Adrenal Steroidogenesis and Congenital Adrenal Hyperplasia

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• Steroidogenesis • Congenital adrenal hyperplasia • 21-Hydroxylase • Androgen
• Steroid hydroxylase • Adrenal insufficiency • Ambiguous genitalia
• Disorder of sex development

KEY POINTS

- Steroidogenesis in the adrenal gland reflects the zone-specific expression of enzymes, which comprise pathways to efficiently complete the biosynthesis of aldosterone, cortisol, and dehydroepiandrosterone sulfate.
- The most common form of congenital adrenal hyperplasia is 21-hydroxylase deficiency, in which a block in cortisol biosynthesis shifts precursors to pathways that make excess adrenal-derived androgens.
- Nonclassic 21-hydroxylase deficiency differs from the classic form in that cortisol deficiency and virilization of newborn girls are absent.
- