Pituitary anatomy and physiology

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The pituitary gland or hypophysis cerebri, derived from Greek terminology for its location as an attachment beneath the brain, was named by Andreas Vesalius in accordance with Aristotle's belief that the pituitary was the organ through which phlegm, one of the body's four essential humors, passed from the brain [1].

Although such notions now seem archaic, the significance of the pituitary has only recently been elucidated. As late as 1909, Harvey Cushing pondered its dispensability in a treatise entitled, ''Is the pituitary gland essential to the maintenance of life?'' [2].

Over the past century, great advances have been made in understanding the physiology of the pituitary and its central role in governing the homeostatic functions of the body. Although the adult hypophysis typically measures less than 1 cm in its greatest dimension and weighs less than 1 g, its small size belies its importance and complexity, including its intricate embryology, structural heterogeneity, and functional diversity. The anterior, intermediate, and posterior lobes of the pituitary gland act as three separate endocrine organs, each characterized by distinct cell populations, secretory products, and regulatory mechanisms.

Embryogenesis of the pituitary gland

The pituitary gland originates from two discrete parts of the developing embryo (Fig. 1): Rathke's pouch, a dorsal evagination of the stomodeum immediately anterior to the buccopharyngeal membrane, and the infundibulum, a ventral extension of the diencephalon just caudal

to the optic chiasm [3]. Another dorsal evagination of the stomodeum, the pouch of Sessel, arises just posterior to the buccopharyngeal membrane. This structure contributes to the formation of the hypophysis in lower vertebrates but not in primates. Nonetheless, it sometimes persists in human beings and can be the source of certain tumors [4].

Morphogenesis

Rathke's pouch and the infundibulum are both derivatives of the ectodermal germ cell layer, but they ultimately generate distinct histologic patterns. The former differentiates into glandular epithelium characteristic of other endocrine organs, whereas the latter becomes organized as exocrine (ductless) tissue. Development of the hypophysis commences when the glandular and neural primordia are induced by the anterior end of the notochord, which is situated just caudal to the stomodeum (see Fig. 1). Reciprocal interactions between these constituents guide subsequent embryogenesis [4].

During the third week of gestation, the infundibulum develops as a ventral diverticulum in the floor of the third ventricle. It extends from the median eminence as the infundibular stem and ends in an expansion called the infundibular process. Simultaneously, an ectodermal placode appears in the roof of the stomodeum and invaginates to form Rathke's pouch, which grows dorsally. In the second month of development, Rathke's pouch flattens itself around the anterior and lateral surfaces of the infundibulum, and these two structures subsequently integrate (see Fig. 1).

The connection between Rathke's pouch and the oral cavity passes between chondrification centers of the developing presphenoid and basisphenoid bones of the skull. Expansion of sphenoidal mesenchyme in the sixth week of gestation

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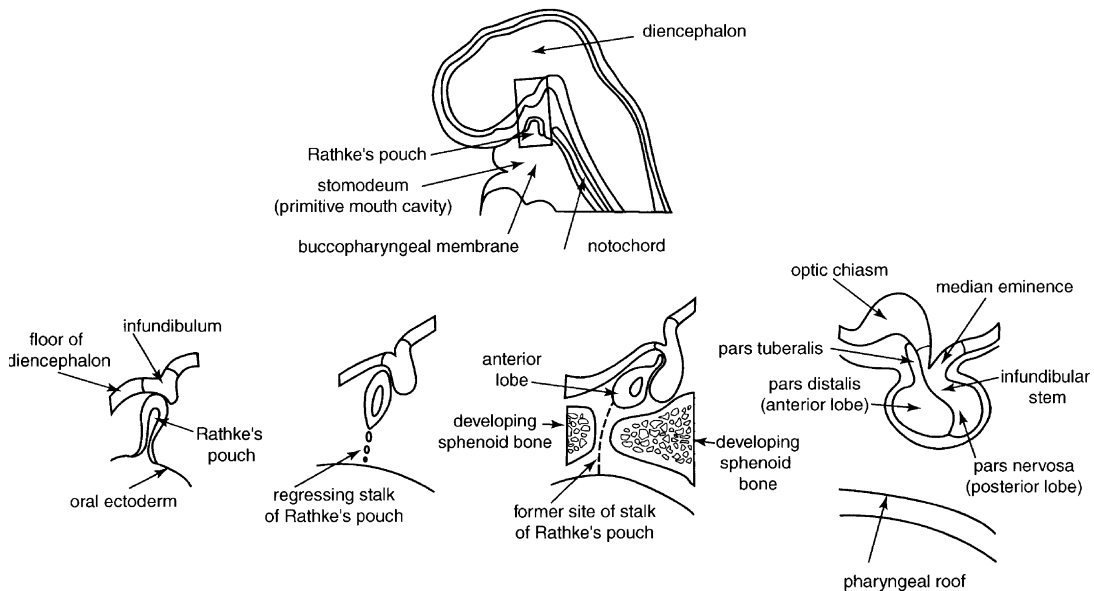*E-mail address:* amar@aya.yale.edu (A.P. Amar).

Fig. 1. Embryogenesis of the pituitary gland.

causes this connection to regress in most cases. In about 1% of newborn skulls, however, a remnant of this passage, the basipharyngeal canal, is visible at autopsy or by radiographs [5]. Similarly, small remnants of Rathke's pouch may occasionally persist in the roof of the oropharynx as the pharyngeal hypophysis (Fig. 2).

