

induce PRL release. With time, suckling-induced responses diminish and interfeeding PRL levels return to normal.

**Action** The PRL receptor is a member of the type I cytokine receptor family that also includes GH and interleukin (IL) 6 receptors. Ligand binding induces receptor dimerization and intracellular signaling by Janus kinase (JAK), which stimulates translocation of the signal transduction and activators of transcription (STAT) family to activate target genes. In the breast, the lobuloalveolar epithelium proliferates in response to PRL, placental lactogens, estrogen, progesterone, and local paracrine growth factors, including insulin-like growth factor I (IGF-I).

PRL acts to induce and maintain lactation, decrease reproductive function, and suppress sexual drive. These functions are geared toward ensuring that maternal lactation is sustained and not interrupted by pregnancy. PRL inhibits reproductive function by suppressing hypothalamic gonadotropin-releasing hormone (GnRH) and pituitary gonadotropin secretion and by impairing gonadal steroidogenesis in both women and men. In the ovary, PRL blocks folliculogenesis and inhibits granulosa cell aromatase activity, leading to hypoestrogenism and anovulation. PRL also has a luteolytic effect, generating a shortened, or inadequate, luteal phase of the menstrual cycle. In men, attenuated LH secretion leads to low testosterone levels and decreased spermatogenesis. These hormonal changes decrease libido and reduce fertility in patients with hyperprolactinemia.

## GROWTH HORMONE

**Synthesis** GH is the most abundant anterior pituitary hormone, and GH-secreting somatotrope cells constitute up to 50% of the total anterior pituitary cell population. Mammosomatotrope cells, which coexpress PRL with GH, can be identified by using double immunostaining techniques. Somatotrope development and GH transcription are determined by expression of the cell-specific Pit-1 nuclear transcription factor. Five distinct genes encode GH and related proteins. The pituitary GH gene (*hGH-N*) produces two alternatively spliced products that give rise to 22-kDa GH (191 amino acids) and a less abundant 20-kDa GH molecule with similar biologic activity. Placental syncytiotrophoblast cells express a GH variant (*hGH-V*) gene; the related hormone human chorionic somatotropin (HCS) is expressed by distinct members of the gene cluster.

**Secretion** GH secretion is controlled by complex hypothalamic and peripheral factors. *GH-releasing hormone* (GHRH) is a 44-amino-acid hypothalamic peptide that stimulates GH synthesis and release. Ghrelin, an octanoylated gastric-derived peptide, and synthetic agonists of the *GHS-R* induce GHRH and also directly stimulate GH release. *Somatostatin* (somatotropin-release inhibiting factor [SRIF]) is synthesized in the medial preoptic area of the hypothalamus and inhibits GH secretion. GHRH is secreted in discrete spikes that elicit GH pulses, whereas SRIF sets basal GH secretory tone. SRIF also is expressed in many extrahypothalamic tissues, including the central nervous system (CNS), gastrointestinal tract, and pancreas, where it also acts to inhibit islet hormone secretion. *IGF-I*, the peripheral target hormone for GH, feeds back to inhibit GH; estrogen induces GH, whereas chronic glucocorticoid excess suppresses GH release.

Surface receptors on the somatotrope regulate GH synthesis and secretion. The GHRH receptor is a G protein-coupled receptor (GPCR) that signals through the intracellular cyclic AMP pathway to stimulate somatotrope cell proliferation as well as GH production. Inactivating mutations of the GHRH receptor cause profound dwarfism. A distinct surface receptor for ghrelin, the gastric-derived GH secretagogue, is expressed in both the hypothalamus and pituitary. Somatostatin binds to five distinct receptor subtypes (SSTR1 to SSTR5); SSTR2 and SSTR5 subtypes preferentially suppress GH (and TSH) secretion.

