Learning Objectives:

1. Identify the hypothalamic factors that control the secretion of each of the anterior pituitary hormones, and describe their route of transport from the hypothalamus to the anterior pituitary.
2. Identify the hormones secreted by the anterior pituitary gland, their target cells, and their major actions.
3. Diagram short and long loop negative feedback control of anterior pituitary hormone secretion. Predict the changes in secretory rates of hypothalamic, anterior pituitary, and target gland hormones caused by over-secretion or under-secretion of any of these hormones or receptor defects for any of these hormones.
4. Describe the stimuli for growth hormone (GH) secretion and the factors that regulate its secretion.
5. Describe the effects of GH on skeletal growth, body composition, and energy metabolism.
6. List the other hormones that “interact with” GH and how they affect GH secretion/action.
7. Describe the consequences of a deficiency or excess in GH secretion.
8. Describe the synthesis, transport, and secretion of posterior pituitary hormones.
9. List the major actions of antidiuretic hormone.
10. List the target cells for oxytocin and describe its effects on each target.

I. The Hypothalamopituitary Axis

The hypothalamus is a collecting center for information associated with the internal well being of the body. Information is processed and converted to signals that control the release of hormones from the pituitary gland.

The pituitary is connected to the hypothalamus by a stalk. It is composed of 2 morphologically and functionally distinct glands: the neurohypophysis and the adenohypophysis.

The neurohypophysis, or posterior lobe, forms as an extension of the developing hypothalamus and is therefore composed of neural tissue. It is a functional part of the hypothalamus.

The adenohypophysis, or anterior lobe, consists of clusters of histologically distinct cells closely associated with blood sinusoids. Six major hormones are secreted into the sinusoids by separate kinds of cells named for the type of hormone they produce.

Adrenocorticotropic hormone (ACTH) is secreted by corticotrophs, thyroid stimulating hormone (TSH) by thyrotrophs, growth hormone (GH) by somatotrophs, prolactin (PRL) by lactotrophs, and follicle stimulating hormone (FSH) and luteinizing hormone (LH) by gonadotrophs.
Almost all secretion by the anterior pituitary is controlled by neurohumoral signals from the hypothalamus. When hypothalamic neurons are stimulated, they secrete releasing or release-inhibiting hormones into portal vessels where they are carried to target cells in the anterior pituitary. These hypothalamic hormones will either stimulate or inhibit the secretion of anterior pituitary hormones.

All hypothalamic releasing hormones, and consequently all anterior pituitary hormones, exhibit pulsatile episodic secretion – short, regular bursts of hormone release – due to intrinsic neural oscillators within hormone-producing cells. This pulsatile release of hormones is essential for normal hypothalamic-pituitary function as information is transferred from the hypothalamus to the pituitary by pulse amplitude and frequency. Pulsatile release of hormones also decreases receptor downregulation. If this pattern of pulsatile secretion is abolished, anterior pituitary hormone secretion is impaired, even if hypothalamic releasing hormone production remains high.

Releasing and inhibiting hormones, produced by particular nuclei in the hypothalamus, are released into the first capillary bed of the hypophyseal portal circulation. They are carried to a second capillary bed in the anterior pituitary where they are released near hormone-producing cells.

Growth hormone-releasing hormone (GRH or GHRH) stimulates synthesis and secretion of GH.

Thyrotropin-releasing hormone (TRH) stimulates synthesis and secretion of thyroid stimulating hormone (TSH) as well PRL (although its role in regulating lactation is debated). A putative prolactin-releasing factor (PRF, PrRP) also stimulates the release of prolactin.

Gonadotropin-releasing hormone (GnRH) stimulates synthesis and secretion of FSH and LH, while corticotropin-releasing hormone (CRH) stimulates synthesis and secretion of POMC and ACTH, respectively.

