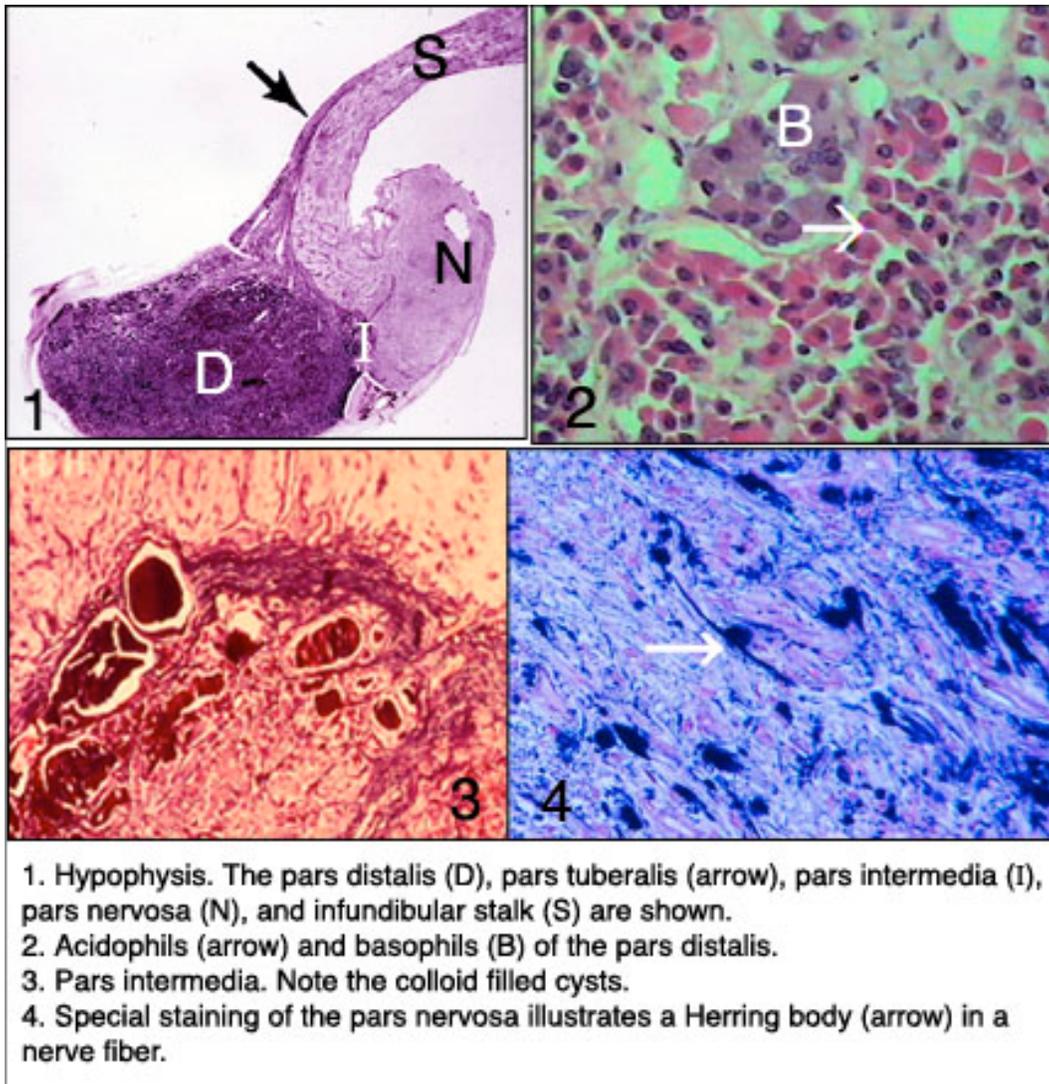


Hypophysis



The hypophysis or pituitary is a complex endocrine gland located at the base of the brain, lying in the sella turcica, a small depression in the sphenoid bone. It is attached to the hypothalamic region of the brain by a narrow stalk and has vascular and neural connections with the brain. The pituitary weighs about 0.5 gm in adults but is slightly heavier in women and in multiparous women may exceed 1 gm in weight. Despite its small size, the pituitary gland produces several hormones that directly affect other endocrine glands and tissues.