With further development, cells in the anterior wall of Rathke's pouch (pars distalis) proliferate rapidly and form the anterior lobe of the pituitary gland, also known as the adenohypophysis (Fig. 3). Differential growth of these cells relative to the surrounding mesenchyme produces a small basin, open above and separated into two compartments by a cellular median septum. Each compartment,
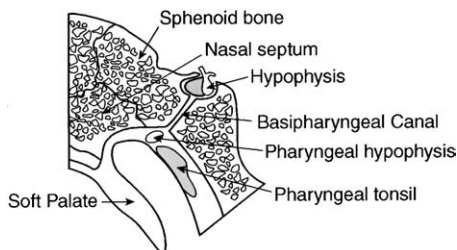

Fig. 2. Remnants of the course of Rathke's pouch may occasionally persist in the roof of the oropharynx as the pharyngeal hypophysis or in the sphenoid bone as the basipharyngeal canal.

or fossa of Atwell, is initially filled with mesenchyme. These fossae subsequently disappear as a result of further cellular proliferation by Rathke's pouch derivatives. The median septum forms the pars medialis, whereas the lateral portions form the pars lateralis of the anterior lobe [4]. Migration of mesenchymal elements from the fossae of Atwell to the anterior surface of the infundibulum carries the mesodermal elements that eventually form the blood vessels of the hypophyseal portal system [1]. A small extension of the median septum, the pars tuberalis, develops from the fusion of paired wing-like buds that grow along the stalk of the infundibulum and eventually encircle it.

Cells of the posterior wall of Rathke's pouch do not proliferate extensively but differentiate into the middle lobe of the pituitary gland, the pars intermedia. The cavity of Rathke's pouch between the anterior and middle lobes becomes effaced in most cases by the incorporation of cells from the anterior and posterior walls but may persist as a narrow cleft (residual lumen, also known as the pituitary fissure).

Along with the pars tuberalis, the infundibular stem comprises the pituitary stalk. The infundibular process gives rise to the posterior lobe of the pituitary gland, also known as the pars nervosa or neurohypophysis. The latter consists of neuroglial cells (pituicytes) as well as the nerve fibers and terminals of cells originating from hypothala-
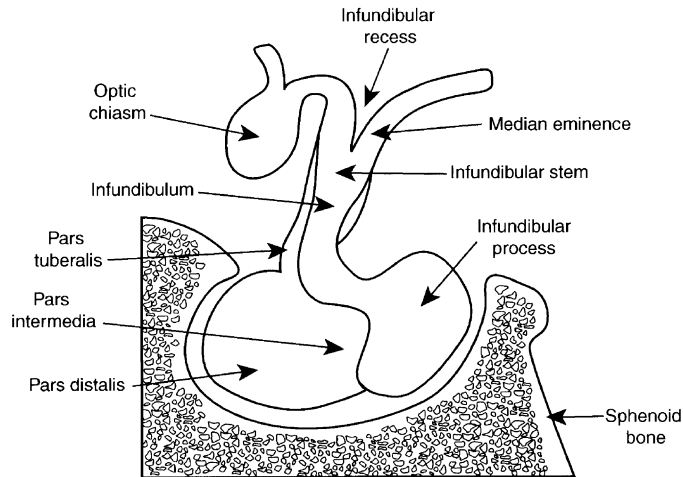
Fig. 3. Midsagittal section of the adult pituitary gland showing the constituents of the adenohypophysis, intermediate lobe, and neurohypophysis.

mic nuclei. Pituicytes are specifically adapted to support the secretion and transport of hormones released by the neurohypophysis. They also have phagocytic properties [1]. The lumen of the infundibulum is obliterated during development, but a small proximal pit, the infundibular recess, persists in the floor of the third ventricle (see Fig. 3) [6].

Histogenesis

By the third and fourth months of gestation, cells of the anterior lobe arrange themselves as cords around blood sinusoids. Glandular organization is induced by the surrounding mesenchyme [4]. Simultaneously, the portal system of blood vessels develops and is fully established by the end of the first trimester. Anterior lobe cells further differentiate into histologically discrete populations characterized by the affinity of their cytoplasm for selected dyes (acidophils, basophils, and chromophobes). The relative density of these cells comports with the bilateral symmetry achieved during morphogenesis of the adenohypophysis. Basophilic cells are concentrated in the pars medialis. Conversely, acidophils tend to be distributed in the pars lateralis (Fig. 4).

The adenohypophysis begins to function during the first trimester. Corticotropin, β-endorphin, luteinizing hormone (LH), and follicle stimulating hormone (FSH) can all be detected early in gestation. Thyrotropin-releasing hormone (TRH)–secreting cells develop early in the second trimester. Growth hormone (GH) and prolactin (PRL) become increasingly synthesized during

the second half of pregnancy [7]. Neurosecretory activity of the posterior lobe begins in late fetal life [8].

Gross anatomy of the pituitary gland

The average weight of the pituitary gland at birth is about 100 mg. Rapid growth occurs in childhood, followed by slower growth until the adult weight (approximately 500–600 mg) is attained in the latter part of the second decade. The adult hypophysis measures approximately 10 mm in length, 10 to 15 mm in width, and about 5 mm in height [9].

On average, the female gland is almost 20% heavier than the male gland primarily because of relative differences in the size of the pars distalis. Furthermore, the weight of the gland increases by 12% to 100% during pregnancy because of enlargement of the pars distalis [10]. Although there exists a rough correlation between body length and the weight of the gland, these differences are also a result of variability in the pars distalis, because the size of the pars nervosa remains relatively constant [9]. The volume of the pituitary gland decreases with aging [11].