Two inhibiting hormones are released from the hypothalamus. Somatostatin (somatotropin release-inhibiting factor or growth hormone inhibiting hormone) inhibits release of growth hormone. Dopamine (prolactin-inhibiting factor, PIF) inhibits release of prolactin can also stimulate the release of growth hormone.
II. Regulation of Secretion of Hormones from the Anterior Pituitary

<table>
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<tr>
<th>Releasing (Inhibitory) Factor Made by Hypothalamus</th>
<th>Target Cell in Anterior Pituitary</th>
<th>Hormone Released by Anterior Pituitary</th>
<th>Target of Anterior Pituitary Hormone</th>
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<tbody>
<tr>
<td>GHRH (inhibited by somatostatin)</td>
<td>Somatotroph (40-50% of pituitary cell population)</td>
<td>GH</td>
<td>Stimulates IGF-I production by multiple somatic tissues, especially liver</td>
</tr>
<tr>
<td>TRH</td>
<td>Thyrotroph (3-5%)</td>
<td>TSH</td>
<td>Thyroid follicular cells (stimulate their production of thyroid hormones)</td>
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<tr>
<td>CRH (augmented by vasopressin)</td>
<td>Corticotroph (15-20%)</td>
<td>ACTH</td>
<td>Adrenal cortex – production of corticosteroids</td>
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<tr>
<td>GnRH</td>
<td>Gonadotroph (10-15%)</td>
<td>FSH</td>
<td>Ovarian follicular cells (synthesize estrogens and progestins) and Sertoli cells (initiate spermatogenesis)</td>
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<tr>
<td>(inhibited by dopamine)</td>
<td>Lactotroph (10-25%)</td>
<td>PRL/TRH</td>
<td>Mammary glands (initiates and maintains milk production)</td>
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A. Thyroid Stimulating Hormones (TSH)

Thyroid stimulating hormone (TSH) regulates the functions of the follicles of the thyroid gland. TSH is the physiologic regulator of thyroid hormone synthesis and secretion. It also maintains the size and functional integrity of the follicular cells of the thyroid gland.
Thyrotropin releasing hormone (TRH) stimulates TSH synthesis and secretion by the thyrotroph. Neurons in the hypothalamus release TRH into the hypophyseal portal circulation at a rather constant or tonic rate. Thus thyrotrophs are continuously exposed to TRH and this has a tonic stimulatory effect on TSH secretion.

However, the main factor that regulates secretion of TSH is the concentration of thyroid hormones circulating in blood. When the concentration of free thyroid hormone in the blood is high, negative feedback on thyrotrophs reduces their response to TRH (probably by reducing TRH receptor numbers). As a result, the rate of TSH synthesis and secretion falls, reducing stimulation of the follicles of the thyroid.

B. Gonadotropins (FSH, LH)

Gonadotropins (FSH and LH) regulate reproduction. Production and secretion of gonadotropins is regulated by the hypothalamic releasing hormone, GnRH. Both FSH and LH are produced by the same gonadotrophs in the anterior pituitary.

The testis and ovary each have two essential functions in reproduction. The first is to produce the sperm and ovum, respectively. The second is to produce steroid and peptide hormones that influence the reproductive process. FSH and LH regulate both of these functions.

Luteinizing hormone (LH) is named for its ability to stimulate the conversion of the ovarian follicle to a corpus luteum. LH helps to maintain the corpus luteum and stimulate its secretion of estrogen and progesterone. A mid-cycle surge of LH is the stimulus for ovulation. If this surge is prevented, ovulation does not occur (part of the mechanism by which oral contraceptives work).

In the male, LH acts on the interstitial cells of Leydig to stimulate production of testicular steroids (androgens). LH also stimulates growth of the testis. Inappropriate use of anabolic steroids (e.g., in bodybuilding) can suppress LH secretion and cause testicular atrophy via feedback inhibition.

In the female, follicle stimulating hormone (FSH) stimulates growth of the ovarian follicle and acts on granulosa cells to stimulate conversion of androgens to estrogens. In the male, FSH acts on Sertoli cells to stimulate estrogen formation from androgens and synergizes with testosterone to stimulate production of androgen-binding protein. Androgen-binding protein is responsible for maintaining high levels of androgens in the vicinity of developing germ cells (sperm).