Organization

The hypophysis consists of two major parts, an epithelial component called the adenohypophysis and a nervous component that forms the neurohypophysis. The adenohypophysis is further subdivided into the pars distalis (anterior lobe) that lies anterior to the residual lumen of Rathke's pouch; pars intermedia, which forms a thin partition behind the residual lumen; and pars tuberalis, which is an extension of pars distalis surrounding the neural stalk.

The neurohypophysis also contains three portions. The major part is pars nervosa, which lies just posterior to pars intermedia and is continuous with the infundibular stalk and the median eminence. Pars intermedia of the adenohypophysis and pars nervosa of the neurohypophysis often are regarded collectively as forming a posterior lobe. A thick connective tissue capsule surrounds the entire hypophysis.

Vascular Supply

The pituitary is supplied by three pairs of arteries: the superior, middle, and inferior hypophyseal arteries, all of which supply directly to the neurohypophysis. The middle hypophyseal artery previously was believed to traverse the parenchyma of the adenohypophysis, but recent evidence has shown that it too passes directly to the neurohypophysis. Thus, the adenohypophysis has no direct arterial blood supply but is linked to the common capillary bed of the neurohypophysis by large-bore, thin-walled veins, the hypophyseal portal veins. The hypophyseal portal veins form an important link between the primary capillary plexus associated with the median eminence and infundibular stalk and the secondary capillary plexus of the portal system associated with the adenohypophysis. Venous drainage occurs through confluent pituitary veins that carry blood from the adenohypophysis, pars intermedia, and neurohypophysis through a common trunk to the venous systemic circulation. Only a few lateral hypophyseal veins extend directly from the adenohypophysis to the cavernous sinus. The only direct drainage of the neurohypophysis is by the neurohypophyseal limbs of the confluent veins located at the lower end of the neurohypophysis. Pars intermedia is relatively avascular and few capillaries traverse it. The most prominent vessels of pars intermedia are confluent pituitary veins.

Pars Distalis (Anterior Lobe)

Pars distalis makes up about 75% of the hypophysis and consists of epithelial cells arranged in clumps or irregular cords. A delicate network of reticular fibers supports the parenchyma and surrounding sinusoids. The parenchymal elements mostly consist of chromophobic and chromophilic cells, distinguished by whether or not they take up stain. Chromophilic cells are further subdivided into acidophilic and basophilic cells according to the staining properties of their secretory granules. All three cell types -chromophobes, acidophils, and basophils - are present in pars distalis.

Acidophilic cells are large, round or ovoid cells, 14 to 19 μm in diameter, with well-developed juxtannuclear Golgi complexes. The secretory granules stain with eosin in standard preparations. Two types of acidophils are present: somatotrophs and mammotrophs. The cytoplasm of somatotrophs contains a well-developed granular endoplasmic reticulum and numerous spherical, electron-dense secretory granules that measure 350 to 400 nm in diameter. Somatotrophs produce somatotropin (growth hormone), a peptide hormone that is important in controlling body growth and development in children and adolescents. It acts primarily on epiphyseal cartilages to increase linear growth of bone; increases organ size and lean body mass and plays a role in regulating body metabolism. Many of the effects attributed to growth hormone are through the production and action of a family of protein molecules known as somatomedins produced in the liver. The principal somatomedins have amino acid sequence homology with proinsulin. This homology and their insulin-like biological activities have led to the term insulin-like growth factors, a synonym for somatomedins. Somatomedins circulate bound to carrier proteins and have half-lives considerably longer than growth

hormone. The second type of acidophil, the mammotroph, tends to be more scattered within the cellular cords. Active cells contain granular endoplasmic reticulum, Golgi complexes, and scattered lysosomes. The cytoplasm also contains irregular granules that measure 550 to 615 nm in diameter. Mammotrophs secrete prolactin, which promotes mammary gland development and lactation. Prolactin together with growth hormone, adrenocorticoids, estrogen and progesterone are necessary for normal breast development to occur. The concentration of prolactin rises progressively during pregnancy but is kept from showing its lactogenic effect by the high concentration of progesterone and estrogen. The effect of these three hormones is to continue to stimulate tubuloalveolar growth of the mammary glands within the breast tissue. The decrease of estrogen and progesterone levels resulting from the loss of the placenta after birth allows the lactogenic effects of prolactin to be expressed and results in milk production.

