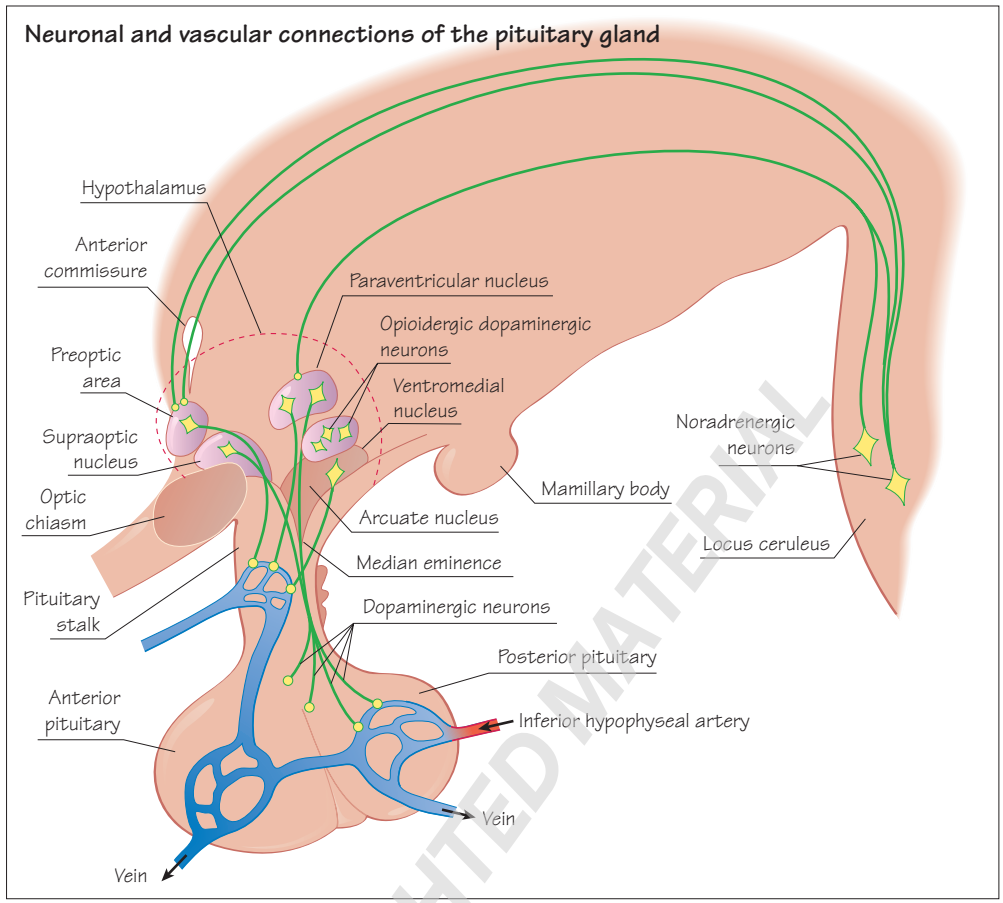
1 The pituitary gland



Structure and function

There are three lobes to the pituitary gland (hypophysis). The **anterior lobe** (adenohypophysis) is derived embryologically from ectoderm lining the dorsal pharynx, which forms an outpocketing known as Rathke's pouch. The **posterior lobe** (neurohypophysis) is much smaller and derived embryologically from neuroectoderm. The **pars intermedia**, a small intermediate structure lying between the anterior and posterior lobes, is actually a subdivision of the anterior lobe. Importantly, the embryological anlage of the pituitary gland is derived from neural crest cells.

The pituitary is connected to the brain via a small stalk of tissue known as the pituitary stalk or infundibulum. The posterior pituitary serves mainly as a storage site. Two hormones are stored here: oxytocin and arginine vasopressin (also known as antidiuretic hormone, ADH). Both are produced in the hypothalamus. Axons from large cell (magnocellular) neurons in the anterior hypothalamus travel into the posterior pituitary through the posterior part of the infundibulum. The oxytocin and ADH synthesized in the neuronal cell bodies of these hypothalamic cells travel down their axons, where the two hormones are then stored in the posterior pituitary. In contrast, the anterior pituitary produces its own tropic hormones under the regulatory control of the hypothalamus. This control is mediated by neuroendocrine signals from the hypothalamus that travel through rich vascular connections surrounding the pituitary stalk. Axons from small cell (parvocellular) neurons in the hypothalamus end in the precapillary space of the primary pituitary portal system that originates at the base of the hypothalamus. Blood flowing through this highly vascular plexus delivers signals to the anterior pituitary gland, regulating production and release of its protein products.

