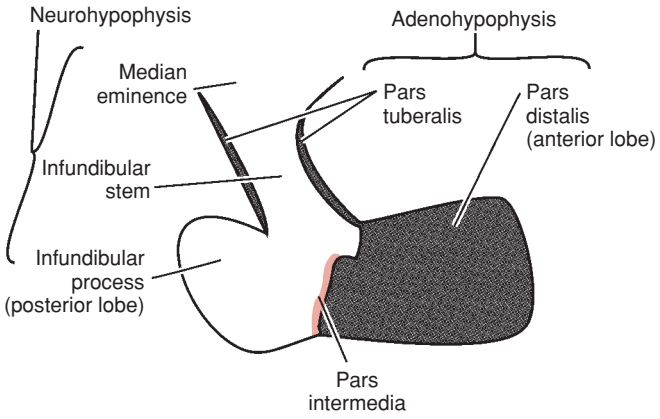


**FIGURE 32.1** **A midsagittal section of the human pituitary gland.**

stalk, and the **pars distalis** or **anterior lobe**. The **neurohypophysis** is composed of the **median eminence** of the hypothalamus, the **infundibular stem**, which forms the inner part of the stalk, and the **infundibular process** or **posterior lobe**. In most vertebrates, the pituitary contains a third anatomically distinct lobe, the **pars intermedia** or **intermediate lobe**. In adult humans, only a vestige of the intermediate lobe is found as a thin diffuse region of cells between the anterior and posterior lobes.

The adenohypophysis and neurohypophysis have different embryological origins. The adenohypophysis is formed from an evagination of the oral ectoderm called **Rathke's pouch**. The neurohypophysis forms as an extension of the developing hypothalamus, which fuses with Rathke's pouch as development proceeds. The posterior lobe is, therefore, composed of neural tissue and is a functional part of the hypothalamus.

## Posterior Pituitary Hormones Are Synthesized by Hypothalamic Neurons Whose Axons Terminate in the Posterior Lobe

The infundibular stem of the pituitary gland contains bundles of nonmyelinated nerve fibers, which terminate on the capillary bed in the posterior lobe. These fibers are the axons of neurons that originate in the **supraoptic nuclei** and **paraventricular nuclei** of the hypothalamus. The cell bodies of these neurons are large compared to those of other hypothalamic neurons; hence, they are called **magnocellular neurons**. The hormones arginine vasopressin (AVP) and oxytocin are synthesized as parts of larger precursor proteins (prohormones) in the cell bodies of these neurons. Prohormones are then packaged into granules and enzymatically processed to produce AVP and oxytocin. The granules are transported down the axons by axoplasmic flow; they accumulate at the axon terminals in the posterior lobe.

Stimuli for the secretion of posterior lobe hormones may be generated by events occurring within or outside the body. These stimuli are processed by the central nervous system (CNS), and the signal for the secretion of AVP or oxytocin is then transmitted to neurosecretory neurons in the hypothalamus. Secretory granules containing the hormone are then released into the nearby capillary circulation, from which they are carried into the systemic circulation.

## Anterior Pituitary Hormones Are Synthesized and Secreted in Response to Hypothalamic Releasing Hormones Carried in the Hypophyseal Portal Circulation

The anterior lobe contains clusters of histologically distinct types of cells closely associated with blood sinusoids that drain into the venous circulation. These cells produce anterior pituitary hormones and secrete them into the blood sinusoids. The six well-known anterior pituitary hormones are produced by separate kinds of cells. **Adrenocorticotropic hormone** (ACTH), also known as **corticotropin**, 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**.

The cells that produce anterior pituitary hormones are not innervated and, therefore, are not under direct neural control. Rather, their secretory activity is regulated by **releasing hormones**, also called **hypophysiotropic hormones**, synthesized by neural cell bodies in the hypothalamus. Granules containing releasing hormones are stored in the axon terminals of these neurons, located in capillary networks in the median eminence of the hypothalamus and lower infundibular stem. These capillary networks give rise to the principal blood supply to the anterior lobe of the pituitary.

The blood supply to the anterior pituitary is shown in Figure 32.2. Arterial blood is brought to the hypothalamic-pituitary region by the superior and inferior hypophyseal arteries. The **superior hypophyseal arteries** give rise to a rich capillary network in the median eminence. The capillaries converge into long veins that run down the pituitary stalk and empty into the blood sinusoids in the anterior lobe. They are considered to be portal veins because they deliver blood to the anterior pituitary rather than joining the venous circulation that carries blood back to the heart; therefore, they are called **long hypophyseal portal vessels**. The **inferior hypophyseal arteries** provide arterial blood to the posterior lobe. They also penetrate into the lower infundibular stem, where they form another important capillary network. The capillaries of this network converge into **short hypophyseal portal vessels**, which also deliver blood into the sinusoids of the anterior pituitary. The special blood supply to the anterior lobe of the pituitary gland is known as the **hypophyseal portal circulation**.

When a neurosecretory neuron is stimulated to secrete, the releasing hormone is discharged into the hypophyseal portal circulation (see Fig. 32.2). Releasing hormones travel only a short distance before they come in contact with their target cells in the anterior lobe. Only the amount of releasing hormone needed to control anterior pituitary hormone secretion is delivered to the hypophyseal portal circulation by neurosecretory neurons. Consequently, releasing hormones are almost undetectable in systemic blood.

A releasing hormone either stimulates or inhibits the synthesis and secretion of a particular anterior pituitary

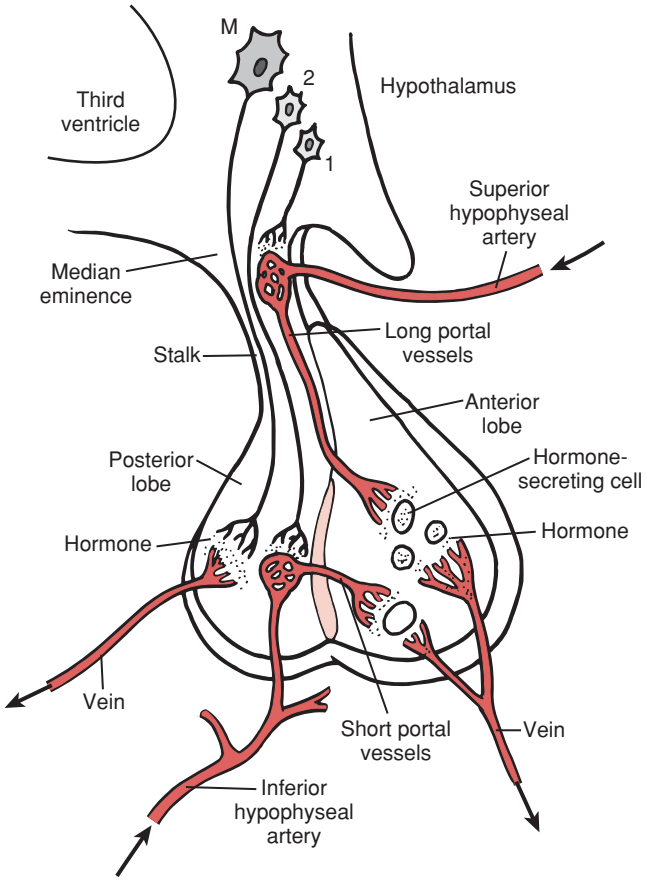


**FIGURE 32.2 The blood supply to the anterior pituitary.** This illustration shows the relationship of the hypothalamic magnocellular neurons and hypothalamic neurosecretory cells that produce releasing hormones to the pituitary blood vessels. M represents a magnocellular neuron releasing AVP or oxytocin at its axon terminals into capillaries that give rise to the venous drainage of the posterior lobe. Neurons 1 and 2 are secreting releasing factors into capillary networks that give rise to the long and short hypophyseal portal vessels, respectively. Releasing hormones are shown reaching the hormone-secreting cells of the anterior lobe via the portal vessels.

hormone. **Corticotropin-releasing hormone** (CRH), **thyrotropin-releasing hormone** (TRH), and **growth hormone-releasing hormone** (GHRH) stimulate the secretion and synthesis of ACTH, TSH, and GH, respectively (Table 32.1). **Luteinizing hormone-releasing hormone** (LHRH), also known as **gonadotropin-releasing hormone** (GnRH), stimulates the synthesis and release of FSH and LH. In contrast, **somatostatin**, also called **somatotropin release inhibiting factor** (SRIF), inhibits GH secretion. All of the releasing hormones are peptides, with the exception of **dopamine**, which is a catecholamine that inhibits the synthesis and secretion of PRL. Releasing hormones can be produced synthetically, and several are currently under study for use in the diagnosis and treatment of diseases of the endocrine system. For example, synthetic GnRH is now used for treating infertility in women.

