Adrenal Cortex, Physiology

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Adrenal Cortex, Physiology☆

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Glossary

Adrenocorticotropic hormone or corticotropin (ACTH) ACTH is synthesized from proopiomelanocortin, a 241-amino acid precursor. Usually, ACTH is derived from the pituitary gland to stimulate the adrenal glands through the melanocortin-2 receptor. ACTH is rarely produced ectopically from neuroendocrine tumors (i.e., in ectopic Cushing syndrome), or in the adrenal glands, as seen in primary bilateral macronodular adrenocortical hyperplasia.

Corticotropin-releasing hormone (CRH) CRH is a hypothalamic 41-amino acid peptide that usually stimulates the pituitary gland to release ACTH.

Hypothalamic–pituitary–adrenal (HPA) axis Hypothalamic-releasing factors including CRH are influenced by central nervous system afferents. For instance, stress can trigger CRH release. The main peptide secreted by corticotroph cells when POMC is activated by CRH is ACTH, which subsequently stimulates the adrenal glands to produce and release steroids, including cortisol. Cortisol, on the other hand, can inhibit further release of CRH and ACTH through a tightly regulated negative feedback loop.

Steroids These members of a large family of compounds that are derived from the cyclopentanoperhydrophenanthrene ring structure that consists of three cyclohexane rings and one cyclopentane ring and are produced by the adrenal glands. The nomenclature denotes rings by a letter and the individual carbon atoms by a number. Gonane is the unsaturated 17′carbon ring structure. Estranes are steroids with 18 carbons (C18 steroids) by adding a methyl group at C13. Androstane is a C19 steroid with two methyl groups. Pregnane is a C21 steroid with methyl and ethyl groups.

Introduction

In 1563, Bartholomeo Eustachius, a famous Italian anatomist and artist, was credited for the first full description of the anatomy of the adrenal glands (Miller, 2013a,b). Subsequently in 1849, Thomas Addison, a renowned 19th-century English physician and scientist, described the central physiologic role of the adrenal glands (Miller, 2013a,b). In the 21st century, our growing understanding of adrenal zonation, genetics, and steroidogenesis has improved our understanding of the pathophysiologic states of the adrenal glands (Xing et al., 2015).

The adrenal glands are divided into two major anatomic areas, cortex and medulla. The adrenal cortex is composed of three zones; glomerulosa (ZG), fasciculate (ZF), and reticularis (ZR). The largest zone in humans is the ZF, where glucocorticoids including cortisol are produced (Xing et al., 2015). In general, extracellular volume status is influenced by aldosterone, the hormone of ZG. Adrenal androgens such as dehydroepiandrosterone (DHEA) are primarily produced by the ZR, which begins to grow at approximately age 4, shortly before adrenarche (Xing et al., 2015).

Corticotropin (ACTH), produced from the pituitary gland, is the principal stimulator for cortisol and/or adrenal androgen production (and to a minor extent, aldosterone) (Margioris and Tsatsanis, 2000). Corticotropin is released under stress and other

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stimuli through hypothalamic corticotropin-releasing hormone (CRH) secretion. Like CRH, arginine-vasopressin (AVP), a hypothalamic hormone, stimulates the pituitary release of ACTH. A tightly regulated feedback loop exists between the hypothalamus (H), pituitary (P), and adrenal glands (A), known as the HPA axis. High peripheral cortisol levels inhibit further release of CRH and corticotropin. Hypothalamic CRH and pituitary corticotropin are suppressed in various conditions (e.g., in conditions of supraphysiologic exogenous glucocorticoid administration), with subsequent atrophy of the adrenal glands due to the lack of corticotropin. The adrenal medulla forms postnatally and exerts effects on the adrenal cortex and vice versa. Adrenomedullary chromaffin cells are intermingled with the adrenal cortex, facilitating interaction between the two layers.