Modern radiographic techniques like MRI allow accurate estimation of the size and shape of the pituitary gland and have supplanted earlier methods based on roentgenographic measurement of the pituitary fossa. Numerous studies have confirmed the inadequacy of the latter techniques. For instance, 22% of pituitary glands studied at
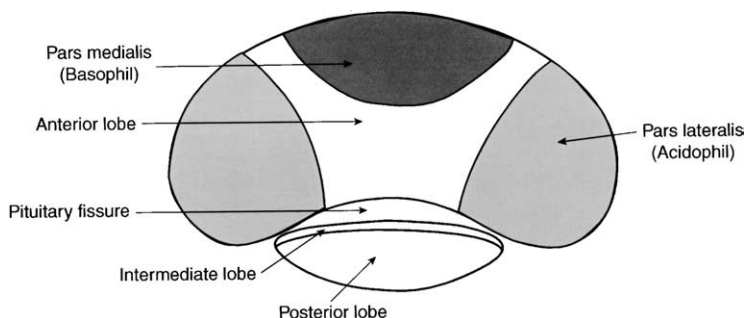
Fig. 4. Cross-section of adult pituitary showing the relative density of acidophilic and basophilic cells.

autopsy are compressed to some degree by the carotid arteries [9,12]. Thus, the transverse dimension of the gland cannot be ascertained simply by determining the width of the dorsum sellae or the floor of the sella turcica [9]. Similarly, although the inferior contour of the pituitary gland corresponds well with the roentgenographic appearance of the sellar floor, the height of the gland and its superior contour cannot be estimated by plain radiographs of the skull. In the previous autopsy study [9], 23% of glands had a superior-to-inferior dimension at least 2 mm less than the depth of the pituitary fossa, with the dimension of some glands being less than half this depth.

Vascular anatomy of the pituitary gland

Neural regulation of pituitary function occurs via two general mechanisms, each contingent on a distinct vascular network (Fig. 5): direct projections of the hypothalamus to the neurohypophysis consisting of axon terminals that terminate in the posterior lobe and release their neurosecretory products directly into the bloodstream and regulation of the adenohypophysis via tropic hormones produced in the hypothalamus and conveyed to the anterior lobe via the portal venous system. The anterior pituitary is the most richly vascularized of all mammalian tissues, receiving about 0.8 mL/g/min of blood from the portal system [10].

The pituitary gland derives its blood supply from two groups of arteries. The superior hypophyseal artery (SHA) primarily supplies the anterior lobe, whereas the inferior hypophyseal artery (IHA) is primarily related to the pars nervosa. The SHA can arise from the supraclinoid portion of the internal carotid artery (ICA) or from the posterior communicating artery, whereas the IHA arises from the meningohypophyseal trunk, a branch of the cavernous segment of the ICA [13].

The SHAs usually consist of a series of small vessels exiting the inferior medial portion of the ICA underneath the optic nerve. They supply the pituitary stalk, adenohypophysis, and inferior surface of the optic nerve and chiasm. These small arteries anastomose with their counterparts from the contralateral side and with the IHAs to form a vascular plexus encircling the median eminence and upper portion of the pituitary stalk. The median eminence receives the endings of hypothalamic cells, which produce releasing and inhibiting factors involved in the control of adenohypophyseal function. This vascular circle divides into a primary plexus of fenestrated capillaries that ramify through the tissues and receive the regulatory factors secreted by them. The capillaries converge into venules that then form a series of small and long portal hypophyseal veins. It has been estimated that the concentrations of hypo-
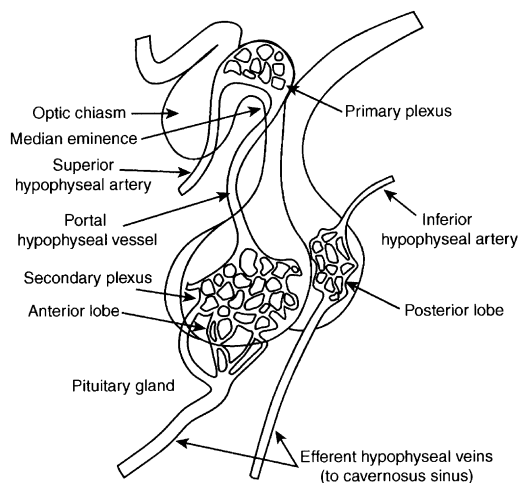

Fig. 5. Diagrammatic representation of the vascular anatomy of the pituitary gland.
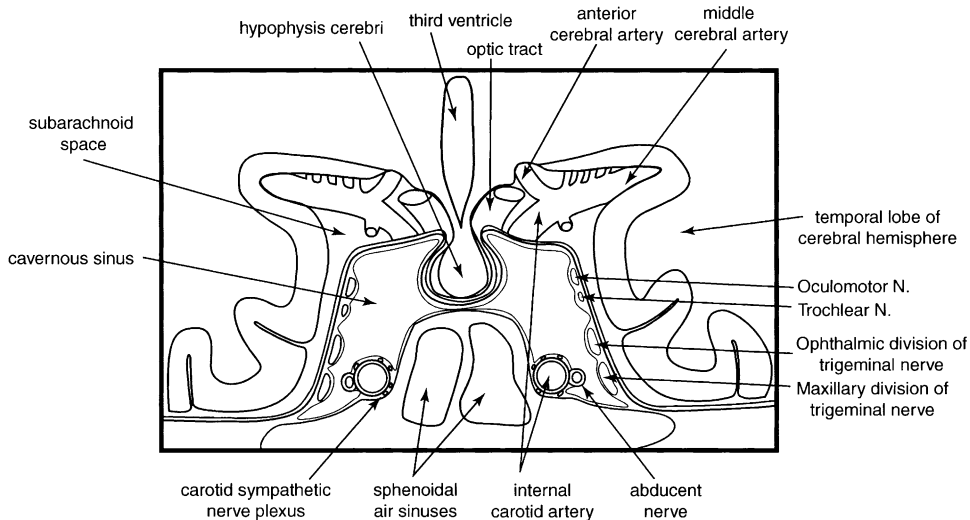
Fig. 6. Coronal section through the body of the sphenoid bone demonstrating the anatomic relations of the hypophysis to sellar and parasellar structures.

thalamic peptides regulating the hypophysis are 10-fold to 1000-fold higher in pituitary portal venous blood than in the peripheral circulation [11,14]. The portal veins pass down the stalk into the pars tuberalis and pars distalis of the anterior lobe, where a secondary plexus of sinusoidal capillaries is formed. After transmitting hypothalamic regulatory factors to the adenohypophysis and receiving hormones secreted by the anterior lobe, the capillaries reconstitute themselves into efferent lateral hypophyseal veins, which drain into the cavernous sinus. Flow may be reversed, however, such that hormones released by the adenohypophysis can reflux to the median eminence and effect feedback modulation of their synthesis [11,15–17]. A countercurrent multiplier action similar to that occurring in the kidney between the loops of Henle and their surrounding capillaries is also postulated to occur in the pituitary gland [13].

