UG CBCS Semester-IV (MJC-7: Endocrinology)
The Mammalian Pituitary

The pituitary or hypophysis of adult mammals is located ventral to the brain just posterior to the optic chiasm, and it remains attached to the hypothalamus by a stalk-like connection (Figure 4-3). Endocrinologists today generally refer to this structure as the pituitary gland rather than the hypophysis, although both terms are technically correct. The term "pituitary gland" is derived from the Latin word for phlegm (pituita), because it was once thought to be the source of this important humour. The term "hypophysis" is derived from the Greek words for growth (physis) and below (hypo) (i.e., below the brain). The pituitary gland is separable into two regions, the adenohypophysis and the neurohemal neurohypophysis.

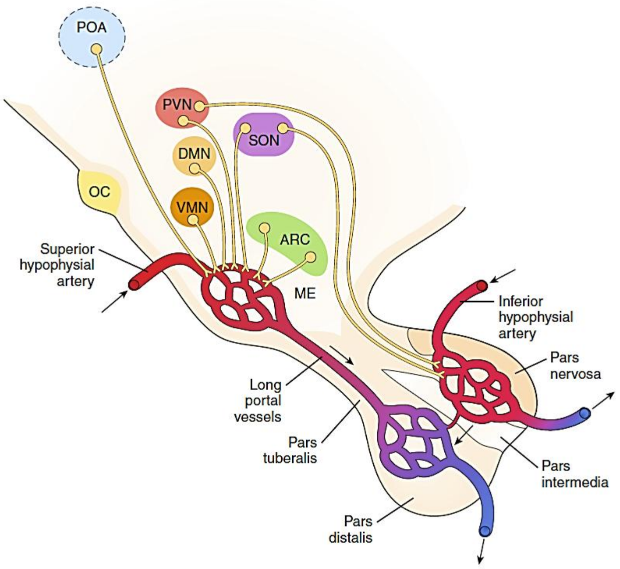

FIGURE 4-3 A generalized mammalian hypothalamus–pituitary axis. The hypothalamus contains several neurosecretory centers including the arcuate (ARC) nucleus, dorsomedial nucleus (DMN), paraventricular nucleus (PVN), preoptic area (POA), supraoptic nucleus (SON), and the ventromedial nucleus (VMN). The median eminence (ME) and pars nervosa are separate neurohemal areas. The superior hypophysial artery supplies blood to the capillaries in the ME. The ME is connected by hypothalamic portal blood vessels passing through the pars tuberalis to the pars distalis where releasing hormones from the hypothalamus stimulate tropic hormone release. The pars nervosa stores nonapeptides and has a separate blood supply. OC, optic chiasm.

The pituitary gland is located directly beneath the third ventricle of the brain. The third ventricle is a cavity continuous with the other ventricles of the brain and the central canal of the spinal cord. It is filled with cerebrospinal fluid (CSF). Studies in the early 1800s determined that the pituitary developed through an apparent fusion of a ventral growth or evagination from the diencephalon, the infundibulum, with an ectodermal sac known as Rathke's pouch (Figure 4-4). The latter developed as an inward pocketing or invagination off the anterior roof of the oral cavity called the stomodeum; hence, it was concluded that cells forming the adenohypophysis arose from non-neural ectoderm. However, numerous studies primarily employing amphibian and bird embryos have shown that the secretory cells of the adenohypophysis and the neurosecretory neurons of the hypothalamus have a common origin from the neural ridge of the embryo (neuroectoderm) (Figure 4-5) and migrate during development to the tissues that ultimately form the hypophysis and hypothalamus.

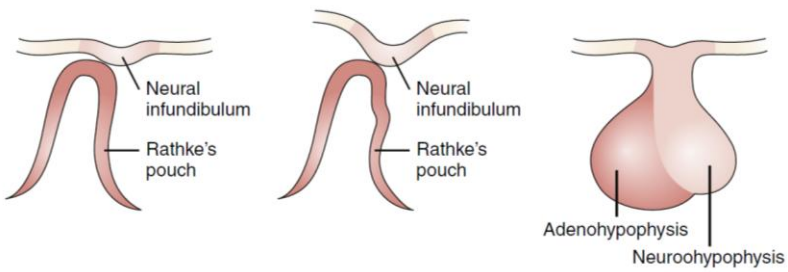

FIGURE 4-4 Pituitary gland development. Early understanding of development of the stomatodeal epidermis into the adenohypophysis from Rathke's pouch and the neurohypophysis from the neural infundibulum. The pars intermedia developed at the point of contact between the neuroinfundibulum and Rathke's pouch. *(Adapted from Dubois, P.M. and El Amraouci, A.,* Trends in Endocrinology and Metabolism, *6, 1–7, 1995. © Elsevier Science, Inc.)*

Evidence also suggests that the hormone-secreting cells of the pituitary are of neural origin. The neurosecretory cells that control reproduction have their origins in a portion of the neural ridge that gives rise to the nasal placodes (olfactory system), and these neurons migrate along the olfactory nerve eventually to take up residence in the hypothalamus.