There are five small cell types in the anterior pituitary that are associated with tropic hormone production: gonadotropes, lactotropes, somatotropes, thyrotropes and corticotropes. These specific cells are responsible for production and secretion of: **follicle-stimulating hormone (FSH)** and **luteinizing hormone (LH)**; **prolactin**; **growth hormone**; **thyroid-stimulating hormone (TSH)**; and **adrenocorticotropic hormone (ACTH)**, respectively. The thyrotropes and gonadotropes closely resemble each other histologically because their secretory products, LH, FSH and TSH, are all glycoprotein hormones (Chapter 2) that stain with carbohydrate-sensitive reagents. LH and FSH are produced by a single cell type, allowing coupled secretion and regulation by a single releasing factor.

Control of pituitary gland activity comes largely from the hypothalamus with important direct modulation by feedback mechanisms. The hypothalamic nuclei associated with reproduction include the supraoptic, paraventricular, arcuate, ventromedial and suprachiasmatic nuclei. Neurons in two less well-defined areas, the medial anterior hypothalamus and the medial preoptic areas, are also involved. The magnocellular (large) neurons that originate in the supraoptic and paraventricular nuclei project into the posterior pituitary and produce the hormones vasopressin and oxytocin. The parvocellular (small)

neurons are found in the paraventricular, arcuate and ventromedial nuclei and the periventricular and medial preoptic areas. The parvocellular neurons produce regulatory peptides that control gonadotrope, lactotrope, somatotrope, thyrotrope and corticotrope cell function.

Those cells in the hypothalamic nuclei that regulate the pituitary have several functions. They receive signals from higher centres in the brain, generate neural signals of their own and have neuroendocrine capabilities. The higher areas of the brain that connect to the hypothalamic nuclei involved with reproduction are the locus ceruleus, the medulla and pons, the midbrain raphe, the olfactory bulb, the limbic system (amygdala and hippocampus), the piriform cortex and the retina. Multiple neurotransmitters are involved in the neural connections to and from the hypothalamus. These include noradrenergic projections from the medulla, pons and locus ceruleus, serotenergic projections from the midbrain raphe and dopaminergic neurons from the limbic system. The retinal connection to the hypothalamus mediates visual influences on neuroendocrine rhythms through melatonin. Endogenous opioids also influence hypothalamic function.

Several intrinsic **neural signals** relevant to reproduction are generated within the hypothalamus itself. These arise from what has been called the **pulse generator** for gonadotropin-releasing hormone (GnRH) and from dopaminergic neurons that project into the median eminence of the hypothalamus. Electrical recordings from the mediobasal hypothalamus reveal a synchronous increase in neuronal activity that corresponds to each pulse of LH released from the anterior pituitary. At baseline, GnRH secretes from the hypothalamus in pulses at a frequency of one pulse per hour. This frequency changes throughout the human menstrual cycle. Dopaminergic signals travel via dopaminergic neurons from the hypothalamus to the pituitary stalk. Similar pathways also project from the hypothalamus back to the limbic system.

The **neuroendocrine signals** generated within the hypothalamus are mediated by peptide-releasing factors that travel through the hypothalamic–pituitary portal system to their site of action in the pituitary gland. **GnRH** is the key tropic hormone for regulating gonadotrope cell function and hence, reproduction (Chapter 2). **Thyrotropin-releasing hormone (TRH)** and **prolactin inhibitory factor (PIF)** also play roles in reproductive regulation. Those hypothalamic neuroendocrine peptides that control GH and ACTH secretion are less directly related to reproduction.