The posterior lobe receives blood from branches of the IHA [9]. This vessel passes medially from its point of origin below the diaphragma sellae to enter the groove between the pars distalis and the pars nervosa. At that point, it divides into ascending and descending branches that unite with corresponding branches from the contralateral IHA to form an arterial ring. This anastomosis then forms arterioles and capillaries that ramify through the pars nervosa, receiving the neurosecretory products elaborated by the axon terminals. Other branches provide arterial supply to the cap-

sule of the pars nervosa and the infundibulum. Venous drainage of the posterior lobe is also primarily to the cavernous sinus and circular sinus.

The intermediate lobe is relatively avascular but may derive collateral supply from anastomotic connections between capillaries of the anterior and posterior lobes.

Surgical anatomy of the pituitary gland

The pituitary gland is situated within the hypophyseal fossa, a fibro-osseous compartment near the center of the cranial base. This fossa is demarcated laterally and superiorly by reflections of dura and elsewhere by the sella turcica, a depression in the body of the sphenoid bone. In that location, the gland has proximity to several important cranial nerves and vascular structures at the skull base (Fig. 6).

Sellar anatomy

The pituitary fossa is limited anteriorly, posteriorly, and inferiorly by bony constituents of the sella turcica. The anterior wall is called the tuberculum sellae, and its posterior wall is named the dorsum sellae. Immediately anterior and slightly superior to the tuberculum lies a transverse groove, the sulcus chiasmaticus, which terminates on each side in the optic foramen. The superolateral margins of the dorsum sellae form rounded knoblike structures, the posterior clinoid processes,

which provide attachment for dural folds. The anterior clinoid processes serve similar functions and are related to the anterolateral aspect of the sella turcica. They are actually medial extensions of the greater sphenoid wing, however, and not part of the sella itself.

The floor of the hypophyseal fossa is formed completely or partially by the roof of the sphenoid sinus, depending on the size of the latter structure. If the sinus is small, its roof forms only the anterior floor of the sella turcica, with the remainder of the floor consisting of the body of the sphenoid bone. The degree of pneumatization of the sphenoid bone and the thickness of bone separating the sphenoid sinus from the hypophyseal fossa are both highly variable. The pattern of bony trabeculae that divide the sphenoid sinus is also quite inconstant. The intrasinus septum is attached to the midpoint of the anterior sellar wall in only about 20% of cases and may be absent altogether [9,18]. In another 20% of cases, the posterior attachment of the intrasinus septum is to the carotid prominence. Thus, this landmark cannot reliably serve to orient the surgeon toward the midline, which is an important objective for averting injury to the carotid arteries situated laterally.

The contour of the sella is also highly variable [19]. Although it usually has a round or oval profile, it may be quite flattened. At birth, the sella turcica consists of a shallow depression and the dorsum is not yet ossified. By approximately 4 years of age, the outline of the sella appears more rounded. The sagittal dimension increases by 0.5 to 1 mm annually until puberty, when the definitive oval shape of the adult sella is attained [9]. The average anteroposterior dimension of the sella in the midsagittal plane is 1.07 cm, whereas the average depth and transverse dimensions are 0.8 cm and 1.21 cm, respectively [9,19]. The average size is equal in males and females [9].

The diaphragma sellae, a fold of dura with a central defect, forms an incomplete roof above the sella turcica. The diaphragma separates the anterior lobe from the overlying optic chiasm. The margins of the diaphragma are attached to the tuberculum sellae, the anterior clinoid processes, the superior aspect of the dorsum sellae, and the posterior clinoid processes. Laterally, the diaphragma is continuous with the folds of dura constituting the lateral walls of the pituitary fossa [9].

The central aperture of the diaphragma is of variable size, ranging from a small foramen in an otherwise complete barrier to a large hole surrounded by a tenuous membrane of tissue [12].

The size of the aperture and the relative competence of the diaphragma are important factors in protecting the gland from transmitted pulsations of the choroid plexus or in defending the visual fibers against suprasellar extension of an expanding pituitary tumor [9].

The central aperture transmits the pituitary stalk and its blood supply. In addition, pneumoencephalographic studies have demonstrated that the subarachnoid space of the chiasmatic cistern extends through the aperture of the diaphragma and into the sella turcica for varying distances about the gland [12]. In some instances, the arachnoid membrane herniates extensively through an incompetent diaphragma sellae. Cerebrospinal fluid then partially fills the sella turcica, leading to remodeling and enlargement of the hypophyseal fossa and flattening of the pituitary gland. This condition, known as the empty sella syndrome, is found in 5% to 23% of cases at autopsy [10]. Causes include a mesenchymal defect leading to congenital incompetence of the diaphragma. In other cases, increased cerebrospinal fluid pressure (eg, pseudotumor cerebri) leads to herniation of the arachnoid through the diaphragma.

Parasellar and suprasellar anatomy

The folds of dura mater that form the lateral walls of the hypophyseal fossa contain the cavernous sinuses, which consist of a series of compartmentalized venous channels separated by fibrous trabeculae. The cavernous sinuses were originally named for their superficial resemblance to the corpora cavernosa of the penis. The two sinuses communicate with one another by means of the anterior and posterior intercavernous sinuses, also known as the circular sinuses. These latter sinuses run in the diaphragma sellae in front of and behind the pituitary stalk, respectively.