Basophilic cells of pars distalis consist of three types of cells: corticotrophs, thyrotrophs, and gonadotrophs. Corticotrophs generally are round or ovoid and larger than most acidophilic cells. They are most numerous in the central anterior portion of pars distalis. In humans, the cells contain numerous secretory granules, 350 to 400 nm in diameter that are similar in appearance to the granules of somatotrophs. The cytoplasm often contains lipid droplets and small filaments ranging from 6 to 8 nm in diameter. Corticotrophs synthesize a glycoprotein prohormone, protropin, that is then cleaved to form adrenocorticotrophic hormone (ACTH), beta-lipotrophic hormone (β -LPH), alpha-melanocyte-stimulating hormone (α -MSH), and beta-endorphin. The different hormones produced by acidophils and basophils in the adenohypophysis also are produced as prohormones, but how these are cleaved to form the active hormone is not well understood.

Adrenocorticotrophic hormone stimulates the zona fasciculata and zona reticularis of the adrenal cortex to produce and release glucocorticoids. Adrenocorticotrophic hormone also is important in stimulating the production of adrenal androgens.

The thyrotroph type of basophil often is angular in shape and may form small groups deep in the parenchymal cords, at some distance from the sinusoids. At 130 to 150 nm in diameter, their secretory granules are the smallest of any granules in the parenchymal cells of the hypophysis. Thyrotrophs secrete a glycoprotein, thyrotropin (thyroid-stimulating hormone), which stimulates the thyroid to produce and release thyroid hormone.

Gonadotrophs are the third type of basophil in the pars distalis. They are generally smaller than corticotrophic basophils, often show only a scattering of granules, and usually are round in shape. They often lie immediately adjacent to sinusoids. The cytoplasm shows profiles of granular endoplasmic reticulum, prominent Golgi complexes, and scattered lysosomes. The few spherical secretory granules present are about 150 nm in diameter. This type of basophil secretes two glycoprotein hormones. Follicle-stimulating hormone (FSH) stimulates growth of ovarian follicles in women and, in men, stimulates synthesis of androgen-binding protein by Sertoli cells in the seminiferous epithelium, thereby activating and promoting spermatogenesis. In women, FSH acts on granulosa cells to produce estrogens from androgens coming from surrounding thecal cells. Luteinizing hormone (LH) is essential for ovulation, for stimulating secretion of estrogen by ovarian follicles, and for promoting luteinization of follicles following development induced by FSH. FSH stimulates granulosa cells of selected ovarian follicles to proliferate and produce estradiol. Simultaneously, LH stimulates thecal cells to produce androgens, which diffuse into the stratum granulosum and are converted into estradiol. The result is increased estradiol production. The rising levels of estradiol stimulate a surge in gonadotropin releasing hormone (GnRH) release from hypothalamic neurons. The resulting increase in LH and FSH secretion induces ovulation. Following ovulation the remaining cells of the ovulated follicle are transformed into a corpus luteum in response to LH. The cells of the

corpus luteum produce large amounts of progesterone and estradiol throughout its life span. Granulosa lutein cells also produce a glycoprotein called inhibin. Estradiol, progesterone and inhibin act together on the hypothalamic/pituitary axis to suppress FSH and LH secretion and thereby temporarily prevent another ovarian cycle from taking place.

The male the equivalent to luteinizing hormone, interstitial cell-stimulating hormone (ICSH), is secreted by this type of basophil in the male. ICSH stimulates production of testosterone by the interstitial cells of the testis. Testosterone is essential for sperm maturation and for development and the maintenance of secondary sex organs and characteristics in men. In men FSH targets the Sertoli cell of seminiferous tubules to produce androgen binding protein (ABP) and inhibin. Androgen binding protein is essential for the normal spermatogenesis and spermiogenesis to occur. Inhibin stops the secretion of FSH by the gonadotrophs and plays an important role in the feedback loop controlling the rate of spermatogenesis.