Fetal Adrenal Gland Development

The fetal adrenal cortex plays a critical role in regulating intrauterine homeostasis and the maturation of fetal organ systems that are necessary for extrauterine life. The important mediators for these functions are steroid hormones from the fetal adrenal glands. Throughout gestation and postnatally, the fetal adrenal glands undergo morphological and functional changes during its transformation to the adult adrenal gland (Ishimoto et al., 2011; Merke et al., 2006).

Following the formation of the adrenal cortex at the fourth week of human embryonic development, a blastema of undifferentiated cells of mesodermal origin forms from either the medial part of the urogenital ridge or mesoderm (Fig. 1) (Xing et al., 2015; Merke et al., 2006). The adrenogonadal primordium cells undergo proliferation and invasion of the underlying mesenchyme that is dependent on the interplay between the transcriptional factors steroidogenic factor 1 (SF1) and DAX1 that ultimately separates from the gonads by day 33 post conception (Xing et al., 2015; Beuschlein et al., 2002; Hammer et al., 1999). Further mesodermal cell proliferation, under the control of fetal corticotropin, forms the first evidence for zonation: a definitive zone (DZ) and a fetal zone (FZ) that arise from the celomic epithelium, while the transitional zone (TZ) originates from the mesonephron and arises from the region of Bowman's capsule. Thus, the progenitor cells of the adrenal cortex stem from a cell lineage that also leads to steroid-secreting cells of the gonads. The FZ consists of large eosinophilic steroid-secreting cells that express high levels of steroid 17α-hydroxylase (CYP17) and DZ consists of cells that do not express CYP17 (Scheys, 2011). The TZ is composed of cells similar to those of the zona fasciculata of the adult adrenal glands (Scheys, 2011).

Several endocrine, paracrine, and autocrine factors influence the steroidogenesis of the fetal adrenal cortex. Between the 8th and 12th embryonic week, sinusoidal vascularization of the glands forms the framework for the zonation of the adult cortex (Scheys, 2011). At gestational week 8, chromaffin cells enter the rudimentary adrenal glands and cluster as discrete islands until day 8 postnatally, before they form a rudimentary adrenal medulla. Cortisol is produced from the rapidly growing FZ at about the 6th week of development, reaching a peak between the 8th and 9th week (Scheys, 2011). Gradually, aldosterone and cortisol are made by DZ and TZ cells, respectively, whereas the FZ, which represents 85% of the cortical volume, produces large amounts of DHEA and DHEA sulfate (DHEAS), that ultimately support estrogen production through the fetal-placental unit. Placental estrogen supports