Releasing hormones are secreted in response to neural inputs from other areas of the CNS. These signals are generated by external events that affect the body or by changes occurring within the body itself. For example, sensory nerve excitation, emotional or physical stress, biological rhythms, changes in sleep patterns or in the sleep-wake cycle, and changes in circulating levels of certain hormones or metabolites all affect the secretion of particular anterior pituitary hormones. Signals generated in the CNS by such events are transmitted to the neurosecretory neurons in the hypothalamus. Depending on the nature of the event and the signal generated, the secretion of a particular releasing hormone may be either stimulated or inhibited. In turn, this response affects the rate of secretion of the appropriate anterior pituitary hormone. The neural pathways involved in transmitting these signals to the neurosecretory neurons in the hypothalamus are not well defined.

## HORMONES OF THE POSTERIOR PITUITARY

**Arginine vasopressin** (AVP), also known as ADH, antidiuretic hormone, and **oxytocin** are produced by magnocellular neurons in the supraoptic and paraventricular nuclei of the hypothalamus. Individual neurons make either AVP or

**TABLE 32.1 Hypothalamic Releasing Hormones**

| Hormone | Chemistry | Actions on Anterior Pituitary |
|---|---|---|
| Corticotropin-releasing hormone (CRH) | Single chain of 41 amino acids | Stimulates ACTH secretion by corticotrophs; stimulates expression of POMC gene in corticotrophs |
| Thyrotropin-releasing hormone (TRH) | Peptide of 3 amino acids | Stimulates TSH secretion by thyrotrophs; stimulates expression of genes for α and β subunits of TSH in thyrotrophs; stimulates PRL synthesis by lactotrophs |
| Growth hormone-releasing hormone (GHRH) | Two forms in human: single chain of 44 amino acids, single chain of 40 amino acids | Stimulates GH secretion by somatotrophs; stimulates expression of GH gene in somatotrophs |
| Luteinizing hormone-releasing hormone (LHRH), gonadotropin-releasing hormone (GnRH) | Single chain of 10 amino acids | Stimulates FSH and LH secretion by gonadotrophs |
| Somatostatin, somatotropin release inhibiting factor (SRIF) | Single chain of 14 amino acids | Inhibits GH secretion by somatotrophs; inhibits TSH secretion by thyrotrophs |
| Dopamine | Catecholamine | Inhibits PRL synthesis and secretion by lactotrophs |

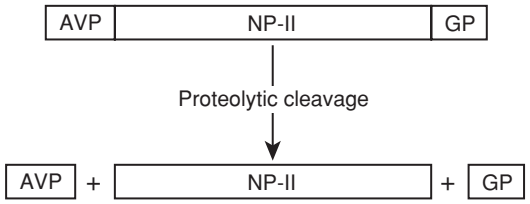


**FIGURE 32.3** **The structural organization and proteolytic processing of AVP from its prohormone.**
AVP, arginine vasopressin; NP-II, neurophysin II; GP, glycoprotein.

oxytocin, but not both. The axons of these neurons form the infundibular stem and terminate on the capillary network in the posterior lobe, where they discharge AVP and oxytocin into the systemic circulation.

AVP and oxytocin are closely related small peptides, each consisting of nine amino acid residues. Two forms of vasopressin, one containing arginine and the other containing lysine, are made by different mammals. Arginine vasopressin is made in humans. Although AVP and oxytocin differ by only two amino acid residues, the structural differences are sufficient to give these two molecules very different hormonal activities. They are similar enough, however, for AVP to have slight oxytocic activity and for oxytocin to have slight antidiuretic activity.