The oculomotor nerve, trochlear nerve, and first two divisions of the trigeminal nerve are embedded in the lateral wall of the cavernous sinus, lying between the endothelial lining and the dura mater, whereas the abducens nerve is contained within the sinus itself. The cavernous sinus also envelops a portion of the ICA and the sympathetic nerve plexus encircling it. The cavernous segment of the ICA extends forward adjacent to the superolateral surface of the body of the sphenoid bone in a groove called the carotid sulcus. The artery then turns superiorly, medial to the anterior clinoid process, at the anterior end of the carotid sulcus, where it pierces the dura and

enters the subarachnoid space. Throughout this course, the medial limit of the cavernous segment of the ICA normally lies approximately 5 mm from the midline, whereas the lateral limit is less constant, varying from 13 to 20 mm from the midline [9,20].

The hypophysis is overlaid by the hypothalamus and visual pathways. Variability in the development of the superior surface of the sphenoid bone just anterior to the hypophyseal fossa produces a great deal of inconsistency in the relation between the pituitary gland, stalk, diaphragma sellae, sulcus chiasmaticus, and optic apparatus. Four patterns have been described [9,12,21]:

1. In some cases, the body of the sphenoid bone develops such that the sulcus chiasmaticus is situated more inferiorly than usual. This, in turn, leads to a lowered position of the optic foramen. Thus, the optic chiasm is much nearer to the diaphragma sellae. The anterior border of the chiasm is closely applied to the sulcus chiasmaticus and may even lie in contact with the upper posterior wall of the sphenoidal sinus, a fact that must be considered during transsphenoidal surgeries. The intracranial course of the optic nerves is relatively short, and the infundibulum is directed posteriorly in its course from the hypothalamus to the opening in the diaphragma sellae. Suprasellar extension of a pituitary tumor distending the diaphragma sellae would therefore exert the greatest pressure over the medial portions of the optic tracts. This pattern is called a prefixed chiasm and is present in 5% to 10% of bodies examined [9,12,21].
2. In other cases, the intracranial course of the optic nerves is slightly longer than that of the preceding pattern, and the entire optic chiasm rests above the anterior part of the diaphragma sellae. The infundibulum has a vertical course in passing from the hypothalamus to the central aperture. The optic chiasm is most vulnerable to suprasellar extension of a pituitary tumor. This configuration is found in about 12% of cases [9,21].
3. In yet another pattern, the optic chiasm is more posteriorly placed than in the previous two arrangements, lying over the posterior aspect of the diaphragma sellae and the anterior part of the dorsum sellae. The infundibulum is directed anteriorly as it passes from the hypothalamus to the diaphragma. These relations are found in approximately 75% of cases [9,21].

4. In the remaining pattern, the optic chiasm is located on and behind the dorsum sellae. The infundibulum is directed acutely forward as it leads to the central aperture. This pattern is designated a postfixed chiasm and is seen in 4% to 11% of cases [9,12,21]. In such cases, the medial aspects of the optic nerves are most vulnerable to suprasellar extension of an intrasellar tumor.

In addition to the preceding arrangements, the variable relation between the optic pathways and the anterior cerebral artery complex is another important determinant of the visual deficits produced by an expanding pituitary tumor, especially if the arteries are hard and noncompliant [9].

Physiology of the anterior lobe

Hormones of the anterior lobe

The adenohypophysis, which constitutes the bulk of the pituitary gland's size and weight, produces six established hormones: thyroid stimulating hormone (TSH), corticotropin, FSH, GH, and PRL. The first five serve tropic functions by stimulating other organs to secrete hormonally active substances, whereas PRL serves a trophic function on breast tissue.

Cells of the anterior lobe also produce pro-opiomelanocortin (POMC), a large (1091–amino acid) precursor glycoprotein that undergoes hydrolytic cleavage at the sites of basic amino acids, such as arginine and lysine, resulting in the production of numerous hormonally active derivatives [14]. POMC is also made by neurons of the hypothalamus and cells of the intermediate lobe as well as by the placenta, lungs, and gastrointestinal tract. These different tissues process POMC into characteristic ratios of the products of proteolysis, which include corticotropin, α- and β-melanocyte stimulating hormone (α-MSH and β-MSH), corticotropin-like intermediate lobe peptide (CLIP), γ-lipotropin (γ-LPH), β-lipotropin (β-LPH), and β-endorphin. The physiologic roles of many of these peptides in neurotransmission, learning, pain, pre- and postnatal endocrinology, mental disorders, and neoplasia are only now being established [22]. In addition to corticotropin, one of the principal products from the anterior lobe is β-LPH, a linear polypeptide containing 91 amino acid residues. Although it contains the sequences of endorphins and enkephalins, small

peptides that bind to opiate receptors, the physiologic significance of β-LPH is uncertain.

Corticotropin, PRL, and GH are simple polypeptides, whereas LH, FSH, and TSH are glycoproteins. The glycoproteins consist of a heterodimer of two subunits, designated α and β. The subunits have some activity independently but must be combined to achieve maximal effects [23]. The α-subunits of all these hormones are products of a single gene on chromosome 6 and have the same amino acid composition, although the carbohydrate residues vary. Conversely, the β-subunits are produced by different genes and vary in structure, thus conferring specificity of hormonal action [23]. Cells that only secrete the α-subunit have been described, especially in the context of some nonfunctioning pituitary adenomas.