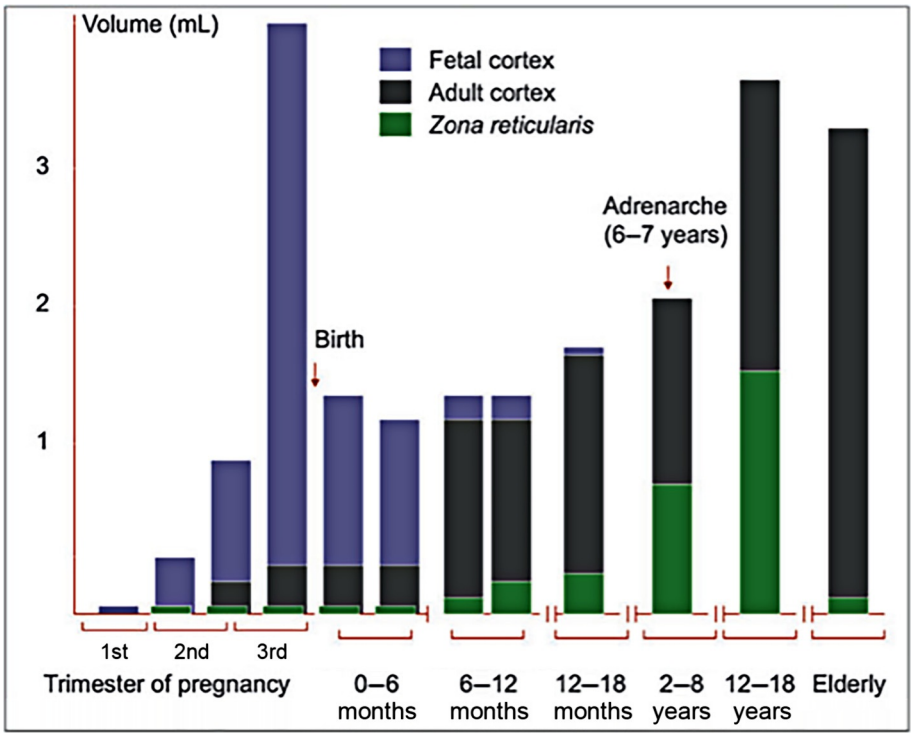

Fig. 1 Fetal and adult adrenal cortex development. Modified from Merke, D. P. et al. (2006). The adrenal life cycle: The fetal and adult cortex and the remaining questions. *Journal of Pediatric Endocrinology and Metabolism* **19**, 1299–1302. Elderly defined as age >65 years.

the fetal adrenal glands to synthesize cortisol (Sidiropoulou et al., 2000). By the 9th week, progenitor populations of the adult adrenal cortex encapsulate the adrenal glands, expressing *Nr5a1* and *Gli1*. Migrating neural crest cells forms the adrenal medulla and intermingles with cortical cells of the FZ, attaining a maximum adrenal size by the 4th month. Thereafter, the gradual receding of FZ, and expansion of DZ and TZ, gives rise to the adult ZG and ZF, respectively (Scheys, 2011). After birth, FZ involutes and the corticomedullary junction separates between steroid hormone-producing and catecholamine-secreting cells. A transition zone of primarily fibrous tissue separates the FZ from the remaining gland. By the end of the second year of life, the first evidence of an anatomically distinct ZR appears; however, steroidogenic activity of this zone is not present until the age of 5 years, concomitant with the onset of adrenarche (Nakamura et al., 2009). The adult adrenal cortex likely reaches maturity as early as 8 years of age to as late as after mid-puberty (Nakamura et al., 2009).

Growth Factors

During the first trimester of pregnancy, human chorionic gonadotropin (HCG) regulates the growth of the fetal adrenal glands. Corticotropin is critical for growth, steroidogenesis, and differentiation of the fetal adrenal glands (Scheys, 2011). Corticotropin becomes the main growth factor after the 5th month of gestation. Corticotropin deficiency leads to increased apoptosis and subsequent atrophy of the adrenal glands, whereas corticotropin excess (e.g., in Cushing syndrome or congenital adrenal hyperplasia) can cause hyperplasia of the adrenal glands. In addition to HCG, corticotropin, and its receptor ACTHR, local growth factors are important for steroidogenesis, growth, and development of the adrenal gland. Insulin-like growth factors 1 and 2 (IGF-1 and IGF-2), their receptors, and binding proteins are all expressed in the fetal adrenal glands. IGF-1 amplifies the effect of corticotropin on the adrenal and enhances adrenal steroidogenesis by increasing the activities of 17α, 21-, and 11β-hydroxylase (Scheys, 2011). Similarly, IGF-2 promotes the action of corticotropin. In addition, IGF-2 helps the fetal adrenal to synthesize cortisol and androgen by regulating the enzymes p450scc, p450c17, and 3β-hydroxysteroid dehydrogenase (Scheys, 2011).

Basic fibroblast growth factor is a mitogenic protein and is more effective (stimulating proliferation) on adrenal cells of the DZ than those of the fetal zone. This may lead to hypertrophy of the fetal adrenal glands. EGF and EGFR play an important role in ACTH secretion from the pituitary gland. The TGF-β family of growth factors, including activin, inhibin, and TGF-β_1, are paracrine/autocrine regulators of growth and steroidogenesis in the fetal adrenal cortex. Activin increases corticotropin-stimulated cortisol production but not DHEAS production in fetal zone cells. In the adult adrenal cortex, activin has no effect on growth or steroidogenesis. In fact, activin may lead to apoptosis and involution of the fetal adrenal cortex postnatally. TGF-β_1 appears to decrease fetal and definitive zone cell proliferation and steroidogenesis.