C. Adrenocorticotropic Hormone (ACTH)

ACTH regulates adrenal cortical function. ACTH is the physiologic regulator of synthesis and secretion of the glucocorticoids (cortisol and corticosterone) by the inner two layers of the adrenal cortex and maintains the size and functional integrity of these two layers. It also promotes expression of genes for various enzymes involved in steroidogenesis. ACTH is NOT an important regulator of aldosterone, another hormone produced by the adrenal cortex.

ACTH is produced from the prohormone proopiomelanocortin (POMC). Corticotrophs cleave POMC to produce ACTH, as well as several other products.
CRH is the main physiologic regulator of ACTH synthesis and secretion. CRH binds to a receptor on the corticotroph and stimulates secretion of ACTH (as well as expression of the POMC gene).

The rise in glucocorticoid concentration in the blood resulting from the action of ACTH on the adrenal cortex inhibits the secretion of more ACTH through negative feedback. If glucocorticoid levels fall, negative feedback is reduced, ACTH secretion is stimulated and glucocorticoid levels are restored. Because of this control loop, glucocorticoid levels remain relatively stable in the resting state, although there is some diurnal variation. However, control is greatly influenced by physical and emotional stresses, making glucocorticoids one of the “stress hormones.”

If the concentration of glucocorticoids in the blood remains high for a long period of time, expression of the POMC gene is inhibited. If an individual is chronically treated with large doses of glucocorticoids, the levels of ACTH drop so much that the adrenal gland can actually atrophy. This is why it is so important to wean patients off steroids to allow normal adrenal function to return.

When an individual experiences physical or emotional trauma, ACTH secretion is increased and glucocorticoid levels rise in the blood. Stress will stimulate the hypothalamopituitary-adrenal axis regardless of the glucocorticoid level prevailing in the blood. This occurs because neural activity generated in higher levels of the CNS stimulates neurons to secrete CRH at a greater rate. Thus stress can override the normal negative feedback operation.

In situations of glucocorticoid deficiency and certain stresses there is an increase in the concentration of antidiuretic hormone (ADH) [a.k.a. arginine vasopressin (AVP)] in hypophyseal portal blood. CRH co-localizes with ADH (AVP) in the paraventricular nuclei of the hypothalamus so that ADH, like CRH, stimulates production of ACTH and can amplify the ability of CRH to stimulate ACTH secretion.

The hypothalamopituitary-adrenal axis functions in a pulsatile manner. However, a diurnal pattern operates on top of this pulsatile rhythm.

Glucocorticoid levels in plasma begin to rise in early morning, peak sometime before noon and then fall gradually to a low level around midnight. This pattern is reversed in individuals who sleep during the day and are awake at night.
D. Growth Hormone (GH)

GH is produced by somatotrophs of the anterior pituitary in response to hypothalamic GHRH. GH regulates body growth during childhood. GH, or somatotropin, promotes growth of the human body by affecting protein synthesis, cell multiplication and cell differentiation. *GH does not affect fetal growth, nor is it an important growth factor during the first few months after birth.* Thereafter, it is essential for the normal rate of body growth during childhood and adolescence.

GH is secreted in a pulsatile fashion by the anterior pituitary throughout life [although less frequently with age] and remains physiologically important even after growth has stopped. GH secretion also shows diurnal rhythms, with peak secretion occurring during deep sleep.

Since GH values fluctuate so much during the day, measurement of GH is not useful. **Insulin-like growth factor-I (IGF-I)** levels can be measured as an indicator of GH release – GH regulates IGF-I secretion and IGF-I half-life is much longer than that of GH.

GH shifts metabolism to lipid use for energy, thereby conserving carbohydrates and proteins. The metabolic effects of GH make the body’s energy supplies (i.e., glucose and fat) available for building new protein. Thus, GH is a **protein anabolic hormone** -- increases amino acid uptake for protein synthesis, but also a **lipolytic hormone** -- activates hormone-sensitive lipase and thereby mobilizes fatty acids and glycerol from triglycerides in adipose tissue. As a result, more fats are used for energy production. Fatty acid uptake and oxidation increases in skeletal muscle and liver. Insulin antagonizes GH action, so when insulin and GH are given together, the lipolytic effects of GH are not seen.

