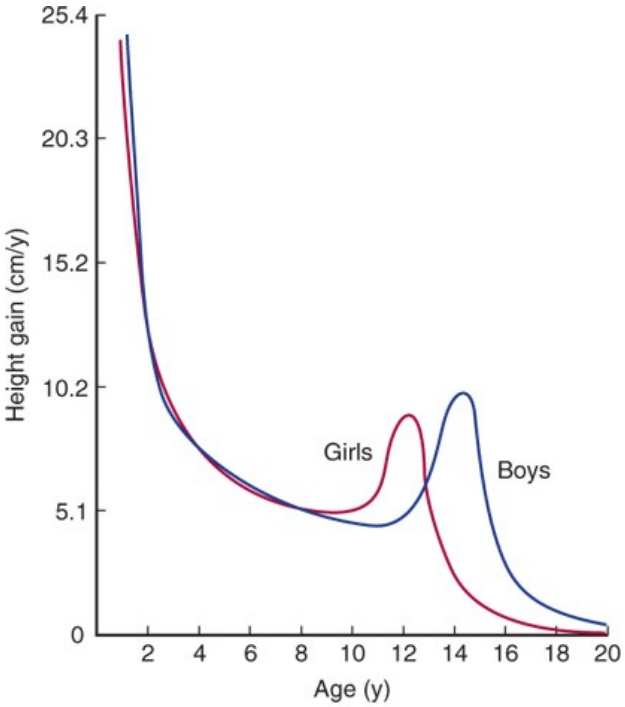
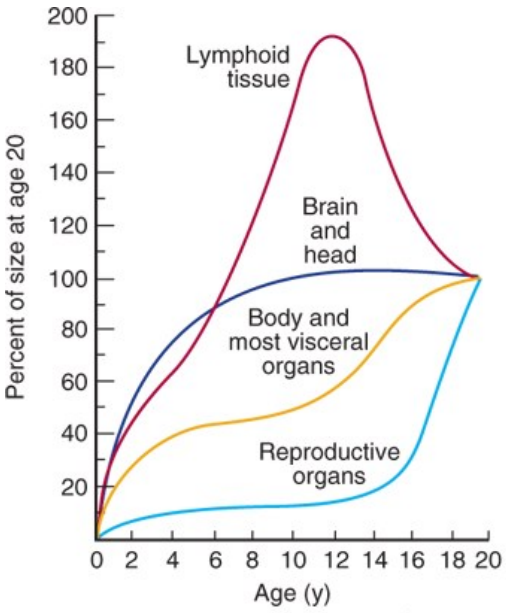


FIGURE 18–8

Growth of different tissues at various ages as a percentage of size at age 20. The curves are composites that include data for both boys and girls.



It is interesting that at least during infancy, growth is not a continuous process but is episodic or saltatory. Increases in the length of human infants of 0.5–2.5 cm in a few days are separated by periods of 2–63 days during which no measurable growth can be detected. The saltatory frequency varies

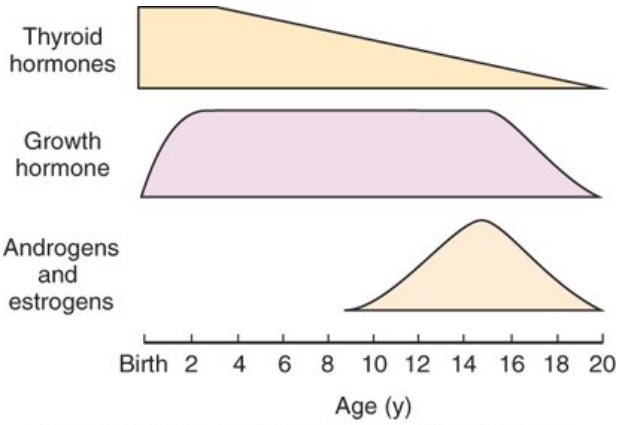
between individuals and summates to final height. This episodic growth apparently reflects discrete times at which chondrocytes are susceptible to differentiation into a hypertrophic phase.