The genes for AVP and oxytocin are located near one another on chromosome 20. They code for much larger prohormones that contain the amino acid sequences for AVP or oxytocin and for a 93-amino acid peptide called **neurophysin** (Fig. 32.3). The neurophysin coded by the AVP gene has a slightly different structure than that coded by the oxytocin gene. Neurophysin is important in the processing and secretion of AVP, and mutations in the neurophysin portion of the AVP gene are associated with **central diabetes insipidus**, a condition in which AVP secretion is impaired. Prohormones for AVP and oxytocin are synthesized in the cell bodies of magnocellular neurons and transported in secretory granules to axon terminals in the posterior lobe, as described earlier. During the passage of the granules from the Golgi apparatus to axon terminals, prohormones are cleaved by proteolytic enzymes to produce AVP or oxytocin and their associated neurophysins.

When magnocellular neurons receive neural signals for AVP or oxytocin secretion, action potentials are generated in these cells, triggering the release of AVP or oxytocin and neurophysin from the axon terminals. These substances diffuse into nearby capillaries and then enter the systemic circulation.

### AVP Increases the Reabsorption of Water by the Kidneys

Two physiological signals, a rise in the osmolality of the blood and a decrease in blood volume, generate the CNS stimulus for AVP secretion. Chemical mediators of AVP release include catecholamines, angiotensin II, and atrial natriuretic peptide (ANP). The main physiological action of AVP is to increase water reabsorption by the collecting ducts of the kidneys. The result is decreased water excretion and the formation of osmotically concentrated urine (see Chapter 23). This action of AVP works to counteract the conditions that stimulate its secretion. For example, reducing water loss in the urine limits a further rise in the osmolality of the blood and conserves blood volume. Low blood AVP levels lead to diabetes insipidus and the excessive production of dilute urine (see Chapter 24).

### Oxytocin Stimulates the Contraction of Smooth Muscle in the Mammary Glands and Uterus

Two physiological signals stimulate the secretion of oxytocin by hypothalamic magnocellular neurons. Breast-feeding stimulates sensory nerves in the nipple. Afferent nerve impulses enter the CNS and eventually stimulate oxytocin-secreting magnocellular neurons. These neurons fire in synchrony and release a bolus of oxytocin into the bloodstream. Oxytocin stimulates the contraction of **myoepithelial cells**, which surround the milk-laden alveoli in the lactating mammary gland, aiding in milk ejection.

Oxytocin secretion is also stimulated by neural input from the female reproductive tract during childbirth. Cervical dilation before the beginning of labor stimulates stretch receptors in the cervix. Afferent nerve impulses pass through the CNS to oxytocin-secreting neurons. Oxytocin release stimulates the contraction of smooth muscle cells in the uterus during labor, aiding in the delivery of the newborn and placenta. The actions of oxytocin on the mammary glands and the female reproductive tract are discussed further in Chapter 39.

## HORMONES OF THE ANTERIOR PITUITARY

The anterior pituitary secretes six protein hormones, all of which are small, ranging in molecular size from 4.5 to 29 kDa. Their chemical and physiological features are given in Table 32.2.

Four of the anterior pituitary hormones have effects on the morphology and secretory activity of other endocrine glands; they are called *tropic* (Greek meaning "to turn to") or *trophic* ("to nourish") hormones. For example, ACTH maintains the size of certain cells in the adrenal cortex and stimulates these cells to synthesize and secrete **glucocorticoids**, the hormones **cortisol** and **corticosterone**. Similarly, TSH maintains the size of the cells of the thyroid follicles and stimulates these cells to produce and secrete the thyroid hormones **thyroxine** ($T_4$) and **triiodothyronine** ($T_3$). The two other tropic hormones, FSH and LH, are called **gonadotropins** because both act on the ovaries and testes. FSH stimulates the development of follicles in the ovaries and regulates the process of **spermatogenesis** in the testes. LH causes **ovulation** and **luteinization** of the ovulated **graafian follicle** in the ovary of the human female and stimulates the production of the female sex hormones **estrogen** and **progesterone** by the ovary. In the male, LH stimulates the **Leydig cells** of the testis to produce and secrete the male sex hormone, **testosterone**.

The two remaining anterior pituitary hormones, GH and PRL, are not usually thought of as tropic hormones because their main target organs are not human endocrine