The serum levels of anterior pituitary hormones as well as that of the α-subunit can now be easily measured by radioimmunoassay. Mathematic modeling of the plasma profiles of these hormones suggests that tonic secretion is negligible. Instead, secretion occurs episodically, prompted by pulses of hypothalamic regulatory factors. Each burst of secretion lasts only a few minutes, but the frequency of bursts along with the relatively slow metabolic clearance produces longer duration of plasma peaks (eg, 90–140 minutes) in response to specific physiologic stimuli [11].

Histology of the anterior lobe

The anterior lobe is composed of interlacing cords of large polygonal cells separated by an extensive network of sinusoidal capillaries [14]. The cytoplasm of these cells contains granules of stored hormone that are released by exocytosis. The endothelium of the capillaries is fenestrated, thus promoting uptake of the secreted hormones.

The cytoplasmic granules allow histologic classification of adenohypophyseal cells. Traditional designations based on the affinity of the granules to various dyes with light microscopy (acidophils, basophils, and chromophobes) have been supplanted by more refined classification schemes emphasizing the nature of the secreted product. Based on modern techniques, such as electron microscopy and immunocytochemistry, at least six cell populations are currently recognized. Somatotropes, which secrete GH, are the most common type and constitute 40% to 50% of cells [11]. They are acidophilic in standard hematoxylin–eosin preparations and are usually located in the lateral portions of the anterior lobe [10]. Mam-

motrophs or lactotropes, which secrete PRL, account for 10% to 25% of cells. They are also acidophilic but are scattered throughout the gland [10]. Corticotrophs, which manufacture corticotropin, β-LPH, and POMC, account for another 15% to 20% of cells. They are basophilic and tend to be distributed in the anteromedial part of the gland [10]. Gonadotrophs, which secrete FSH and LH, make up 10% to 15% of anterior pituitary cells. They originate from basophil-staining cells and are located throughout the entire anterior lobe [10]. Thyrotrophs, which secrete TSH, account for only 3% to 5% of cells [11]. Because of their glycoprotein product, they are basophilic and also stain positively with the periodic acid–Schiff (PAS) stain [10].

In spite of this taxonomy, it is now recognized that some cells may produce more than one hormone [14]. For instance, mammosomatotrophs contain both GH and PRL [10]. In addition, another population of cells corresponding to the chromophobes of the earlier classification consists of inactive secretory cells that have few secretory granules. These cells have been called null cells and may be the precursors to nonfunctioning pituitary adenomas [10]. Other chromophobes are probably folliculostellate cells that send processes between the established secretory cells. Folliculostellate cells contain and secrete the cytokine inerleukin-6, but their physiologic relevance is uncertain [23].

Corticotropin

The action of corticotropin on the adrenal gland is necessary for the basal secretion of glucocorticoids and aldosterone as well as for the increased secretion of these hormones provoked by various stresses. Hypophysectomy leads to rapid atrophy of the adrenal cortex.

The corticotropin molecule is a single-strand polypeptide containing 39 amino acids [11]. Its half-life in the circulation is approximately 10 minutes. This property allows it to participate in rapid adjustments of circulating levels of glucocorticoid. For instance, glucocorticoid synthesis declines rapidly within 1 hour of hypophysectomy, whereas injections of corticotropin lead to a rise in glucocorticoid output within a few minutes [24]. The effects of corticotropin are mediated by a cell surface receptor coupled to the adenylyl cyclase enzyme via a guanosine triphosphate (GTP)–binding protein. Binding of the corticotropin molecule leads to an increase in the cyclic adenosine

monophosphate (cAMP) molecule that activates protein kinase A.

Corticotropin is secreted in irregular bursts throughout the day, most frequently in the early morning 2 to 4 hours before awakening [11]. The biologic clock responsible for the diurnal rhythm of corticotropin secretion is located in the suprachiasmatic nuclei of the hypothalamus [24].

Secretion of corticotropin is stimulated by corticotropin-releasing hormone (CRH), which is produced in the medial part of the paraventricular nuclei [25]. The axons of these cells project to the median eminence, where their product is secreted into the primary plexus and conveyed to the adenohypophysis via the portal system. Physical injury, emotional stress, hemorrhage, and other physiologic challenges produce afferent impulses that converge on the paraventricular nuclei, leading to increased CRH and corticotropin output. Conversely, glucocorticoids themselves block corticotropin secretion through feedback inhibition exerted at the hypothalamic and pituitary levels [24].

Thyroid stimulating hormone

The TSH molecule is a glycoprotein containing 211 amino acids. It consists of two subunits that are noncovalently linked. Its biologic half-life is approximately 60 minutes [26]. TSH secretion is pulsatile, with peak output around midnight.

Like many other hormones of the anterior pituitary gland, TSH acts on a cell surface receptor that activates adenylyl cyclase through a GTP-binding protein. It also activates phospholipase C. Binding of TSH to its receptor on thyroid cells results in increased synthesis of thyroxine (T4) and triiodothyronine (T3) as well as increased secretion of stored thyroglobulin [26].

Secretion of TSH is stimulated by TRH, a tripeptide that is produced in the medial part of the paraventricular nuclei. Somatostatin, produced in the periventricular nuclei of the hypothalamus, inhibits its release [25]. The axons of these cells project to the median eminence, where their products are secreted into the primary plexus and conveyed to the adenohypophysis via the portal system. Exposure to cold temperature increases TRH. T3 and T4 act at the hypothalamic and pituitary levels to block the secretion of TSH via feedback inhibition. The day-to-day maintenance of thyroid secretion depends on this interplay of thyroid hormones with TSH and TRH [26].

Luteinizing hormone and follicle stimulating hormone

The gonadotropins LH and FSH stimulate the gonads of both sexes and are necessary for the production of germ cells (gametogenesis) as well as the secretion of androgens and estrogens by those tissues [14]. They are also necessary for the ovulatory cycles of women. The half-life of LH (60 minutes) and FSH (170 minutes) is enhanced by the carbohydrate moiety of the β-subunit glycoprotein [27]. The effects of LH and FSH are mediated by adenylyl cyclase activity, which is coupled to their receptors through a GTP-binding protein.