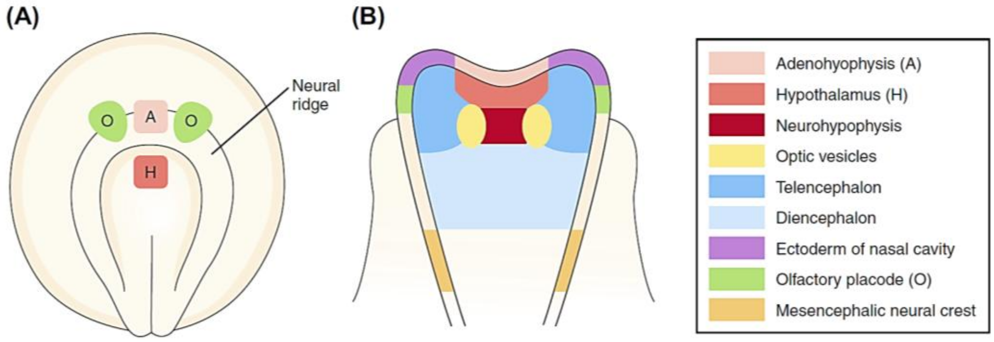

FIGURE 4-5 Anterior neural ridge origin of the hypothalamic and pituitary endocrine cells. (A) Dorsal view of neurula stage of anuran embryo showing close proximity for origins of hypothalamic neurons (H), pituitary endocrine cells (A), and the olfactory placodes (O). GnRH cells of the hypothalamus originate from the olfactory placodes. (B) Similar origins are shown for an avian embryo. *(Redrawn from several sources.)*

The adenohypophysis is an epithelial glandular structure (adeno, gland) and can be subdivided into three anatomical regions or pars (¼ bodies): the pars anterior or pars distalis, the pars tuberalis, and the pars intermedia. Pars distalis is used more commonly than pars anterior. Each region of the adenohypophysis is distinguished by cytological features as well as by anatomical relationships to the neurohypophysis. Two subregions can be identified in the neurohypophysis: the more anterior pars eminens or median eminence and the pars nervosa. These neurohemal regions consist mostly of aminergic and peptidergic axonal endings mixed with blood capillaries and what are probably modified neuroglial cells called pituicytes. An extensive venous portal system, the hypothalamus-hypophysial portal system, develops between capillary beds in the median eminence of the neurohypophysis and capillary beds in the pars distalis of the adenohypophysis (Figure 4-3).

A. Subdivisions of the Adenohypophysis

The adenohypophysis of most mammals consists of three subdivisions: pars tuberalis, pars intermedia, and pars distalis.

The pars tuberalis consists of a thin layer of cells projecting rostrally (anteriorly and dorsally) from the adenohypophysis. It is in contact with the median eminence of the neurohypophysis, and the portal vessels of the portal system pass near or through the pars tuberalis en route to the capillary beds of the pars distalis. The portion of the adenohypophysis that makes contact with the pars nervosa of the neurohypophysis is defined as the pars intermedia. Indeed, differentiation of the pars intermedia occurs only if physical contact takes place between the developing adenohypophysis and the infundibulum that will become the pars nervosa.

The major portion of the adenohypophysis originally was designated as the pars anterior, and a variety of cellular types were identified there by selective staining procedures. In these animals lacking a true pars intermedia, the pars anterior was called the pars distalis. However, this latter term is now applied routinely as if it were synonymous with the pars anterior, especially since pars distalis was the appropriate term for adult humans and was so named in most textbooks. Because of extensive use of pars distalis in the literature for both anatomical designations, we use the term pars distalis. Likewise, the term anterior lobe is applied loosely to mean either the pars distalis or the pars anterior plus the pars intermedia. Posterior lobe often is used in place of neuro-intermediate lobe, but at other times this term indicates only the pars nervosa in animals lacking a pars intermedia. Because of their variable meanings, the terms anterior lobe and posterior lobe are not used here.