GH secretion is pulsatile, with highest peak levels occurring at night, generally correlating with sleep onset. GH secretory rates decline markedly with age so that hormone levels in middle age are about 15% of pubertal levels. These changes are paralleled by an age-related decline in lean muscle mass. GH secretion is also reduced in obese individuals, although IGF-I levels may not be suppressed, suggesting a change in

the setpoint for feedback control. Elevated GH levels occur within an hour of deep sleep onset as well as after exercise, physical stress, and trauma and during sepsis. Integrated 24-h GH secretion is higher in women and is also enhanced by estrogen replacement likely reflective of increased peripheral GH-resistance. Using standard assays, random GH measurements are undetectable in ~50% of daytime samples obtained from healthy subjects and are also undetectable in most obese and elderly subjects. Thus, single random GH measurements do not distinguish patients with adult GH deficiency from normal persons.

GH secretion is profoundly influenced by nutritional factors. Using newer ultrasensitive GH assays with a sensitivity of 0.002 µg/L, a glucose load suppresses GH to <0.7 µg/L in women and to <0.07 µg/L in men. Increased GH pulse frequency and peak amplitudes occur with chronic malnutrition or prolonged fasting. GH is stimulated by intravenous L-arginine, dopamine, and apomorphine (a dopamine receptor agonist), as well as by α-adrenergic pathways. β-Adrenergic blockade induces basal GH and enhances GHRH- and insulin-evoked GH release.

**Action** The pattern of GH secretion may affect tissue responses. The higher GH pulsatility observed in men compared with the relatively continuous basal GH secretion in women may be an important biologic determinant of linear growth patterns and liver enzyme induction.

The 70-kDa peripheral GH receptor protein has structural homology with the cytokine/hematopoietic superfamily. A fragment of the receptor extracellular domain generates a soluble GH binding protein (GHBP) that interacts with GH in the circulation. The liver and cartilage contain the greatest number of GH receptors. GH binding to preformed receptor dimers is followed by internal rotation and subsequent signaling through the JAK/STAT pathway. Activated STAT proteins translocate to the nucleus, where they modulate expression of GH-regulated target genes. GH analogues that bind to the receptor but are incapable of mediating receptor signaling are potent antagonists of GH action. A GH receptor antagonist (pegvisomant) is approved for treatment of acromegaly.

GH induces protein synthesis and nitrogen retention and impairs glucose tolerance by antagonizing insulin action. GH also stimulates lipolysis, leading to increased circulating fatty acid levels, reduced omental fat mass, and enhanced lean body mass. GH promotes sodium, potassium, and water retention and elevates serum levels of inorganic phosphate. Linear bone growth occurs as a result of complex hormonal and growth factor actions, including those of IGF-I. GH stimulates epiphyseal prechondrocyte differentiation. These precursor cells produce IGF-I locally, and their proliferation is also responsive to the growth factor.

**Insulin-Like Growth Factors** Although GH exerts direct effects in target tissues, many of its physiologic effects are mediated indirectly through IGF-I, a potent growth and differentiation factor. The liver is the major source of circulating IGF-I. In peripheral tissues, IGF-I also exerts local paracrine actions that appear to be both dependent on and independent of GH. Thus, GH administration induces circulating IGF-I as well as stimulating local IGF-I production in multiple tissues.

Both IGF-I and IGF-II are bound to high-affinity circulating IGF-binding proteins (IGFBPs) that regulate IGF bioactivity. Levels of IGFBP3 are GH-dependent, and it serves as the major carrier protein for circulating IGF-I. GH deficiency and malnutrition usually are associated with low IGFBP3 levels. IGFBP1 and IGFBP2 regulate local tissue IGF action but do not bind appreciable amounts of circulating IGF-I.

Serum IGF-I concentrations are profoundly affected by physiologic factors. Levels increase during puberty, peak at 16 years, and subsequently decline by >80% during the aging process. IGF-I concentrations are higher in women than in men. Because GH is the major determinant of hepatic IGF-I synthesis, abnormalities of GH synthesis or action (e.g., pituitary failure, GHRH receptor defect, GH receptor defect or pharmacologic GH receptor blockade) reduce IGF-I levels. Hypocaloric states are associated with GH resistance; IGF-I levels are therefore low with cachexia, malnutrition, and sepsis. In acromegaly, IGF-I levels are invariably high and reflect a log-linear relationship with circulating GH concentrations.