Nuclear Receptors

The proliferation and invasion of adrenogonadal primordium cells are dependent on the interplay between the transcriptional factors SF1, DAX1 and estrogen receptor (ER) (Hanley et al., 2006; Lin et al., 2006). These factors belong to the nuclear receptor superfamily. Members of this family are transcription factors that are important for regulating expression of genes involved in cellular growth control and differentiation. SF-1 is classified as an orphan receptor because its ligand is unknown. The human cDNA sequence of SF-1 is highly homologous (>95%) to murine and bovine sequences. Human adrenal cortex, ovaries, testes, and spleen show high SF-1 mRNA expression. In human placenta, SF-1 is not or only minimally expressed. SF-1 plays an essential role in the organogenesis of the fetal adrenal glands and also in regulating genes that code for steroidogenic enzymes (Hanley et al., 2006). SF-1 stimulates the promoter activities of genes encoding steroidogenic acute regulatory (StAR) protein, the scavenger receptor-type class BI (SR-BI), and the corticotropin receptor. StAR protein is critical in the translocation process of cholesterol from the outer to the inner mitochondrial membrane. In contrast to the adult adrenal glands, the fetal adrenal glands uses low-density lipoprotein (LDL) rather than high-density lipoprotein (HDL) cholesterol as the main source for steroid biosynthesis (Miller, 2013a,b). It appears that SR-BI binds to LDL with high affinity. SF-1 influences the constitutive activity of the human corticotropin receptor gene promoter and regulates steroid hydroxylase enzymes (Miller, 2013a,b). In addition, SF-1 regulates the genes coding for the β-subunit of luteinizing hormone, the α-subunit of the glycoprotein hormones, gonadotropin-releasing hormone receptor, prolactin receptor, oxytocin, Mullerian inhibiting substance, and aromatase (Hammer et al., 1999). Furthermore, SF-1 interacts with other proteins and cofactors.

DAX1 is an orphan nuclear receptor that is highly expressed in the fetal and adult adrenal glands, gonads, ventromedial hypothalamus (VMH), testes, ovaries and the pituitary gonadotropes (Hanley et al., 2006). Together with SF-1, they may coregulate steroidogenesis as well as adrenal and gonadal organogenesis. DAX-1 can block steroidogenesis by inhibiting the activity of StAR and the expression of p450scc and 3β-hydroxysteroid dehydrogenase (Margioris and Tsatsanis, 2000). Estrogens are important in cell differentiation, growth, and function of various tissues. Estrogen receptors are members of the steroid receptor superfamily and mediate the action of estrogens. ERβ is highly expressed in the fetal adrenal gland, in contrast to ERα.

Mice that are knockouts (KO) for Sf1 have complete absence of the adrenal glands, whereas mice KO for Dax1 have developmental adrenal gland defects without adrenal insufficiency (AI) (Scheys, 2011; Miller, 2013a,b). In humans, X-linked DAX1 (mutations in *NR0B1*) defects cause the most common human form of congenital adrenal insufficiency (Lin et al., 2006). These patients are usually 46,XY phenotypic boys and may have hypogonadotropic hypogonadism and a family history of male-

only congenital adrenal insufficiency. Additionally, gene deletions at Xp21/22, where the DAX-1 gene is located, may lead to glycerol kinase deficiency, hypogonadotropic hypogonadism, and/or Duchenne's muscular atrophy. Humans with heterozygous *SF1* (coded by the *NR5A1* gene) mutations have adrenal insufficiency and gonadal abnormalities (Zanaria et al., 1994). More recently, patients with isolated adrenal insufficiency and heterozygous *NR5A1* mutations have been described. SF1 gene mutations were also found in patients who also had isolated 46,XY gonadal dysgenesis and have been rarely identified in patients with congenital adrenal insufficiency without evidence of gonadal defects.

Adult Adrenal Cortex

Steroid Biosynthesis and Regulation of Cortisol Production

The normal adult human adrenal glands weighs approximately 5 g. Ninety percent of this weight is contributed by the adrenal cortex, which is composed of three zones (from outside to inside): the ZG, ZF, and the ZR. The adrenal medulla forms postnatally and is composed of chromaffin cells, some of which may still be intermingled and spread within the adrenal cortex. The adult adrenal cortex produces glucocorticoids, mineralocorticoids, and adrenal androgens (Fig. 2 and Table 1) (Hammer et al., 1999; Miller, 2013a,b). The blood flow in the adrenal glands is centripetal (from outside to inside), which exposes the inner zones and the adrenal medulla to increasing concentrations of adrenal steroids. High cortisol levels in the medulla are needed to induce enzymes for epinephrine biosynthesis. In fact, patients with congenital adrenal hyperplasia have a compromised development and function of the adrenomedullary system due to cortisol deficiency.

Seventy-five percent of the adrenal glands weight is due to the ZF, the largest zone and the one that synthesizes glucocorticoids. The ZF and ZR also produce DHEA and DHEAS, whereas cortisol is primarily produced in the ZF. In contrast to the ZF, the ZR is small and not very involved in adrenal androgen production until adrenarche. The precursor for glucocorticoid

