UG CBCS Semester-IV (MJC-7: Endocrinology)

The Mammalian Adrenal

The responses an animal makes to adverse or stressful stimuli, called stressors, leads to a physiological response, stress, that includes the release of hormones from the adrenal glands and their subsequent effects to enable the animal to cope with the stressor. These responses are controlled largely through the hypothalamus-pituitary-adrenal (HPA) axis and secretion of corticotropin-releasing hormone (CRH) and corticotropin (ACTH). The adrenal hormones induce changes in metabolism and/or ionic regulation that work to combat physiological and psychological factors and eventually to eliminate or at least neutralize the stressor. Knowledge of this stress system contributes to our understanding of how animals adapt physiologically to physical and psychological traumas. In addition, these adrenal hormones play other important roles.

Mammals typically possess two adrenal glands, one located superior to each kidney (ad-renal or supra-renal; Figure 8-1). This anatomical arrangement is responsible for their present name, adrenals or adrenal glands, and for an alternative name in humans, the suprarenal glands. Each adrenal gland actually consists internally of three almost separate endocrine glands. The outer portion or adrenal cortex represents three glandular regions and is composed largely of lipid-containing, steroidogenic adrenocortical cells. The adrenal cortex surrounds a fourth endocrine region consisting of an inner mass of chromaffin cells called the adrenal medulla. Chromaffin cells are so named because they contain intracellular granules containing catecholamines that can be stained by certain chromium compounds.

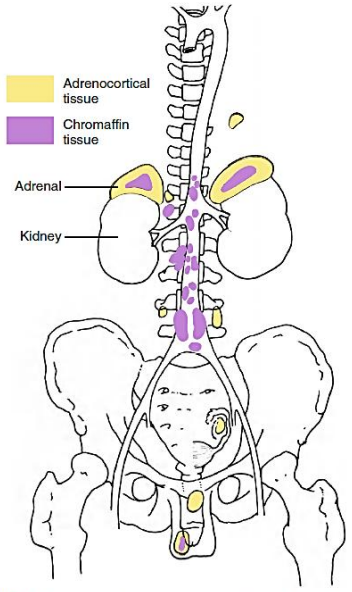

FIGURE 8-1 **Location of adrenal tissue in the human.** Note in addition to the expected location of adrenocortical and chromaffin cells in the adrenal gland heterotopic locations where either tissue may be found in either sex. *Adapted with permission from Bethune, J.E. The Adrenal Cortex: A Scope Monograph. Upjohn Co., 1974.)*

The adrenocortical cells are derived from the coelomic epithelium in the pronephric region of the embryo adjacent to the genital ridge that gives rise to the gonads. These cells produce steroid hormones including glucocorticoids, mineralocorticoids, and weak androgens such as dehydroepiandrosterone, DHEA. Two regions secrete glucocortiocoids and DHEA, respectively, under the direct stimulatory influence of ACTH from the pituitary gland, although DHEA secretion also may be stimulated by LH and LH-like hormones. Secretion of mineralocoticoids by the third region is stimulated by the renin-angiotensin system. Glucocorticoids are named for their influences on glucose metabolism and mineralocorticoids for their effects on Na^+ and K^+ balance. The major glucocorticoids synthesized by mammals are cortisol, corticosterone, and to some extent 11-deoxycortisol. The major mineralocorticoids are aldosterone and deoxycorticosterone.

The chromaffin cells originate from the neural crest, and the medulla functions essentially like a modified sympathetic ganglion. The adrenal medulla is under direct neural control (preganglionic cholinergic sympathetic neurons originating in the thoracic spinal cord) and releases norepinephrine and/or epinephrine into the blood. These secretions are usually termed "hormones," but, considering the embryonic origin of the medulla, they could also be called "neurohormones." At first glance, there seems to be no functional significance for the close anatomical relationship of the adrenocortical and chromaffin cells. Although there is

participation of both systems with respect to adaptations to stressors, the factors controlling release of their secretions differ in significant ways and their biological actions at the receptor level do not overlap. The anatomical closeness of the cortex and medulla in mammals, as well as relationships of their homologous tissues in non-mammals, may simply be a function of the physical closeness of their embryological sites of origin, although the progressive evolution of this arrangement is obvious when non-mammals are examined. CRH, ACTH, and glucocorticoids do have effects on catecholamine synthesis by chromaffin cells, and these systems are not entirely independent.

THE MAMMALIAN ADRENAL CORTEX

The adrenal cortex of adult mammals may be subdivided by means of histological criteria into three well-defined regions: zona glomerulosa, zona fasciculata, and zona reticularis (Figure 8-2). These regions are arranged as concentric shells surrounding the adrenal medulla. In addition, there are inner zones described between the outer zones and the medulla in some mammals. These regions may perform unique functions and may be transitory.

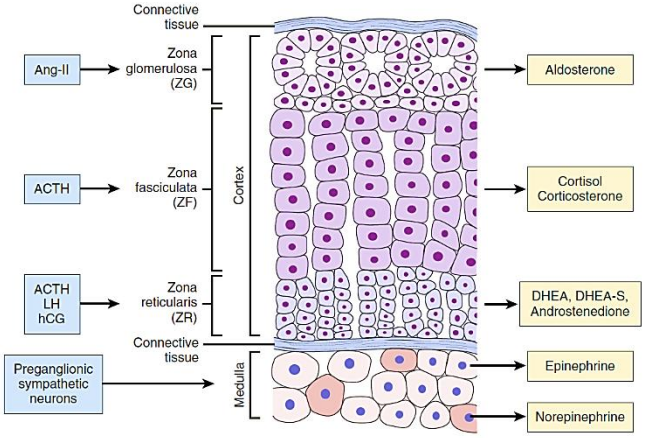

FIGURE 8-2 Zonation of the adrenal gland. The cortex consists of an outermost layer of connective tissue (CT); the zona glomerulosa (ZG), which produces aldosterone; the zona fasciculata (ZF), which secretes most of the glucocorticoids (cortisol and/or corticosterone); and the inner zona reticularis (ZR), which specializes in adrenal androgen production (DHEA, DHEA-S, androstenedione). The adrenal medulla is separated from the cortex by another layer of CT and consists primarily of chromaffin cells that secrete epinephrine or norepinephrine. Numerous other secretions have been associated with the adrenal medulla, including dopamine and endogenous opiates (EOPs).

A. Zonation of the Adrenal Cortex

The cells of the outermost region of the adrenal cortex, the zona glomerulosa, are smaller and more rounded and contain less lipid than those of the more central zona fasciculata. The zona glomerulosa is responsible for synthesis of aldosterone as well as some other corticosteroids. There are few cytological changes in the zona glomerulosa following hypophysectomy or administration of ACTH, suggesting that the secretion of aldosterone is independent of pituitary control. Although ACTH is not necessary for the synthesis and release of aldosterone, the responsiveness of the glomerulosal cells to agents that normally elicit these events is reduced in hypophysectomized mammals and is enhanced with ACTH treatment. Consequently, ACTH does have a permissive effect on cells of the zona glomerulosa.

The zona fasciculata is the largest zone in the adrenal cortex. It is located between the zona glomerulosa and the innermost zona reticularis and is histologically distinct from both. It consists of polyhedral (many-sided) cells that are sources of the glucocorticoids. The cells of the zona fasciculata are arranged in narrow columns or cords surrounding blood sinusoids that allow the cells to be bathed directly with blood (i.e., there is no tissue-blood barrier). The proportion of cortisol and corticosterone secreted differs markedly, from secretion of primarily cortisol (human), through mixtures of both (cat, deer), to primarily corticosterone (rat). Thickness of the zona fasciculata is most sensitive to circulating levels of ACTH. It exhibits hypertrophy and hyperplasia in response to prolonged elevation of ACTH secretion caused by stress or treatment with the drug metyrapone, which blocks the 11-hydroxylation step necessary

for glucocorticoid synthesis and hence elevates ACTH in the blood. Unlike the zona glomerulosa, the zona fasciculata atrophies markedly following hypophysectomy or prolonged glucocorticoid therapy and hypertrophies as a result of prolonged ACTH therapy.
The zona reticularis typically borders the adrenal medulla, and it contains numerous thin, extracellular reticular fibers (hence its name). It is a primary source of adrenal androgens but some glucocorticoids may be synthesized here as well. The zona reticularis also hypertrophies in response to ACTH and atrophies following hypophysectomy, but not so dramatically as the zona fasciculata. Gonadotropins (luteinizing hormone [LH] or human chorionic gonadotropin [hCG]) can also stimulate secretion of adrenal androgens. It should be noted that the "typical" anatomical pattern described here within the adrenal cortex and the anatomical relationship of cortex to medulla varies considerably within mammals as a group. Furthermore, ectopic nodules of functional cortical tissue are not uncommon (Figure 8-1), and this accessory adrenocortical tissue may become a source for corticosteroids following surgical adrenalectomy.

B. Additional Zonation

Several unique adrenocortical zones are known only for certain species, but the adrenals of most mammalian species have not been examined in detail. These special zones may be conspicuous only at certain times in the life of an animal or in only one sex.

1. The Fetal Zone

In primates, a very conspicuous zone occupies the bulk of the adrenal gland prior to birth. This region is called the fetal zone and is responsible for the relatively large size of the adrenal at birth (Figure 8-3). In humans, the neonate adrenal may be as large as the adrenal gland of a 10- to 13-year-old. During gestation, the fetal zone, which is found between the cortex and the medulla, synthesizes and releases relatively large quantities of DHEA and lesser amounts of its sulfated derivative, DHEA-S. These adrenal androgens serve as precursors for the synthesis of estrogens by the placenta. Failure of the fetal zone to produce adequate amounts of DHEA/DHEA-S results in premature termination of gestation. Formerly, it was believed that CG from the placenta was responsible for stimulating fetal adrenal androgen production necessary to maintain pregnancy, but recent studies suggest that adrenal androgen secretion is strongly influenced by other placental hormones, too. The fetal adrenal and placenta also play important roles in the birth process.