HORMONAL EFFECTS

The contributions of hormones to growth after birth are shown diagrammatically in **Figure 18–9**. Plasma growth hormone is elevated in newborns. Subsequently, average resting levels fall but the spikes of growth hormone secretion are larger, especially during puberty, so the mean plasma level over 24 h is increased; it is 2–4 ng/mL in normal adults, but 5–8 ng/mL in children. Plasma IGF-I levels also rise during childhood, reaching a peak at 13–17 years of age. In contrast, IGF-II levels are constant throughout postnatal growth.

FIGURE 18–9

Relative importance of hormones in human growth at various ages. Thyroid hormones and growth hormones drive the rapid growth rate in the neonatal period and for the first few years of life, with the effect of the thyroid hormones tapering off thereafter. The growth spurt of puberty, on the other hand, involves interactions between the effects of growth hormone and the sex steroids. (Used with permission of D. A. Fisher.)



The growth spurt that occurs at the time of puberty (Figure 18–7) is due in part to the secretion of adrenal androgens at this time in both sexes and the protein anabolic effect of these androgens; however, it is also due to an interaction among sex steroids, growth hormone, and IGF-I. Treatment with estrogens and androgens increases the secretion of growth hormone in response to various stimuli and increases plasma IGF-I secondary to this increase in circulating growth hormone. This, in turn, causes growth.

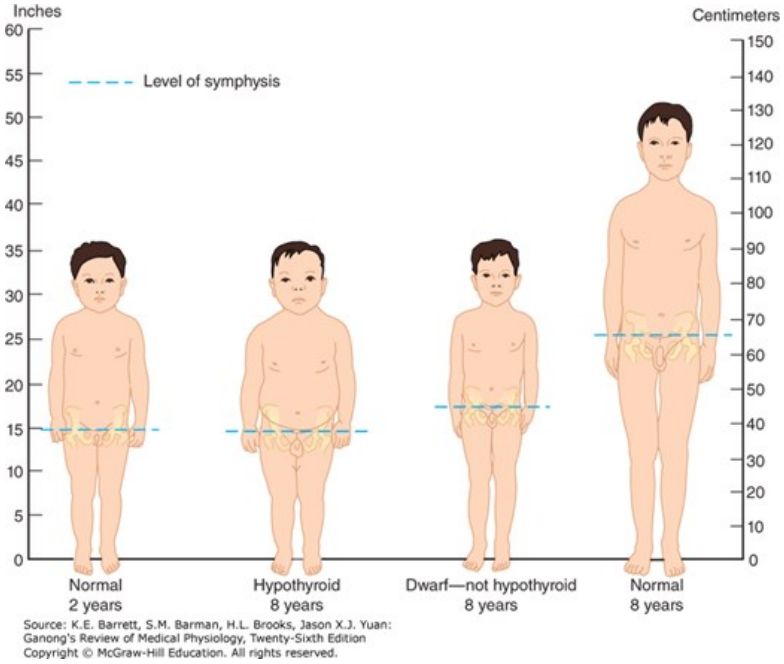
Although androgens and estrogens initially stimulate growth, estrogens ultimately terminate growth by causing the epiphyses to fuse to the long bones (epiphysial closure). Once the epiphyses have closed, linear growth ceases (see Chapter 21). This is why patients with sexual precocity are apt to be dwarfed. On the other hand, men who were castrated before puberty tend to be tall because their estrogen production is decreased and their epiphyses remain open, allowing some growth to continue past the normal age of puberty.

In hypophysectomized animals, growth hormone increases growth, but this effect is potentiated by thyroid hormones, which by themselves have no effect on growth. The action of thyroid hormones in this situation is therefore permissive to that of growth hormone, possibly via potentiation of the actions of somatomedins. Thyroid hormones also often appear to be necessary for stimulated growth hormone secretion; basal growth hormone levels are normal in hypothyroidism, but the response to hypoglycemia is frequently blunted. Thyroid hormones have widespread effects on the ossification of cartilage, the growth of teeth, the contours of the face, and the proportions of the body. Hypothyroid dwarfs (also known as **cretins**) therefore have infantile features **(Figure 18–10)**. Patients who are dwarfed because of panhypopituitarism have features consistent with their chronologic age until puberty, but since they do not mature sexually, they have juvenile features in adulthood **(Clinical Box 18–2)**.