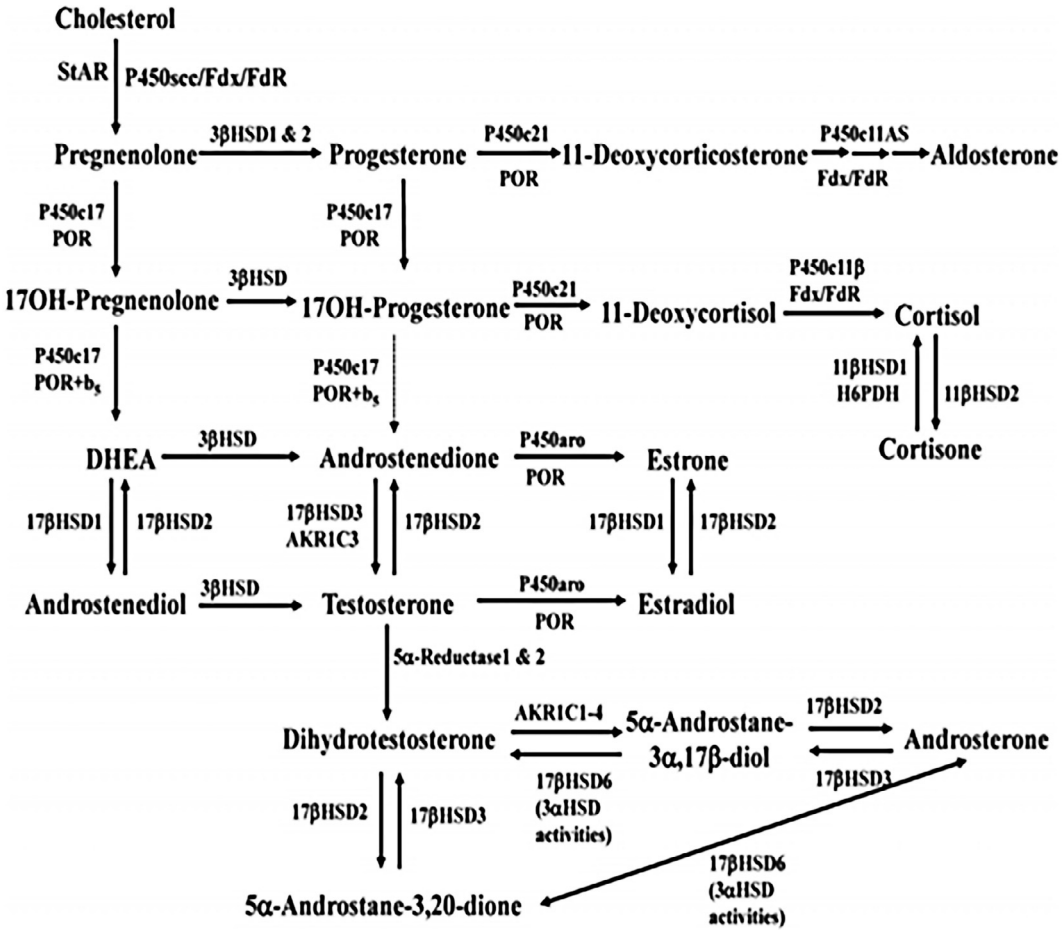

Fig. 2 Adrenal steroidogenesis. In brief, desmolase converts cholesterol to pregnenolone, 3β-OH-steroid dehydrogenase I/II convert pregnenolone to progesterone, 17-OH-pregnenolone converts progesterone to 17-OH-progesterone, P450c11 converts deoxycorticosterone to 18-OH-corticosterone and 11-deoxycortisol to cortisol, etc. Not all intermediate steroids, pathways, and enzymes are shown. Adapted with permission from Miller, W. L. et al. (2011). The molecular biology, biochemistry, and physiology of human steroidogenesis and its disorders. *Endocrine Reviews* **32**, 81–151. © 2011 by The Endocrine Society.

Table 1 Key human steroidogenic enzymes and cofactor proteins (A) and their location (B).

(A)

Enzyme	*Gene*	*Chromosomal location*
StAR	*STAR*	8p11.2
P450scc	*CYP11A1*	15q23-24
P450c11β	*CYP11B1*	8q21-22
P450c17	*CYP17A1*	10q24.3
P450c21	*CYP21A2*	6p21.1
P450aro	*CYP19A1*	15q21.1
3βHSD1	*HSD3B1*	1p13.1
3βHSD2	*HSD3B2*	1p13.1
5-α-Reductase 1	*SRD5A1*	5p15
5-α-Reductase 2	*SRD5A2*	2p23
SULT2A1	*SULT2A1*	19q13.3

(B)

Endoplasmic reticulum	*Cytoplasm*	*Mitochondria*
11β-HSD I and II	3α-HSD	3β-HSD II
5α-Reductase I and II	17β-HSD V	StAR
17β-HSD I–III	17β-HSD I	Adrenodoxin reductase
3β-HSD II	3β-HSD II	P450c11AS
Cytochrome b_5	StAR	P450c11β
P450 oxidoreductase	Adrenodoxin	P450scc
P450aro		
P450c21		
P450c17		

Modified from Auchus et al. The principles, pathways, and enzymes of human steroidogenesis, *Endocrinology* 6th edn., 2010).

production is cholesterol, which is initially converted to pregnenolone in the adrenal cortex. Steroids are derived from the cyclopentanoperhydrophenanthrene four-ring hydrocarbon nucleus, a relatively inert structure. Depending on the presence of several enzymes in the respective adrenal cortex zone, several steroid hormones can then be synthesized. Cytochromes P450 are categorized into two classes: type 1 enzymes that reside in the mitochondria and type 2 enzymes located at the smooth endoplasmic reticulum (Table 1) (Miller et al., 2011).