The remaining general cell type, the chromophobes, usually are small and are confined to the interior of the parenchymal cords. Lacking granules, they fail to color with routine stains, hence their name. Their existence as a separate cell type is under debate. They may represent a reservoir of cells from which chromophilic cells originate. This accords with the hypothesis that cells of the pars distalis cycle, first accumulating secretory granules and then releasing them. Occasionally, cyst-like follicles, lined by nonsecretory (follicular) cells and filled with a colloid type of material, may be seen in the pars distalis. Microvilli and occasional tufts of cilia extend from the apices of the cells into the follicular lumen. The follicular cells are unusual in that they also have long basal processes that extend between adjacent secretory cells. Similar cells called folliculostellate cells are not organized into follicles and extend long branching processes between secretory epithelial cells. Gap junctions unite the processes of folliculostellate cells, which form a network. Their cytoplasm contains intermediate filaments (glionfibrillary acid protein) and suggests a function similar to that of glial cells in the central nervous system, ie, providing a supporting framework and monitoring a microenvironment for the secretory epithelial cells.

The various epithelial cell types forming the anterior pituitary (pars distalis) have a regional distribution and show a variation in number. The lateral regions contain the greatest number of somatotrophs while corticotrophs are concentrated in the medial posterior region adjacent to the pars nervosa of the posterior pituitary. Thyrotrophs are concentrated in the medial anterior region. Gonadotrophs and mammotrophs are scattered throughout the pars distalis. Somatotrophs make up about 40-50%, mammotrophs 20-25%, corticotrophs 15-20%, thyrotrophs about 10%, and gonadotrophs about 10% of the epithelial cells forming the pars distalis.

Pars Tuberalis

Pars tuberalis forms a sleeve of epithelial cells, up to 60 μm thick, around the infundibular stalk. It is thickest anteriorly and may be incomplete posteriorly. Pars tuberalis is characterized by longitudinally arranged cords of parenchymal cells separated by sinusoids. The parenchyma of pars tuberalis is continuous with that of pars distalis and consists of acidophils, basophils, and undifferentiated cells. The latter usually are columnar, and their cytoplasm shows numerous small granules and large amounts of glycogen. Nests of squamous cells may be present. Pars tuberalis has no known distinct hormonal function.

Pars Intermedia

Pars intermedia is rudimentary in humans, in whom it forms only about 2% of the hypophysis. It consists of chromophobe and basophil cells, the latter often encroaching into pars nervosa. Colloid-filled cysts lined by chromophobes or basophilic cells also may be present, and remnants of Rathke's cleft may persist as fluid-filled cysts lined by ciliated columnar epithelium. Pars intermedia in some species is responsible for the secretion of melanocyte-stimulating hormone (MSH), a polypeptide hormone. Its role in mammals is unknown, but it may be involved in melanocyte stimulation. Only the precursor molecule for MSH occurs in humans. MSH contains amino acid sequences that are identical to portions of the ACTH molecule, and the occurrence of these structurally similar regions is believed to account for the melanocyte-stimulating effect of ACTH.

Control of the Adenohypophysis

Secretions from target endocrine glands that are under control of the adenohypophysis influence cells in the adenohypophysis through regulatory neurons of the hypothalamus. This important region of the brain consists only of about 4 grams of tissue. The perikarya of the hypothalamic neurons are located primarily in the paraventricular nucleus, arcuate nucleus, and medial preoptic nucleus of the hypothalamus. Axons from these neurons project into the median eminence where the axon terminals secrete releasing and inhibiting hormones. These small peptides, released in a pulsatile fashion, enter the primary capillaries surrounding the infundibular stalk and then are transported to the secondary capillaries of pars distalis via the hypophyseal portal veins where they stimulate specific target cells to release hormones. Hypothalamic releasing factors are known for somatotropin (growth hormone releasing hormone (GHRH)), primarily from neurons of arcuate nuclei; thyrotropin (thyrotropin releasing hormone (TRH)), primarily from neurons of dorsomedial nuclei; corticotropin (corticotropin releasing hormone (CRH)), primarily from neurons in anterior paraventricular nuclei; and gonadotropin (gonadotropin releasing hormone (GnRH)), primarily from neurons in arcuate nuclei and preoptic area; and their amino acid sequences have been determined. Inhibitory hormones such as somatostatin (a peptide of 14 amino acids) also are secreted by hypothalamic neurons. Somatostatin inhibits the secretion of growth hormone, thyroid stimulating hormone and prolactin. Dopamine also inhibits prolactin secretion and is thought to be the most important factor in the control of prolactin release. Other factors having this action are oxytocin and thyrotropin releasing hormone. Somatostatin is released by neurons within the paraventricular nuclei and dopamine by neurons within the arcuate nuclei.