1. The Pars tuberalis

The pars tuberalis is characteristic of all tetrapod vertebrates, but understanding of its physiological significance is limited. The presence of cells containing certain tropic hormones has led to the suggestion that the pars tuberalis is only an extension of the pars distalis related primarily to reproduction. However, recent studies have demonstrated that the pars tuberalis is an important endocrine link between the pineal gland and the prolactin-secreting cells of the pars distalis. Structurally the cells of the pars tuberalis are connected to the cerebrospinal fluid of the third ventricle in the brain through cellular processes originating in modified ependymal cells known as tanycytes. Ependymal cells are epithelial cells that line the ventricles of the brain and form a protective layer that surrounds the nervous system. It has been suggested that tanycytes may selectively remove molecules, including various types of regulators, from cerebrospinal fluid and transfer them to cells of the pars tuberalis, causing the latter to release their stored products. Although this is a highly speculative idea, such an interesting anatomical relationship demands some imaginative research to provide a better understanding of both tanycytes and the cells of the pars tuberalis.

2. Pars Intermedia

Only one glandular cell type appears in the mammalian pars intermedia, and it is responsible for secretion of the peptide hormone melanocyte-stimulating hormone or melanotropin (a-MSH). An alternative name for a-MSH is melanophore-stimulating hormone, based on its effects in a unique pigment cell not found in mammals, the melanophore. In mammals, a-MSH stimulates skin cells, known as melanocytes, to synthesize a brown pigment, melanin, which causes increased deposition of pigment in the skin or hair. The term neurointermediate lobe designates both the pars intermedia and the pars nervosa as an anatomical unit although they are not functionally related. In some species, the pars intermedia is separated from the remainder of the adenohypophysis by a cavity or cleft. Some mammals, such as whales, manatees, elephants, armadillo, pangolin, beaver, and adult humans, lack a pars intermedia. Most of those mammals lacking a pars intermedia lack hair and/or have few if any integumentary melanocytes.

3. Pars Distalis

Five cellular types are present in the pars distalis and are responsible for secretion of six pituitary tropic hormones: corticotropin, or adrenocorticotropic hormone (ACTH); thyrotropin, or thyroid-stimulating hormone (TSH); growth hormone (GH) or somatotropin; prolactin (PRL); and two gonadotropins, or gonadotropic hormones (GTHs). The two GTHs are follicle-stimulating hormone or follitropin (FSH) and luteinizing hormone or lutropin (LH), both of which are named for their effects in female mammals but have equally important and similar roles in males. All of these hormones are polypeptides or proteins. In addition, a-MSH, a peptide secreted from the pars intermedia, often is included as one of the tropic hormones.

In addition, peptides known as lipotropins (LPH) and endorphins (e.g., β-endorphin) may be released from the adenohypophysis. Although not listed here as tropic hormones, they may perform endocrine functions. β-endorphin is one of several peptides known as endogenous opioid peptides (EOPs) that bind to the same receptors as the drug morphine, an exogenous opioid derived from the plant product opium. The term "endorphin" as a contraction of "endogenous morphine" was suggested for the natural internal substance that bound to what had been called opioid receptors in the central nervous system (CNS).

B. Cellular Types of the Adenohypophysis

The cellular phenotypes in the pars distalis and the pars intermedia first were distinguished by utilizing special dyes in particular staining combinations. The electron microscope also has been used to characterize cellular types of the pars distalis on the basis of general cellular morphology and the size and shape of electron-dense cytoplasmic storage granules containing tropic hormones. A combination of ultrastructural, tinctorial (staining with dyes), and immunocytochemical techniques leaves little doubt as to the cellular origins of the tropic hormones. Ultrastructural features of some pars distalis cells can be seen in Figure 4-6. More recently immunocytochemical methods have been used to determine cellular phenotypes in the pars distalis.