FIGURE 18–10

Normal and abnormal growth. Hypothyroid dwarfs (cretins) retain their infantile proportions, whereas dwarfs of the constitutional type and, to a lesser extent, of the hypopituitary type have proportions characteristic of their chronologic age. See also Clinical Box 18–2. (Reproduced with

permission from Wilkins L: *The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence*, 3rd ed. Thomas; 1966.)



CLINICAL BOX 18–2

Dwarfism

The accompanying discussion of growth control should suggest several possible etiologies of short stature. It can be due to GHRH deficiency, growth hormone deficiency, or deficient secretion of IGF-I. Isolated growth hormone deficiency is often due to GHRH deficiency, and in these instances, the growth hormone response to GHRH is normal. However, some patients with isolated growth hormone deficiency have abnormalities of their growth hormone secreting cells. In another group of dwarfed children, the plasma growth hormone concentration is normal or elevated, but their growth hormone receptors are unresponsive as a result of loss-of-function mutations. The resulting condition is known as **growth hormone insensitivity** or **Laron dwarfism.** Plasma IGF-I is markedly reduced, along with its binding protein. African pygmies have normal plasma growth hormone levels and a modest reduction in the plasma level of growth hormone–binding protein. However, their plasma IGF-I concentration fails to increase at the time of puberty and they experience less growth than nonpygmy controls throughout the prepubertal period.

Short stature may also be caused by mechanisms independent of specific defects in the growth hormone axis. It is characteristic of childhood hypothyroidism (cretinism) and occurs in patients with precocious puberty. It is also part of the syndrome of **gonadal dysgenesis** seen in patients who have an XO chromosomal pattern instead of an XX or XY pattern (see Chapter 22). Various bone and metabolic diseases also cause stunted growth, and in many cases there is no known cause ("constitutional delayed growth"). Chronic abuse and neglect can also cause dwarfism in children, independent of malnutrition. This condition is known as **psychosocial dwarfism** or the **Kaspar Hauser syndrome,** named for the patient with the first reported case. Finally, **achondroplasia,** the most common form of dwarfism in humans, is characterized by short limbs with a normal trunk. It is an autosomal dominant condition caused by a mutation in the gene that codes for **fibroblast growth factor receptor 3 (FGFR3).** This member of the fibroblast growth receptor family is normally expressed in cartilage and the brain.

THERAPEUTIC HIGHLIGHTS

The treatment of dwarfism is dictated by its underlying cause. If treatment to replace the relevant hormone is commenced promptly in appropriate childhood cases, almost normal stature can often be attained. Thus, the availability of recombinant forms of growth hormone and IGF-I has greatly improved treatment in cases where these hormones are deficient.

The effect of insulin on growth is discussed in Chapter 24. Diabetic animals fail to grow, and insulin causes growth in hypophysectomized animals. However, the growth is appreciable only when large amounts of carbohydrate and protein are supplied with the insulin.

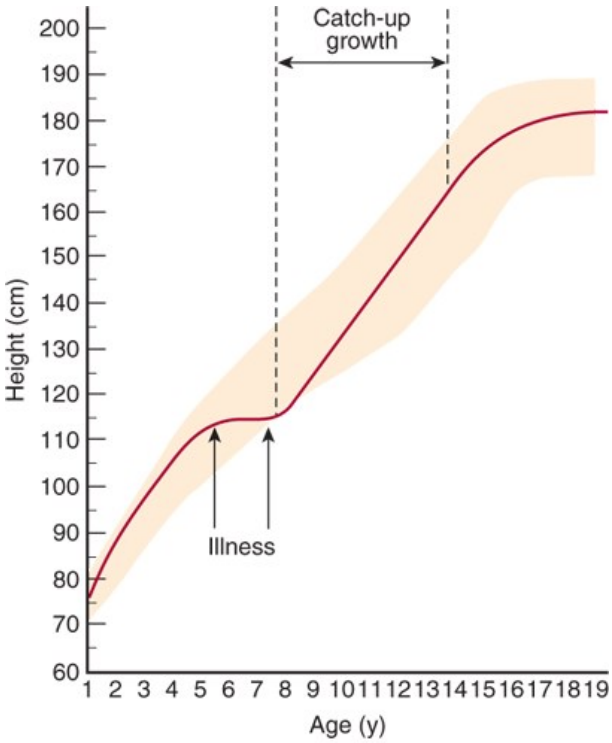
Adrenocortical hormones other than androgens exert a permissive action on growth in the sense that adrenalectomized animals fail to grow unless their blood pressure and circulations are maintained by replacement therapy. On the other hand, glucocorticoids are potent inhibitors of growth because of their direct action on cells, and treatment of children with pharmacologic doses of corticosteroids slows or stops growth for as long as the treatment is continued.

CATCH-UP GROWTH

Following illness or starvation in children, a period of **catch-up growth** (**Figure 18–11**) takes place during which the growth rate is greater than normal. The accelerated growth usually continues until the previous growth curve is reached, then slows to normal. The mechanisms that bring about and control catch-up growth are poorly understood.

FIGURE 18–11

Growth curve for a normal boy who had an illness beginning at age 5 and ending at age 7. The shaded area shows the range of normal heights for a given age. The red line shows actual growth of the boy studied. Catch-up growth eventually returned his height to his previous normal growth curve. (Modified with permission from Boersma B, Wit JM: Catch-up growth. Endocr Rev 1997 Oct;18(5):646–661.)



PITUITARY GONADOTROPINS & PROLACTIN

CHEMISTRY

FSH and LH are each made up of an α and a β subunit. They are glycoproteins, and their carbohydrate residues increase their potency by markedly slowing their metabolism. The half-life of human FSH is about 170 min; the half-life of LH is about 60 min. Loss-of-function mutations in the FSH receptor cause hypogonadism. Gain-of-function mutations cause a spontaneous form of **ovarian hyperstimulation syndrome,** a condition in

which many follicles are stimulated and cytokines are released from the ovary, causing increased vascular permeability and shock.

Human pituitary prolactin has considerable structural similarity to human growth hormone and human chorionic somatomammotropin (hCS). The half-life of prolactin, like that of growth hormone, is about 20 min. Structurally similar prolactins are secreted by the endometrium and by the placenta.

REGULATION OF PROLACTIN SECRETION

The regulatory factors for prolactin secretion by the pituitary overlap, in part, with those causing secretion of growth hormone, but there are important differences, and some stimuli increase prolactin secretion while decreasing that of growth hormone (and vice versa) **(Table 18–4)**. The normal plasma prolactin concentration is approximately 5 ng/mL in men and 8 ng/mL in women. Secretion is tonically inhibited by the hypothalamus, and section of the pituitary stalk leads to an increase in circulating prolactin. Thus, the effect of the hypothalamic prolactin-inhibiting hormone, dopamine, must normally be greater than the effects of the various hypothalamic peptides with prolactin-releasing activity. In humans, prolactin secretion is increased by exercise, surgical and psychological stresses, and stimulation of the nipple (Table 18–4). The plasma prolactin level rises during sleep, the rise starting after the onset of sleep and persisting throughout the sleep period. Secretion is increased during pregnancy, reaching a peak at the time of parturition. After delivery, the plasma concentration falls to nonpregnant levels in about 8 days. Suckling produces a prompt increase in secretion, but the magnitude of this rise gradually declines after a woman has been nursing for more than 3 months. With prolonged lactation, milk secretion occurs with prolactin levels that are in the normal range.

TABLE 18–4

Comparison of factors affecting the secretion of human prolactin and growth hormone.

Factor	Prolactin	Growth Hormone
Sleep	I+	I+
Nursing	I++	N
Breast stimulation in nonlactating women	I	N
Stress	I+	I+
Hypoglycemia	I	I+
Strenuous exercise	I	I
Sexual intercourse in women	I	N
Pregnancy	I++	N
Estrogens	I	I
Hypothyroidism	I	N
TRH	I+	N
Phenothiazines, butyrophenones	I+	N
Opioids	I	I
Glucose	N	D
Somatostatin	N	D+
L-dopa	D+	I+
Apomorphine	D+	I+
Bromocriptine and related ergot derivatives	D+	I

D, moderate decrease; D+, marked decrease; I, moderate increase; I+, marked increase; I++, very marked increase; N, no change; TRH, thyrotropin-releasing hormone.