Secretion of LH and FSH is stimulated by gonadotropin-releasing hormone (GnRH), a decapeptide that is primarily produced in the medial preoptic area of the hypothalamus [11,25]. The axons of these cells project to the median eminence, where their product is secreted into the primary plexus and conveyed to the adenohypophysis via the portal system. Secretion of LH and FSH is under complex positive and negative feedback mechanisms interacting with GnRH [10]. It seems that the secretion of GnRH, however, must be pulsatile to achieve proper reproductive and endocrine function [14]. In addition, regulation entails both diurnal variation and patterns appropriate to different stages of life [11]. Inhibin, a polypeptide made by the gonads of both sexes, inhibits FSH secretion [27].

Growth hormone

Of all the hormones produced by the hypophysis, GH is the most abundant. The pituitary gland contains an amount of GH that is 20 to 40 times greater than that of corticotropin and 50 to 100 times greater than that of PRL [14].

GH exists in several forms in the body, all encoded by a cluster of genes on chromosome 17. The pituitary gland normally secretes a product with a molecular weight of 22,000 [11]. A smaller form produced by alternative mRNA splicing is also biologically active and accounts for 10% of circulating GH [23]. About half of the GH in the plasma is bound to a protein that consists of a cleavage product of the GH receptor. This provides a reservoir that compensates for the wide fluctuations in the rate of secretion and the short half-life (6–20 minutes) of GH [23].

The GH receptor consists of a transmembrane protein with a large extracellular domain. Binding of GH leads to homodimerization of the receptor, which then activates several second-messenger

cascades. In addition to direct activation of various genes, GH leads to the production of somatomedins, a group of polypeptide growth factors secreted by the liver, cartilage, and other tissues. The best-characterized somatomedins, insulin-like growth factor I (IGF-I, also known as somatomedin c) and IGF-II, seem to mediate many of the actions of GH. The plasma concentration of IGF-I peaks in puberty and declines to low levels in old age. IGF-II plays a role in growth of the fetus before birth, but in adults, its gene is only expressed in the choroid plexus and meninges [23].

GH has widespread effects throughout the body. Before the age of epiphyseal fusion in children, GH leads to the growth of long bones and chondrogenesis. GH is a protein anabolic hormone and produces a positive nitrogen balance, leading to an increase in lean body mass and a decrease in body fat. GH increases hepatic glucose output and exerts an anti-insulin effect in muscle. The general metabolic rate is also amplified [23].

Secretion of GH is regulated by two hormones produced in the hypothalamus. Growth hormone–releasing hormone (GRH) is made in the arcuate nuclei. Another hormone, formerly called growth hormone–inhibiting hormone (GIH), has now been identified as somatostatin, which is produced in the periventricular nuclei [25]. The axons of these cells project to the median eminence, where their products are secreted into the primary plexus and conveyed to the adenohypophysis via the portal system. The secretion of GRH is episodic, whereas that of somatostatin is more tonic. The stimuli that increase GH secretion include hypoglycemia, exercise, sleep, and various stresses. GH secretion is inhibited by glucose and cortisol. Like other hormones of the anterior pituitary, GH is also under feedback control. IGF-I directly inhibits secretion of GH from the pituitary and also stimulates somatostatin secretion from the hypothalamus [14,23].

Prolactin

PRL contains 198 amino acid residues and three disulfide bridges [11]. It has structural similarity and a comparable half-life (20 minutes) to GH [27]. Its receptor also resembles the GH receptor and undergoes dimerization before activating several intracellular enzyme cascades.

In conjunction with estrogen and progesterone, PRL causes milk secretion from the female breast. PRL also inhibits the actions of gonadotropins on the ovary. This may be the mechanism by which it prevents ovulation in lactating women or those with PRL-secreting tumors [27]. The role of PRL in men is uncertain, but excessive levels are known to produce impotence.

TRH and other polypeptides found in the hypothalamus stimulate PRL secretion. The principal means of regulation is via tonic inhibition, however. Prolactin-inhibiting factor (PIF), now identified as dopamine, is produced in the arcuate nucleus [25]. The axons of these cells project to the median eminence, where their products are secreted into the primary plexus and conveyed to the adenohypophysis via the portal system. Exercise, stress, sleep, pregnancy, and stimulation of the nipple all increase PRL secretion. PRL facilitates the release of dopamine from the median eminence and thus acts in a negative feedback loop to inhibit its own secretion [27].

Physiology of the intermediate lobe

Hormones of the intermediate lobe

In human beings and some other mammals, the intermediate lobe is rudimentary. Cells of the pars intermedia make up 3.5% of the glandular mass of the pituitary in the human fetus but less than 1% in the adult [28]. These facts led to the prevailing belief that the intermediate lobe only plays a physiologic role in fetal life and is vestigial in adults. Nonetheless, recent evidence challenges this notion [22].

Like corticotrophs of the pars distalis, cells of the intermediate lobe synthesize POMC as a large protein precursor. The products resulting from proteolytic cleavage of this molecule, however, differ between the two lobes. In the anterior lobe, POMC is hydrolyzed to corticotropin, β-LPH, and a small amount of β-endorphin. All these products are secreted into the bloodstream [23]. In contrast, the principal products of POMC hydrolysis in the intermediate lobe are CLIP, γ-lipotropin, and β-endorphin. The function of these first two peptides is unknown. In addition, the intermediate lobe forms two melanotropins, α-MSH and β-MSH. In some species, these latter hormones control the migration of pigment molecules in and out of cells for the purposes of thermoregulation, camouflage, and behavioral display [23]. In human beings, MSH molecules can bind to melanotropin-1 receptors on melanocytes, leading to increased melanin synthesis and darkening of the skin. Nevertheless, it seems that neither α-MSH nor β-MSH is secreted in human beings,

thus calling their significance into question. Corticotropin, which does circulate in the blood, can also activate melanotropin-1 receptors. This observation explains the pigmentary changes associated with some endocrine disorders [23]. For instance, pallor is a hallmark of hypopituitarism as a result of decreased levels of corticotropin. Conversely, hyperpigmentation occurs in patients with primary adrenal insufficiency, which stimulates the release of excessive amounts of corticotropin.