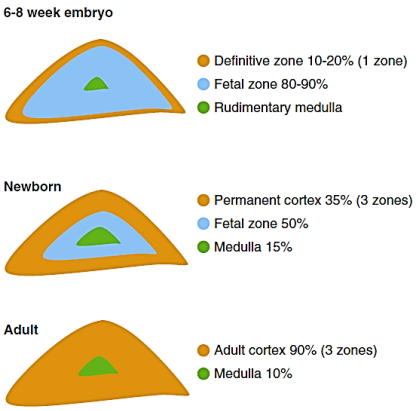

FIGURE 8-3 **Comparison of fetal zone to remainder of adrenal gland in humans.** Prior to birth, the bulk of the adrenal consists of the androgen-secreting fetal zone that regresses rapidly after birth. Whereas the fetal zone is gone by one year of age, the medulla and cortex continue to grow until puberty. In the actual adrenal gland, the fetal zone appears between the zona reticularis and the medulla but is shown above the cortex here for effect. *Adapted with permission from Tsakiri, S.P., Chrousos, G.P., and Margioris, A.N., Molecular development of the hypothalamic-pituitary-adrenal (HPA) axis. In E,A. Euguster and O.H. Pescovitz, eds. "Contemporary Endocrinology: Developmental Endocrinology" From Research to Clinical Practice, Humana Press, Inc., pp 359-380.*

Following birth, the fetal zone ceases to function in humans and degenerates rapidly. The fetal zone typically disappears completely by one year of age. The zona reticularis begins to synthesize DHEA/DHEA-S at about age 5 or 6, and DHEA synthesis accelerates during puberty. Maximal DHEA production is achieved around age 20, after which its production slowly declines. It has been suggested that DHEA may be an anti-tumor substance and/or a precursor for synthesis of other androgens or estrogens, especially in postmenopausal women.

2. The Mouse X-Zone

The cortex of the mouse adrenal contains a unique X-zone located between the zona reticularis and the medulla. The X-zone appears to be unrelated to the fetal zone of primates, although it appears in the same anatomical location. This zone degenerates in males at puberty and in females of most mouse strains during the first pregnancy. Degeneration in the males is correlated with production of androgens by the testes. The function of this X-zone is not known.

3. The "Special Zone"

In at least one marsupial, the brush-tailed possum (*Trichosurus vulpecula*), there is a large inner special zone that appears only in the adult female. Its function has not been elucidated, and it is not known whether it is comparable to either the primate fetal zone or the X-zone of mice.

THE MAMMALIAN ADRENAL MEDULLA

The medullary portion of the mammalian adrenal consists of sympathetic preganglionic neuronal endings (cholinergic) and modified cells derived from neural crest and homologous to postganglionic sympathetic neurons (adrenergic). In other words, the adrenal medulla is a modified sympathetic ganglion that secretes either norepinephrine or epinephrine directly into the blood. Both epinephrine and norepinephrine (as well as small quantities of dopamine) can be extracted from the adrenal medulla, but the ratio in most adult mammals strongly favors epinephrine. The proportion of norepinephrine to epinephrine may vary throughout life, however. Fetal and neonatal adrenals secrete predominantly norepinephrine followed by a gradual increase for most species in the proportion of epinephrine so that eventually epinephrine dominates in adults. Whales are an apparent exception in that the adult whale adrenal consists of about 83% norepinephrine.

Treatment of adrenal medullary cells with potassium dichromate or chromic acid results in formation of a yellowish or brown oxidation product, the chromaffin reaction. Cells that exhibit a positive chromaffin reaction are termed chromaffin cells. The catecholamine-secreting cells of the adrenal medulla show a positive chromaffin reaction, but so do other catecholamine-secreting cells in the body (for example, in the brain, intestinal epithelium, and skin). Cells containing the tryptophan derivative serotonin also exhibit a positive chromaffin reaction; however, the term "chromaffin cell" is usually applied only to catecholamine-secreting cells of the adrenal medulla.

Norepinephrine-secreting cells can be distinguished from epinephrine-secreting cells by the formaldehyde treatment devised by Hillarp and Falck. Formaldehyde combines chemically with norepinephrine storage granules, and the resulting complex will fluoresce. Today, we can readily separate epinephrine- and norepinephrine-secreting cells using immunohistochemical techniques to localize either the specific catecholamine or the enzyme responsible for synthesis of epinephrine.

References

- Norris DO & James AC (2013). Vertebrate Endocrinology (5th edition). Academic Press, USA. http://dx.doi.org/10.1016/B978-0-12-394815-1.00001-X.