Because GH increases fat mobilization and oxidation, the increased fatty acids inhibit glucose uptake by skeletal muscle or adipose tissue. The result is a rise in blood glucose. Liver glucose output also increases but this is due to gluconeogenesis from the resultant rise in acetyl CoA from oxidation of fatty acids and by the rise in glycerol and lactate.

GH antagonizes the action of insulin by decreasing sensitivity to insulin (in muscle and adipose tissue, NOT liver) and stimulating gluconeogenesis by the liver. Because GH can cause insulin insensitivity (i.e., increases blood glucose), it is sometimes considered a **diabetogenic hormone**.

GH increases skeletal and visceral growth (children without GH show stunted growth). It INDIRECTLY increases cartilage growth, long-bone length, and periosteal growth of bones via the stimulation of IGF release. GH causes differentiation of prechondrocytes into chondrocytes that secrete IGF-1. IGF-1 promotes chondrocyte proliferation and subsequent long bone growth.

IGFs regulate cell proliferation, differentiation, and cell metabolism. They are produced by many cells (but liver is the predominant source of circulating IGFs) and act in an endocrine, paracrine and/or autocrine fashion. At **very high** concentrations, IGFs can mimic the metabolic actions of insulin (due to
cross-reaction at the insulin receptors). IGF-binding proteins mediate transport and bioavailability of the IGFs (increase their half-life and slow their degradation in the liver).

When an individual is well fed, increased plasma amino acids stimulate GH and insulin secretion and increased glucose levels further stimulate insulin release. The combination of high nutrient supply along with GH and insulin stimulates IGF release, and these conditions are appropriate for growth.

With a diet high in carbohydrates but low in amino acids, insulin alone is secreted to stimulate glucose uptake for storage as glycogen or fat. These conditions are not favorable for tissue growth.

Under fasting conditions, when nutrient availability decreases, GH levels rise and insulin levels fall (because of hypoglycemia). Under these conditions, GH secretion is beneficial because it promotes fat mobilization while minimizing tissue protein loss. In the absence of insulin, the rise in blood glucose helps to ensure glucose availability for the brain.

The hypothalamus regulates GH synthesis and release by balancing GHRH and somatostatin (a.k.a. growth hormone inhibiting hormone, GHIH) release. Somatostatin acts in the anterior pituitary to inhibit both GH and TSH release.

Normally, a child has bursts of GH secretion during both the awake and sleep periods. The largest bursts of GH secretion occur during sleep [1-2 hours after onset of deep sleep]. Arousal from deep sleep inhibits GH secretion. As the child ages, episodes of GH secretion during the awake period become less frequent. By adulthood, bursts of GH secretion normally occur only in response to deep sleep. As we age, the amplitude of the GH peak declines.

Hypoglycemia is a stimulus for GH secretion (although its secretion is not regulated by minor variations in blood glucose). GH is referred to as a hyperglycemic hormone since it raises blood glucose. A fall in blood glucose due to the action of insulin is a strong stimulus for GH release [insulin-induced hypoglycemia is sometimes used as a test of a person’s ability to release GH].

A rise in certain amino acids is a stimulus for GH secretion (e.g., arginine and leucine). Deep sleep as well as stress and exercise also stimulate GH. GH is classified as one of the “stress hormones.” ADH and glucagon, two other stress hormones, stimulate GH as a part of the response to stress. Cortisol increases GH release, facilitating the body’s response to hypoglycemia. Dopamine (or its agonists) also stimulates GH release.

GH secretion is under negative feedback control. The inhibitory signals are the products of GH action, principally IGF-1. Increased circulating free fatty acids or glucose (resulting from GH action) exert inhibitory effects and decrease GH secretion by increasing somatostatin release. IGF-1 can act at the hypothalamus to stimulate somatostatin release and at the anterior pituitary to decrease somatotroph response to GHRH. GH may feed back to the anterior pituitary to inhibit its own secretion or inhibit GHRH release from the hypothalamus (which inhibits GH release).
The thyroid hormone T3 regulates the sensitivity of somatotrophs to GHRH, increasing GH synthesis. Consequently, children with hypothyroidism exhibit impaired growth.