Histology of the intermediate lobe

Most of the glandular cells of the intermediate lobe are agranular, although there are often a few basophilic elements resembling anterior lobe cells. Nonglandular stellate cells are also present. Like glial cells of the brain, stellate cells may be involved in ionic regulation of the pars intermedia. The demonstration of glial fibrillary acid protein (GFAP) provides further evidence of their astrocytic origin [29]. The residual lumen, which separates the intermediate lobe from the anterior lobe, may contain small follicles containing a colloid-like substance of uncertain function [23]. This observation has raised speculation that this cleft may store circulating products [29]. Compared with the anterior lobe, the pars intermedia is relatively avascular but contains abundant innervation [29].

Physiology of the posterior lobe

Hormones of the posterior lobe

The posterior lobe secretes oxytocin and vasopressin. The latter is also sometimes called antidiuretic hormone (ADH), because one of its principal physiologic effects is retention of water by the kidney. These peptides are produced in the hypothalamus and then pass to the neurohypophysis via the 100,000 nerve fibers comprising the hypothalamo-hypophyseal tract [10]. From the posterior lobe, the hormones are released into the general circulation in response to electrical activity at the axon endings.

Oxytocin and vasopressin are both nonapeptides with a disulfide ring at one end [25]. They differ from one another at only two sites. The genes that encode them occupy adjacent loci on chromosome 20 but in opposite transcriptional orientations [14]. These hormones are synthesized in the cell bodies of the magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus. Cells make one or the other hormone,

but cells of each type are found in both nuclei. Most of the supraoptic fibers end in the posterior lobe itself, whereas some of the paraventricular fibers end in the median eminence as well [25].

Both oxytocin and vasopressin are synthesized as part of larger precursor proteins that undergo extensive posttranslational processing. These molecules are packaged into secretory granules known as Herring bodies [11]. The precursor undergoes cleavage as it is transported by axoplasmic flow to the endings in the posterior pituitary. There, the other products of proteolysis are stored along with oxytocin and vasopressin, but their function is unknown. One group of proteins, the neurophysins, represents the adjacent portions of the precursor molecules. Although they are cosecreted with oxytocin and ADH, they have no known endocrine function. Nevertheless, they seem necessary for the posttranslational processing of the neurohypophyseal hormones [14]. Release of the stored hormones is triggered by calcium-dependent exocytosis in response to action potentials reaching the nerve endings.

Histology of the posterior lobe

The posterior lobe is largely composed of the endings of axons that originate from cell bodies in the hypothalamus. These axon terminals are closely related to blood vessels, allowing them to secrete their products into the bloodstream. Pituicytes are also present throughout the posterior lobe. These neuroglial cells are specifically adapted to support the secretion and transport of hormones released by the neurohypophysis. They may also have phagocytic properties [1].

Oxytocin

Oxytocin acts through a G-protein–coupled cell surface receptor that triggers an increase in intracellular calcium in response to activation. The principal targets of oxytocin action are the breasts and uterus.

In mammary tissue, oxytocin causes contraction of the myoepithelial cells that line the breast ducts. This causes milk to flow from alveoli of the lactating breast to the nipple, where it is excreted. The milk ejection response is initiated by tactile stimulation of the nipples. Impulses generated by touch receptors are relayed to oxytocin-producing neurons of the hypothalamus, which undergo synchronous high-frequency discharge of action potentials leading to oxytocin release from the posterior pituitary gland.

Oxytocin also causes contraction of the smooth muscle of the uterus. During delivery, descent of the fetus down the birth canal initiates afferent impulses that are relayed to the supraoptic and paraventricular nuclei. Subsequent secretion of oxytocin enhances labor. Oxytocin may also act on the nonpregnant uterus to facilitate the passage of sperm to the fallopian tubes. In men, circulating oxytocin increases at the time of ejaculation. This event might be responsible for the contraction of smooth muscle of the vas deferens that propels sperm toward the urethra [25].

Vasopressin

Vasopressin acts through three separate receptors on the cell surface to exert its many physiologic effects throughout the body. All are serpentine, transmembrane, G-protein–coupled receptors that trigger the formation of second messengers in response to vasopressin binding. The biologic half-life of vasopressin is only 18 minutes [25].

In the collecting ducts of the kidney, vasopressin causes the translocation of water channels called aquaporins from endosomal compartments to the luminal membrane. This increases the permeability of the collecting duct, enabling water to enter the hypertonic interstitium of the renal pyramid. As a result, the urine volume decreases and its concentration (specific gravity) increases. Water is retained in excess of solute, and the overall plasma osmolality decreases. Vasopressin secretion is increased by many situations in which this effect is salutary, such as decreased effective circulating volume (eg, hemorrhage), increased plasma osmotic pressure, and increased angiotensin II levels. Pain, emotion, exercise, and nausea are also potent stimuli to vasopressin release. Alcohol inhibits the secretion of ADH.

Vasopressin, as its name implies, is also a potent constrictor of vascular smooth muscle. This effect on systemic blood pressure is offset by the effect of vasopressin on the area postrema of the brain, however, which serves to decrease cardiac output.

The anterior pituitary gland contains a unique class of vasopressin receptor. Corticotrophs increase corticotropin secretion in response to activation of this receptor [25]. Thus, vasopressin may act in a paracrine fashion on the hypophysis itself.

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