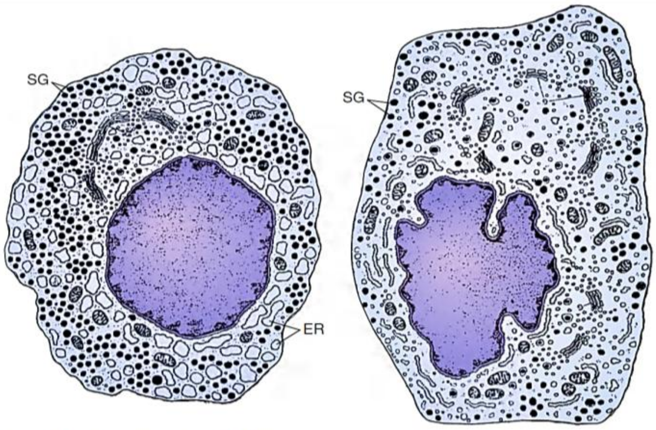

FIGURE 4-6 Gonadotrope (left) and corticotrope (right) cell types. Note the differences in abundance and size of electron dense granules. Compare to the lactotrope and somatotrope in Figure 4-7. *(Adapted with permission from Norman, A.W. and Litwack, G., "Hormones," 2nd ed., Academic Press, San Diego, CA, 1997.)*

1. Cytology of the Pars Distalis

Originally using differential staining combined with experimental manipulations, it was determined that there was one cellular type responsible for synthesis and release of each tropic hormone with one exception. These initial observations were later supported and refined by immunocytochemical studies using antibodies prepared against each pituitary hormone. In the following descriptions, the traditional mammalian designation for each of these five cellular types is given. The cells responsible for secreting tropic hormones are designated with the suffix -trope. Because tropic hormones were formerly called "trophic hormones," some authors still refer to the cell types with the suffix "-troph."

The thyrotrope is the least common of the secretory cell types in the pars distalis. Thyrotropes have long cytoplasmic processes and contain spherical secretory granules. They occur primarily in the anterioremedial portion of the pars distalis and show little variations with sex or age. Despite the chemical similarity of GTHs and TSH, the gonadotrope has been readily distinguishable from the thyrotrope by cytological and immunological techniques. Gonadotropes represent about 15 to 20% of the pars distalis cells and are distributed throughout the pars distalis. Two populations of spherical or slightly irregular secretory granules can be distinguished on the basis of size. At least three gonadotropic subtypes were identified by differences in immunoreactivity. One subtype contains only FSH, one contains only LH, and the third contains both LH and FSH.

Two separate cell types in the pars distalis are considered to be sources for GH and PRL, respectively (Figure 4-7). The somatotrope is the most abundant cell type in the pars distalis, representing about 50% of the cells, and is found mostly along the lateral margins of the pars distalis. The second acidophil, called a lactotrope, secretes PRL. The lactotropes account for between 10 and 25% of the cells in the pars distalis, with the lower figure being common in men and nulliparous women (never having borne children). There are relatively few PRL secreting cells in children. Lactotropes are distributed throughout the pars distalis, often found associated with gonadotropes. At least two lactotropes have been identified using ultrastructural criteria. One is very common, a sparsely granular cell with smaller spherical, oval, or irregular granules. The second type is uncommon, is densely granular, and typically occurs adjacent to capillaries. A third lactotrope has been described, the mammo-somatotrope, which secretes both GH and PRL, especially during pregnancy.

Corticotropes producing ACTH are located in a central wedge within the pars distalis and represent 10 to 15% of the total cells. They contain a variety of granules that are somewhat larger than those of thyrotropes and are immunoreactive for ACTH, LPH, and β-endorphin. Corticotropes also are immunoreactive for the protein cytokeratin that occurs in the perinuclear area and typically is not found in other tropic cells. The number of corticotropes does not vary with age or sex but may vary markedly in a number of pathological states.

Careful studies of hormone distribution, receptors present in pituitary tropic cells, and the diversity of hormone genes expressed by each tropic cell have painted a much more dynamic picture of the pars distalis than previously thought. Not only do we have multiple populations of GTH-secreting cells and PRL-secreting cells, but we are also finding some cells that are making a greater variety of tropic hormones than previously suspected. For example, not only do some gonadotropes produce GTHs but they may also produce GH. Furthermore, these GTH-GH cells possess receptors for both hypothalamic releasing hormones, suggesting that these cells are secreting both hormones. Corticotropes have been observed to vary with respect to the type of receptors they express for corticotropin-releasing hormone (CRH) and in their ability to also bind the neuropeptide vasopressin.