Hypothyroid individuals have severely decreased levels of GH due to decreased amplitude of secretory pulses and possibly due to a decrease in frequency as well. There is almost complete cessation of GH synthesis by the anterior pituitary. Thyroid hormone treatment restores GH levels in these individuals.

Insulin-induced hypoglycemia and other stimuli for GH secretion produce abnormally small increases in the concentration of GH in hypothyroid individuals.

Thyroid hormones also increase the sensitivity of target cells to GH, thus increasing the efficacy of GH. T3 and T4 potentiate the effect of GH on growth of long bones and increase its effects on protein synthesis in muscle and liver.

Blood levels of IGF-I are decreased in hypothyroid individuals, partly because of decreased circulating GH and partly because of decreased hepatic responsiveness to GH. Target cells may be less responsive to IGF-I as well.

**PATHOPHYSIOLOGY of GH.** If a GH deficiency occurs before puberty, growth is severely impaired. These individuals have a small stature but are normally proportioned. If only GH is deficient, these individuals can have a normal life span. They are sometimes “pudgy” due to the loss of GH-induced lipolysis. They may also exhibit hypoglycemia, insulinopenia, and increased insulin sensitivity.

A GH hormone deficiency can also occur in adulthood after growth is completed. This may be one of many explanations for hypoglycemia. Long-term GH deficiency can lead to a change in body composition – more fat, less protein. In addition, muscle weakness and early exhaustion are symptoms of GH deficiency.

GH excess prior to puberty results in **giantism** -- leads to an increase in body weight as well as height. These individuals frequently have glucose intolerance and hyperinsulinemia, often leading to diabetes. Excess growth of viscera can lead to problems – e.g., cardiac hypertrophy.

When excessive GH secretion occurs in an adult, further linear growth does not occur because the growth plates of the long bones have calcified. Instead, bones of the face, hands, and feet become thicker and certain organs, such as the liver, undergo hypertrophy. This condition is known as acromegaly:
E. **Prolactin (PRL)**

The predominant action of PRL in humans is the initiation and maintenance of **lactation**. During pregnancy, alveolar cells of the mammary glands develop the capacity to synthesize milk in response to stimulation by a variety of hormones. Milk synthesis begins shortly after childbirth, following a surge in cortisol during delivery and a drop in estrogen and progesterone levels. To continue to synthesize milk, these cells must be stimulated periodically by PRL.

PRL is synthesized and secreted by lactotrophs in the anterior pituitary in response to estrogens and other hormones, such as TRH, that stimulate expression of the PRL gene. A **prolactin-releasing factor (PRF) or peptide (PrRP)** exists but its exact role is not known. Nursing and breast stimulation are the strongest stimulators of PRL secretion.

**UNIQUE** to this hormone, **prolactin is tonically inhibited** by the hypothalamus. **Dopamine** acts as a **prolactin inhibitory factor**. Dopamine, transported via the hypophyseal portal system, inhibits synthesis of PRL by the anterior pituitary.

III. **Circadian Rhythms, the Hypothalamus and the Pineal Gland**

ACTH/cortisol and melatonin secretion are driven by the body’s internal “clock” thought to reside in the hypothalamic suprachiasmatic nucleus (SCN), directly above the optic chiasm. The SCN receives direct innervation from the eye (retinohypothalamic projection). Neurons in the SCN show inherent cyclical activity (metabolic and electrical) that is independent of any input. This clock is synchronized to the light-dark cycle – thus it is in time with the environment.

Neurons from the SCN project to the pineal gland indirectly via hypothalamic connections. Pinealocytes are controlled by the norepinephrine output from the sympathetic system. Melatonin is synthesized from tryptophan. Synthesis is greatest at night (in the absence of light) while natural or bright artificial light inhibits synthesis (by inhibiting the activity of the enzyme N-acetyltransferase). Melatonin treatment in humans causes sleepiness and thus is used to improve sleep patterns and treat jet lag. It has also been used to help shift-workers adapt their sleeping patterns.
IV. Hormones of Posterior Pituitary

Posterior pituitary hormones -- antidiuretic hormone (ADH [originally called arginine vasopressin, AVP]) and oxytocin -- are synthesized by hypothalamic neurosecretory cells whose axons terminate in the posterior lobe of the pituitary. Secretion from the posterior pituitary is controlled by nervous signals that originate in the hypothalamus and terminate in the posterior pituitary.