The secretion and synthesis of cortisol are regulated by the hypothalamic–pituitary–adrenal (HPA) axis. Certain stimuli including stress lead to the release of CRH in the hypothalamus. CRH then stimulates corticotropin release from the pituitary gland (Fig. 3). Corticotropin binds to corticotropin receptors located on adrenocortical cells and stimulates the release of cortisol through cyclic adenosine monophosphate (cAMP). Cortisol leads to an increase in energy-providing compounds, including glucose, free fatty acids, and free amino acids. As mentioned previously, corticotropin is also growth promoting on the adrenal cortex; that is, continuous stimulation by corticotropin may lead to adrenal hypertrophy, whereas a lack of corticotropin may lead to adrenal atrophy. The HPA axis is very sensitive to exogenous and chronic glucocorticoid exposure, which can easily lead to corticotropin suppression through a negative feedback loop on CRH, and ACTH in corticotroph cells. In normal individuals who are not working in (night) shifts, there is a diurnal variation of cortisol production, with serum cortisol being highest in the morning and lowest at midnight. In patients with Cushing syndrome (hypercortisolism), these normal physiologic circuits are disturbed. Prolonged (7–48 h) increases in corticotropin leads to an increased synthesis of all the steroidogenic enzymes, especially P450scc, as well as an increased uptake of cholesterol from the circulation (Hanley et al., 2006; Miller et al., 2011). Chronic lack of corticotropin (e.g., through exogenous glucocorticoid administration) leads to adrenal atrophy. Therefore, the exogenous glucocorticoid has to be tapered to allow the pituitary and adrenal glands to recover in order to synthesize normal levels of cortisol on its own. Depending on the level of suppression, this may take weeks or months.

Biosynthesis and Regulation of Aldosterone Production

Aldosterone, the major human mineralocorticoid, is produced in the ZG of the adrenal cortex. Its secretion is stimulated mainly by potassium, angiotensin II (and III) through the renin–angiotensin–aldosterone system and, to a lesser extent, by corticotropin. Chronic infusion of corticotropin stimulates aldosterone secretion for only 24 h. Less potent stimulators of aldosterone secretion are endothelin and serotonin. Also, increases in potassium concentrations stimulate aldosterone production (Hattangady et al., 2012). An increase in serum potassium of 0.1 mmoL/L can elevate plasma aldosterone by 35%. On the other hand, a decrease in

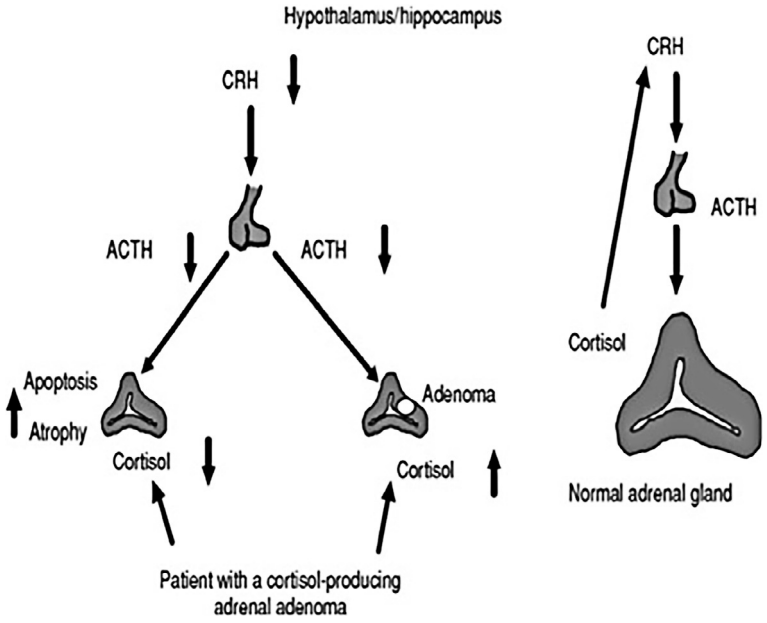

Fig. 3 The HPA axis. Modified from Koch, C.A. and Chrousos, G.P. (2001). Editorial: Is the diminuto/dwarf1 gene involved in physiologic adrenocortical size regulation and tumor formation? *The Journal of Clinical Endocrinology & Metabolism* **86**, 5127–5129.

serum potassium of 0.3 mmoL/L can reduce plasma aldosterone by 46%. Aldosterone promotes potassium excretion, sodium reabsorption and fluid retention, thereby increasing the extracellular fluid volume. However, after a few days of extracellular fluid expansion by increased aldosterone levels, the individual will be protected from continuous expansion through a so-called "escape" mechanism that denotes attaining a new equilibrium of sodium balance and the formation of a new steady state (Hattangady et al., 2012).