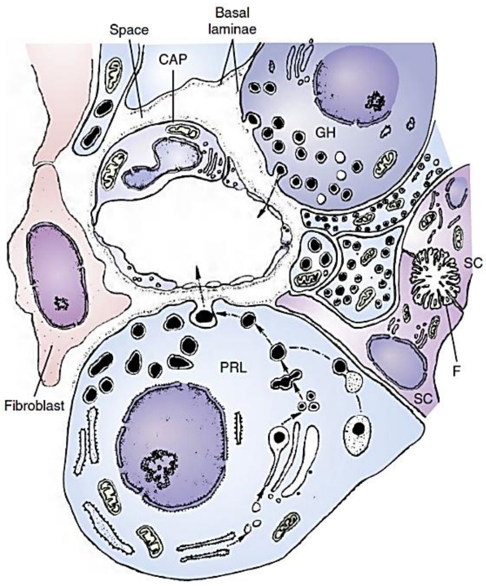

FIGURE 4-7 **Somatotrope (GH), lactotrope (PRL), and follicostellate cells (SC).** All three cell types are located near a capillary (CAP). The GH and PRL cells are distinguished by the different size and relative abundance of secretion granules, whereas the SC are not granulated and show a tendency to form a follicular structure (F) where they contact one another. Compare to gonadotropes and corticotropes in Figure 4-6. *(Adapted from Baker, B.L., Yu, Y. U. Cell and Tissue Research 156, 443–449, 1975.)*

A sixth cellular type found in the mammalian pars distalis is the nongranulated cell that is not distinguished by selective staining techniques. Nongranulated cells may represent inactive, depleted, or undifferentiated cells, and some of the latter may differentiate into hormone-secreting cells, depending upon the stage of development or physiological conditions or in response to experimental manipulations. One type of nongranulated cell is the null cell that has no special histologic, immunoreactive, or ultrastructural features other than the presence of a few small cytoplasmic granules. Null cells are thought to be the source of certain pituitary adenomas. A special type of nongranulated cell, the follicostellate cell, has been observed in all vertebrates with the aid of the electron microscope. Follicostellate cells exhibit S-100 protein, a characteristic of neuroglial cells in the brain, and the S-100 protein is not found in any other cells of the adenohypophysis. The cytoplasmic processes of these glial-related stellate (starshaped) cells are very long and form a sort of network or reticulum between capillaries throughout the pars distalis. They are referred to as follicular because of the way their stellate processes will sometimes surround or enclose tiny spaces. Each of these follicles consists of an extracellular space surrounded completely by processes of the follicostellate cells and are filled with fluid (Figure 4-7).

2. Cytology of the Pars Intermedia

The melanotrope is the only glandular epithelial cell in the mammalian pars intermedia. The pars intermedia also contains nongranulated stellate cells of unknown function that are interspersed among the a-MSH-secreting cells. In most mammals, the cleft that separates the pars intermedia from the pars distalis is lined by ependymal-like cells called epithelial cleft cells. The cleft cells often are ciliated, and, while they resemble the ciliated ependymal cells that line the brain ventricles, their functional role has not been worked out.

3. Cytology of the Pars Tuberalis

Several cell types have been reported in the pars tuberalis of mammals. One cell type reacts specifically with antibody to pituitary LH, and a second type specifically binds antibody to TSH. Occasionally, one or two rare cells are observed in primates that bind antibody to ACTH and GH. Another special cell type is the tuberalin cell that secretes tuberalin, a peptide that stimulates PRL secretion by lactotropes in the pars distalis. The majority of pars tuberalis cells are chromophobic in most mammals, but all are stainable types in humans. The pars tuberalis may represent a “fragment” of the pars distalis, and it may function as an additional, but limited, source of tropic hormones.

C. Subdivisions of the Neurohypophysis

The mammalian neurohypophysis consists of two distinct neurohemal components, the median eminence and the pars nervosa. The median eminence is defined as the more anterior portion of the neurohypophysis that has a blood supply in common with the adenohypophysis-specifically, the portal system. An abundant but separate blood supply characterizes the pars nervosa (Figure 4-3), which is that posterior portion of the neurohypophysis in contact with the pars intermedia. In species lacking a pars intermedia, the pars nervosa is defined on the basis of what neuropeptides are present. Both the median eminence and the pars nervosa are composed of capillaries, pituicytes, and axonal tips of NS neurons originating in hypothalamic NS nuclei. Pituicytes probably are derived from ependymal or neuroglial cells, and they could play a role as supportive elements or may be involved actively in storage and release of neurohormones from the neurohypophysis, similar to the role of stellate cells of the adenohypophysis.

References

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