ADH and oxytocin are produced by neurons in the supraoptic and paraventricular nuclei of the hypothalamus. They are synthesized as preprohormones in the cell bodies of these neural cells. The precursor proteins are then packaged into granules where they are enzymatically processed to produce active hormones. The hormones are transported down axons by axonal flow loosely bound to carrier proteins called neurophysins and accumulate at the axon terminals in the posterior pituitary. The hormones are released after a nerve impulse in the hypothalamus is transmitted down the axon to release neurosecretory vesicles by exocytosis. During this process, the hormone dissociates from its neurophysin and enters the bloodstream. Neurophysins are released along with these hormones but have no known function after leaving the nerve terminals.

Two physiologic signals—a rise in blood osmolality and a decrease in blood volume—generate the CNS stimulus for ADH secretion. Main physiologic action of ADH is to increase water reabsorption by the kidneys, resulting in decreased water excretion and formation of osmotically concentrated urine. ADH can also cause vasoconstriction—hence its alternate name, vasopressin.

ADH can also act on the anterior pituitary to stimulate secretion of ACTH (potentiates CRH). ADH is a stress hormone, so its role in stimulating cortisol release is important in times of stress.

ADH is secreted in response to extracellular fluid osmolality, sensed by osmoreceptors. The actual cells producing ADH are not thought to be osmoreceptors. However they are in close apposition to osmoreceptors. When extracellular fluid osmolality is high, fluid shifts out of the osmoreceptor cells. The resultant cellular dehydration generates nervous signals that stimulate ADH release from the posterior pituitary.
A drop in blood volume is sensed by volume [stretch] receptors in the atria, great veins and pulmonary vasculature (low-pressure receptors) and in the aortic arch and carotid sinus by baroreceptors (high-pressure receptors). The predominant regulator seems to be the atrial volume receptors. Decreases in blood volume over 8% stimulate large increases in ADH release. When blood volume drops, the ADH secretion is more sensitive to a rise in serum osmolality, and when blood volume rises, the sensitivity of ADH release to osmotic stimuli decreases.

A deficiency in ADH production results in diabetes insipidus – an inability to concentrate urine, normally resulting in the excretion of large amounts of urine.

Two physiologic signals stimulate secretion of oxytocin by the hypothalamus. First, suckling of the mammary gland by the nursing infant stimulates sensory nerves in the nipple. The afferent nerve impulses that are generated enter the hypothalamus and stimulate oxytocin-secreting neurons. The release of oxytocin stimulates contraction of myoepithelial cells that surround milk-laden alveoli in the lactating mammary gland, aiding in milk ejection (not production).

Oxytocin secretion is also stimulated by neural input from the female reproductive tract during childbirth. Cervical dilatation before the beginning of labor stimulates stretch receptors in the cervix. The afferent impulses generated stimulate oxytocin secretion. Oxytocin release stimulates contraction of smooth muscle cells in the uterus during labor, thus aiding in delivery of the fetus and placenta. Although uterine responsiveness to oxytocin increases around the time of parturition, oxytocin is not thought to be the initiating factor for labor (since oxytocin secretion does not increase until after labor has begun). Increased oxytocin levels help reduce post-partum bleeding.

Oxytocin release is also stimulated during sexual intercourse and is thought to aid in sperm transport in the female reproductive tract (increases uterine contractility).

The Hypothalamic-Pituitary Axis:
V. Classification of Endocrine Disorders

Endocrine disorders are classified as primary, secondary or tertiary. A **primary endocrine disorder** is one in which the target gland itself (e.g., thyroid, adrenal, or ovary) is not functioning normally. A **secondary endocrine disorder** is one in which the initial disorder is in the pituitary and the problem in the target organ is secondary to the pituitary disorder. A **tertiary endocrine disorder** is one in which the problem originates in the hypothalamus.