L-dopa decreases prolactin secretion by increasing the formation of dopamine; bromocriptine and other dopamine agonists inhibit secretion because they stimulate dopamine receptors. Chlorpromazine and related drugs that block dopamine receptors increase prolactin secretion. Thyrotropin-releasing hormone (TRH) stimulates the secretion of prolactin in addition to TSH, and additional polypeptides with prolactin-releasing activity are present in hypothalamic tissue. Estrogens produce a slowly developing increase in prolactin secretion as a result of a direct action on the lactotropes.

It has now been established that prolactin facilitates the secretion of dopamine in the median eminence. Thus, prolactin acts in the hypothalamus in a negative feedback manner to inhibit its own secretion.

RECEPTORS

The receptors for FSH and LH are G-protein-coupled receptors coupled to adenylyl cyclase through a stimulatory G-protein (G_s; see Chapter 2). In addition, each has an extended, glycosylated extracellular domain.

The human prolactin receptor resembles the growth hormone receptor and is one of the superfamily of receptors that includes the growth hormone receptor and receptors for many cytokines and hematopoietic growth factors (see Chapters 2 and 3). It dimerizes and activates the Janus kinase/signal transducers and activators of transcription (JAK–STAT) pathway and other intracellular enzyme cascades (Figure 18–4).

ACTIONS OF FSH, LH, & PROLACTIN

The testes and ovaries become atrophic when the pituitary is removed or destroyed. The related actions of prolactin and the gonadotropins FSH and LH, as well as those of the gonadotropin secreted by the placenta, are described in detail in Chapters 22 and 23. In brief, FSH helps maintain the spermatogenic epithelium by stimulating Sertoli cells in the male and is responsible for the early growth of ovarian follicles in the female. LH is tropic for the Leydig cells and, in females, is responsible for the final maturation of the ovarian follicles and estrogen secretion from them. It is also responsible for ovulation, the initial formation of the corpus luteum, and secretion of progesterone.

Prolactin causes milk secretion from the breast after estrogen and progesterone priming. Its effect on the breast involves increasing messenger RNA (mRNA) levels and subsequent production of casein and lactalbumin. However, the action of the hormone is not exerted on the cell nucleus and is prevented by inhibitors of microtubules. Prolactin also inhibits the effects of gonadotropins, possibly by an action at the level of the ovary. It thereby prevents ovulation in lactating women. The function of prolactin in normal males is unsettled, but excess prolactin secreted by tumors causes erectile dysfunction.

EFFECTS OF PITUITARY INSUFFICIENCY

CHANGES IN OTHER ENDOCRINE GLANDS

The widespread changes that develop when the pituitary is removed surgically or destroyed by disease in humans or animals are predictable in terms of the known hormonal functions of the gland. In hypopituitarism, the adrenal cortex atrophies and the secretion of adrenal glucocorticoids and sex hormones falls to low levels. Stress-induced increases in aldosterone secretion are absent, but basal aldosterone secretion and increases induced by salt depletion are normal, at least for some time. Since no mineralocorticoid deficiency is present, salt loss and hypovolemic shock do not develop, but the inability to increase glucocorticoid secretion makes patients with pituitary insufficiency sensitive to stress. The development of salt loss in long-standing hypopituitarism is discussed in Chapter 20. Growth is inhibited (see Clinical Box 18–2). Thyroid function is depressed to low levels, and cold is tolerated poorly. The gonads atrophy, sexual cycles stop, and some of the secondary sex characteristics disappear.

INSULIN SENSITIVITY

Hypophysectomized animals have a tendency to become hypoglycemic, especially when fasted. Hypophysectomy ameliorates diabetes mellitus (see Chapter 24) and markedly increases the hypoglycemic effect of insulin. This is due in part to the deficiency of adrenocortical hormones, but hypophysectomized animals are more sensitive to insulin than adrenalectomized animals because they also lack the anti-insulin effect of growth hormone.