Prolactin is unique among the pituitary hormones in that it is under tonic inhibitory control by the hypothalamus. Transection of the pituitary stalk therefore results in an increase in the production of prolactin, but a decrease in all other pituitary hormones. Prolactin inhibitory factor is none other than the neurotransmitter dopamine, which is secreted by the hypothalamic tuberoinfundibular neurons. Prolactin is also unique among the pituitary hormones in that its secretion is not regulated by classic feedback loops involving its target organs. Instead, prolactin secretion is controlled by local autocrine and paracrine factors, neurotransmitters and peripherally produced steroid hormones. The two major positive stimuli for prolactin secretion are TRH and oestradiol. TRH acts within the pituitary while oestradiol is active in both the hypothalamus and pituitary. Other stimuli for prolactin secretion include serotonin, opioids, oxytocin, histamine, neurotensin and substance P, all at the level of the hypothalamus. GnRH, vasoactive intestinal peptide (VIP) and angiotensin II promote prolactin secretion at the level of the posterior pituitary. The main reproductive function of prolactin is initiation and maintenance of lactation (Chapter 20). Prolactin and growth hormone share significant structural similarities and both play important roles in immune function.

Thyroid disorders are very common during the reproductive years, especially in women. While few of these originate within the hypothalamus or pituitary, under- and overactivity of the thyroid gland can interfere with reproductive function. Abnormal amounts of circulating thyroid hormone can affect reproductive function via two mechanisms: direct effects of thyroid hormones on peripheral cells whose genes contain thyroid response elements or indirectly through the action of TRH on prolactin secretion. Most thyroid disease occurs due to inappropriate autoimmune recognition of the thyroid gland, resulting in either stimulation or destruction of the gland. This typically leaves the hypothalamic–pituitary axis intact. TSH secretion, like that of the gonadotropins, is under hypothalamic regulation by its releasing hormone, TRH. Products of the peripheral target organ, such as thyroxine, regulate the secretion of TRH and TSH via negative feedback on the hypothalamus and pituitary, respectively. Women with underactive thyroid glands have elevated levels of TRH and TSH and women with overactive thyroid glands have virtually undetectable TRH and TSH. As mentioned above, TRH is a very potent stimulant for prolactin release by the pituitary and therefore hypothyroidism often causes hyperprolactinaemia. Elevated levels of circulating prolactin are associated with menstrual irregularities (Chapter 32).

The posterior pituitary hormones, oxytocin and vasopressin-ADH, are cyclic nona-peptides secreted by the neurons of the supraoptic and paraventricular nuclei. Their identification and synthesis in the early 1950s represented the first concrete evidence that the hypothalamus exhibited endocrine function. Oxytocin has effects on uterine smooth muscle and special myoepithelial cells in the breast, promoting muscular contractions in the former and milk letdown in the latter. Oxytocin may also act on the smooth muscle in the ejaculatory tract in men. Vasopressin-ADH has its greatest effects on vascular smooth muscle and on the collecting ducts of the kidney where it regulates intravascular volume and osmolality. Vasopressin-ADH may also play a role in sexual arousal.

Circadian rhythms

In humans exposed to normal day/night cycles, vital body functions change with a 24-h periodicity. This rhythm is known as the circadian rhythm and is entrained by environmental cues. The most important mediator of these cues is **melatonin**, a hormone secreted by the pineal gland. Melatonin is synthesized from serotonin by two enzymes known as *N*-acetyltransferase (NAT) and hydroxyindole-*O*-methyltransferase (HIOMT). Darkness activates melatonin secretion and light inhibits it. Light signals are transmitted to the pineal gland via neural pathways. These pathways pass through a **circadian oscillator in the hypothalamus**, down the spinal cord and through the superior cervical ganglion to the pineal gland. The dark-induced release of norepinephrine onto the pinealocytes activates β-adrenergic receptors that are coupled to cyclic adenosine monophosphate (cAMP) and NAT activity. Activation of this β-adrenergic sympathetic synapse stimulates melatonin secretion. Nocturnal melatonin secretion is associated with sleepiness, decreased core temperature and heart rate, and increased prolactin release. Melatonin has been implicated in the regulation of seasonal variations in fertility in regions with stark contrasts in day length, such as the Arctic and Scandinavia, where summer days and winter nights can be 20 h long. Melatonin concentrations are highest and conception rates are lowest during the months with the longest nights. The site of action for melatonin appears to be the suprachiasmatic nucleus of the hypothalamus. Here, it inhibits metabolic activity.