key. The hormonal function of the pars distalis therefore may be augmented by secretory contributions from the pars tuberalis.

HORMONES OF THE PITUITARY

A number of peptide hormones are produced by the pituitary. These hormones regulate such target organs as the gonads, the adrenals, and the thyroid gland. The mammary glands, uterus, kidneys, and other tissues are also controlled by hypophysial hormones. Two gonadotropins are present: *follicle-stimulating hormone* (FSH), or *follitropin*, and *luteinizing hormone* (LH), or *lutropin*. A *thyroid-stimulating hormone* (TSH), or *thyrotropin*, and an *adrenal cortical-stimulating hormone* (ACTH), or *adrenocorticotropin (corticotropin)*, regulate thyroid and adrenal activity, respectively. A *growth hormone* (GH), which has generalized growth-promoting effects, and a *prolactin* (PRL), which has more specific growth-promoting action on the mammary glands, are also present in some species. A melanocyte-stimulating hormone (α-MSH, α-melanotropin) is produced by cells of the pars intermedia, or possibly by cells within the pars distalis (of birds). The neurohypophysial hormones, *oxytocin* and the *vasopressins*, are elaborated within neurons of the neurohypophysis, whose cell bodies originate within the hypothalamus. A melanin-concentrating hormone is also present within the neurohypophysis of teleost fishes [5] (see Chap. 8). The pituitary hormones are released into the bloodstream where they circulate to interact with their target organs.

Families of Pituitary Hormones

The hormones of the pituitary can be classified into four groups based on their structural similarity and presumed evolutionary origin. Growth hormone and prolactin possess numerous similar sequences of amino acids within their individual structures, and they are also structurally related to placental lactogen. Thyrotropin, follitropin, and lutropin are glycoproteins and are related in structure to each other and to chorionic gonadotropin (choriogonadotropin), a hormone of placental origin. α-Melanotropin and corticotropin contain a sequence of amino acids in common, which accounts for their overlapping actions and suggests a related evolutionary origin. Two neurohypophysial hormones are present in the neurohypophysis, and they are structurally related to each other.

Growth Hormone and Prolactin

These hormones of the pituitary exert profound effects on body growth. In the young animal, GH plays an essential role in general body growth, whereas PRL stimulates the growth of specialized tissues such as the mammary gland during pregnancy and lactation.

Growth Hormone. The existence of a hormone that is responsible for general somatic growth was suggested by the early experiments of Evans and Long (1922) and Smith (1926) [13]. Hypophysectomized young rats failed to grow to adult size, but extracts of the pituitary stimulated growth in these rats and in rats of normal growth. Human GH is also effective in promoting linear growth in children with congenital GH deficiency. In young animals, the epiphyses of the long bones are separated from the shaft of the bones by an epiphyseal cartilaginous plate. Chondrogenesis is accelerated by GH, which results in a widening of the epiphyseal plates as more extracellular matrix (chondroitin sulfate) is synthesized and released by chondrocytes. This widening has been used as a bioassay for GH (tibia test).

Growth hormone accounts for 4% to 10% of the wet weight of the anterior pituitary in the human adult (5 to 10 mg per gland). GH circulates in the plasma complexed to one or more binding proteins, and basal (resting or nonstressed) levels of immunoassayable GH in the plasma range from 1 to 5 ng per milliliter. The circulating levels of the hormone decline during the first 2 or 3 weeks after birth to then reach the basal levels characteristic of the adult human. Age-related changes in total 24-hour secretion of GH have been described. Although GH levels remain rather constant during the period of accelerated growth in early childhood, there is an appreciable increase during the period of maximal growth in adolescence. Interestingly, a substantial part of the 24-hour secretion of GH occurs during the first 90 minutes of nocturnal sleep. In every mammalian species studied so far, spontaneous episodes of GH secretion occur several times over a 24-hour period. Particularly in the rat, GH release follows a rhythm with high-amplitude GH secretory bursts occurring at regular 3.3-hour intervals. In the intervening trough periods, basal plasma GH levels are undetectable. Both a hypothalamic growth-hormone-releasing hormone (GHRH/somatocrinin), as well as a GH release-inhibiting factor (somatostatin, SST) control GH secretion.

Growth hormone is a polypeptide synthesized by certain acidophils (somatotrophs) of the pars distalis. GH is derived from a prohormone in the pituitary cells but is rapidly converted to GH by proteolysis. The human hormone consists of 191 amino acids with two intramolecular disulfide bonds. The hormone is strikingly similar in structure to PRL and placental lactogen. The latter molecule also contains 191 amino acids and possesses S–S bonds in exactly the same locations as in GH; in 161 positions, the amino acids are identical. The structural homologies between GH, PRL, and placental lactogen suggest a single progenitor molecule that arose early in vertebrate evolution (see Fig 12.12).

GH is a protein anabolic hormone in that it enhances amino acid incorporation into muscle protein and stimulates extracellular collagen deposition (Chap. 12). Thus, it produces a positive nitrogen and phosphorus balance and a concomitant fall in blood urea nitrogen and amino acid levels. Urinary excretion of Na^+ and K^+ is also decreased, probably due to the increased uptake of these ions by growing tissue. These effects of GH on protein metabolism and electrolyte balance are mediated indirectly through the actions of *somatomedins* released from the liver in response to GH stimulation of hepatocytes. These somatomedins (insulinlike growth factors, IGFs) stimulate cellular growth in a variety of tissues and organs (see Fig. 12.2).

The absence of GH secretion leads to short stature in the young child, whereas overproduction of GH during early postnatal development leads to gigantism. In the adult excess GH secretion leads to acromegaly. Short stature may result from a pituitary failure of GH production (hypopituitary short stature) or from a failure of the liver to respond to GH and synthesize somatomedins (Laron syndrome). The pathogenesis of acromegaly has been explained by a "pituitary" or a hypothalamic hypothesis. In the former view, overproduction of GH may result from GH-secreting tumors of the adenohypophysis (intrasellar tumors). The hypothalamic hypothesis implicates the defect as residing within the central nervous system, possibly from an overproduction of GHRH or an underproduction of somatostatin. The secretion of either of these hypophysiotropic factors is controlled by other neural inputs (e.g., dopaminergic neurons) that may contribute indirectly to the etiology of acromegaly. Nevertheless, the vast majority of patients with acromegaly have identifiable pituitary tumors, but whether these tumors arise from long-term overstimulation by the hypothalamus or are independent of hypothalamic influence, possibly due to cellular mutagenesis of somatotrophs or a related stem cell, is still unclear [18, 19].

The acromegalic characteristics of GH overproduction probably result from the direct effects of GH on target tissues, as well as growth effects mediated through the somatomedins. The growth changes in bones and soft tissues are most noticeable