WATER METABOLISM

Although selective destruction of the supraoptic–posterior pituitary causes diabetes insipidus (see Chapter 17), removal of both the anterior and posterior pituitary usually causes no more than a transient polyuria. In the past, there was speculation that the anterior pituitary secreted a “diuretic hormone,” but the amelioration of the diabetes insipidus is actually explained by a decrease in the osmotic load presented for excretion. Osmotically active particles hold water in the renal tubules (see Chapter 38). Because of the ACTH deficiency, the rate of protein catabolism is decreased in hypophysectomized animals. Because of the TSH deficiency, the metabolic rate is low. Consequently, fewer osmotically active products of catabolism are filtered and urine volume declines, even in the absence of vasopressin. Growth hormone deficiency contributes to the depression of the glomerular filtration rate in hypophysectomized animals, and growth hormone increases the glomerular filtration rate and renal plasma flow in

humans. Finally, because of the glucocorticoid deficiency, there is the same defective excretion of a water load that is seen in adrenalectomized animals. The “diuretic” activity of the anterior pituitary can thus be explained in terms of the actions of ACTH, TSH, and growth hormone.

OTHER DEFECTS

When growth hormone deficiency develops in adulthood, it is usually accompanied by deficiencies in other anterior pituitary hormones. The deficiency of ACTH and other pituitary hormones with MSH activity may be responsible for the pallor of the skin in patients with hypopituitarism. There may be some loss of protein in adults, but wasting is not a feature of hypopituitarism in humans, and most patients with pituitary insufficiency are well nourished.

CAUSES OF PITUITARY INSUFFICIENCY IN HUMANS

Tumors of the anterior pituitary cause pituitary insufficiency. Suprasellar cysts, remnants of Rathke pouch that enlarge and compress the pituitary, are another cause of hypopituitarism. In women who have an episode of shock due to postpartum hemorrhage, the pituitary may become infarcted, with the subsequent development of postpartum necrosis **(Sheehan syndrome).** The blood supply to the anterior lobe is vulnerable because it descends on the pituitary stalk through the rigid diaphragma sellae, and during pregnancy the pituitary is enlarged. Pituitary infarction is usually extremely rare in men.

CHAPTER SUMMARY

- The pituitary gland consists of two functional sections in humans: the anterior lobe, which secretes mainly tropic hormones; and the posterior lobe, which contains nerve endings that project from the hypothalamus and release oxytocin and vasopressin. The anterior lobe receives almost all of its blood supply from the portal hypophysial vessels that carry regulatory factors released by the hypothalamus.
- The pituitary plays a critical role in regulating the function of downstream glands, and also exerts independent endocrine actions on a wide variety of peripheral organs and tissues. Cell types in the anterior lobe include somatotropes (growth hormone), lactotropes (prolactin), corticotropes (ACTH), thyrotropes (TSH), and gonadotropes (FSH, LH), which release the hormones listed in parentheses. The relative proportions of each cell type vary depending on needs at different life stages.
- Corticotropes of the anterior lobe synthesize proopiomelanocortin, which is the precursor of ACTH, endorphins, and melanotropins. ACTH is a primary regulator of skin pigmentation in mammals.
- Growth hormone is synthesized by somatotropes. It is secreted in an episodic manner in response to hypothalamic factors, and secretion is subject to feedback inhibition. A portion of the circulating pool is protein-bound.
- Growth hormone activates growth and influences protein, carbohydrate, and fat metabolism to react to stressful conditions. Many, but not all, of the peripheral actions of growth hormone can be attributed to its ability to stimulate production of IGF-I.
- Growth reflects a complex interplay of growth hormone, IGF-I, and many other hormones as well as extrinsic influences and genetic factors. The consequences of overproduction or underproduction of such influences depends on whether this occurs before or after puberty. Deficiencies in components of the growth hormone pathway in childhood lead to dwarfism; overproduction results in gigantism, acromegaly, or both.
- The pituitary also supplies hormones that regulate reproductive tissues and lactation—FSH, LH, and prolactin. Prolactin, in particular, is regulated by many of the factors that also regulate growth hormone secretion, although specific regulators may have opposing effects.
- Pituitary insufficiency is accompanied by atrophy of the adrenal cortex, sensitivity to stress, growth inhibition, depressed thyroid function, hypoglycemia, pallor, and atrophy of the gonads. Pituitary insufficiency may be caused by tumors or, in women, by infarction following shock due to postpartum hemorrhage.