Neurohypophysis

Macroscopically, the neurohypophysis consists of the median eminence, infundibular stalk, and infundibular process (pars nervosa). The greater part of the neurohypophysis consists of unmyelinated nerve fibers of the hypothalamohypophysial tract, which originates mainly from neurons in the supraoptic and paraventricular nuclei. The tract receives additional nerve fibers from other hypothalamic regions. The fibers end blindly in the pars nervosa, close to a rich capillary plexus. The axons comprising the hypothalamohypophysial tract commonly contain spherical masses of secretory material that vary considerably in size. These are the Herring bodies, which consist of large accumulations of dense secretory granules that vary from 120 to

200 nm in diameter. Hormones within the secretory granules are synthesized in the perikarya of neurons forming the supraoptic and paraventricular nuclei. They then pass down the axons to be stored in the nerve terminals that form the pars nervosa. When released, the hormones cross a thin, fenestrated endothelium to enter the capillaries in the pars nervosa and thence into hypophyseal veins to finally enter the systemic circulation.

Scattered among the nerve fibers are cells called pituicytes, which vary in size and shape and may contain pigment granules. Pituicytes are considered to be the equivalent of neuroglial cells of the central nervous system, but whether they have only a supportive function or actively participate in the secretory processes of adjacent nerve terminals is not known.

Two cyclic polypeptide hormones, oxytocin and antidiuretic hormone (vasopressin), are stored and released from axons forming the pars nervosa. During axonal transport, each hormone is bound to a carrier protein called neurophysin, and it is the neurophysin-hormone complex that forms the major part of the Herring bodies.

Oxytocin is released from neurons in lactating women by means of a neuronal reflex that is initiated during suckling and transmitted to the hypothalamus through the cerebral cortex. Oxytocin causes contraction of myoepithelial cells around the alveoli of the mammary gland and helps to express milk into the ductal system during nursing. Oxytocin also is released in response to vaginal stimulation during sexual intercourse resulting in smooth muscle contractions within the wall of the uterus as well as the oviduct. This action may facilitate sperm transport within the female reproductive tract. Oxytocin levels rise and increase uterine smooth muscle contractions during labor. Oxytocin also is believed to play a major role in certain behaviors such as pair bonding and affection between adults and bonding between mother and child.

Antidiuretic hormone (ADH) acts primarily on the collecting tubules of the kidney to increase their permeability to water and urea, thus promoting the resorption of water from the glomerular filtrate. Antidiuretic hormone acts primarily on the principal cells of the collecting duct. In the presence of this hormone, intracellular vesicles containing proteins (aquaporin-2 and urea channels) are delivered to and inserted into the apical plasmalemma of this cell type making them permeable to water. The net effect of this action is the concentration of urine and the reabsorption of water by the kidney.

Afferent nerve fibers traveling within the vagus and glossopharyngeal nerves from the carotid and aortic bodies carry baroreceptor input to a vasomotor center located in the medulla of the brain stem. Perikarya of neurons in the supraoptic and paraventricular nuclei of the hypothalamus receive input from these peripheral baroreceptors as well as input from osmoreceptors and secrete in response to an increase in the osmolarity of the body fluids as well as other factors. Decreased blood volume and pressure, increased body fluid osmolality and increased angiotensin II levels stimulate ADH secretion resulting in a small volume of concentrated urine being produced by the kidney. Increased blood volume and pressure, decreased body fluid osmolality, and atrial natriuretic peptides inhibit ADH secretion resulting in a large volume of dilute urine produced by the kidney. Pharmacologic doses of ADH cause contraction of vascular smooth muscle and elevate blood pressure. As a result of this action, this hormone is sometimes referred to as vasopressin.