Target tissues of aldosterone, including kidney (distal tubules and cortical collecting ducts), colon, and salivary glands, have mineralocorticoid receptors that bind aldosterone. In the distal nephron, cortisol is a potent agonist at the mineralocorticoid receptor. Among inhibitors of aldosterone secretion are atrial natriuretic peptide (ANP) and dopamine (Hattangady et al., 2012). ANP strongly inhibits stimulated (e.g., low sodium intake) aldosterone secretion, with much less effect on basal (e.g., normal or high sodium intake) activity. Chronic sodium restriction leads to increased activity of aldosterone synthase and a higher content of this enzyme in the ZG. The first steps of aldosterone biosynthesis are identical to those of cortisol biosynthesis (Fig. 2). The synthesis of cortisol, however, depends on 17α-hydroxylation of pregnenolone by 17α-hydroxylase (P450c17), which is exclusively expressed in the ZF (Hanley et al., 2006; Miller et al., 2011). On the other hand, aldosterone synthase is normally expressed only in the ZG.

Regulation of Adrenal Androgen Production

At approximately 4 years of age, in both sexes the ZR forms and continues to grow until the mid-20's. After age 40, this zone gradually regresses. Corticotropin and prolactin stimulate adrenal androgen secretion in the fetal adrenal zone (Sidiropoulou et al., 2000). Postnatally, the ZR responds to corticotropin, as exemplified in congenital adrenal hyperplasia in which corticotropin and androgen hypersecretion can occur. During infancy, only small amounts of androgens are secreted, and it is unknown how adrenarche, the time point at which a slight amount of pubic hair develops, is regulated. Seventy percent of circulating testosterone in women with normal menstrual cycles derives from the conversion of adrenal DHEA. The principal androgens secreted by the adrenals are DHEA, DHEAS, androstenedione, and (minimally) testosterone (Nakamura et al., 2009). DHEAS per se has only weak androgenic effects. Peripheral conversion of the aforementioned precursors leads to more potent androgens, such as testosterone and dihydrotestosterone. Major conversion sites include the hair follicles, sebaceous glands, external genitalia, and prostate. Peripheral adipose tissue can convert androgens into estrogens by the highly active enzymes aromatase and 17-ketosteroid reductase. Glucocorticoids stimulate aromatase. Inactivation or degradation of androgens and their metabolites occur at different sites, including the liver and kidneys. Exogenous adrenal androgen administration can suppress gonadotropin secretion. Excess endogenous androgen production can be caused by several conditions, including congenital adrenal hyperplasia, polycystic ovary syndrome and adrenal tumors.

Impact of the Sympathoadrenal System on the Regulation of Adrenocortical Function

Adrenocortical steroid hormones influence the differentiation and hormone production of adrenal chromaffin cells. On the other hand, the sympathoadrenomedullary system modulates diurnal variations of steroidogenesis in the adrenal cortex. The adrenal

cortex is innervated by neurons originating in cell bodies within the adrenal medulla and by nerves that have cell bodies outside the adrenal, reaching the cortex via blood vessels. Adrenal chromaffin cells contain many neuropeptides that regulate adrenocortical steroid production in many species. Adrenomedullary cells are found throughout the adrenal cortex, which facilitates the paracrine action of their products. Another avenue for adrenomedullary secretory products reaching the adrenal cortex is the lymphatics.

Conclusion

The adrenal cortex fulfills important and essential functions throughout a persons lifespan. Prenatally, the fetal adrenal cortex is large and consists of the fetal zone, which produces large amounts of DHEAS, a hormone that serves as a precursor for other androgens. DHEAS is used by the placenta to synthesize estriol and to regulate intrauterine homeostasis as well as maturation of fetal organ systems that are necessary for life after birth. Cortisol and aldosterone, both vital for homeostatic functions, are produced in the adrenal cortex and play important physiological functions in various tissues. Postnatally, the adrenal cortex becomes a three zoned structure with the ZF being the largest zone. All three zones gradually regress during a life span and their dysfunction could lead to serious illness.

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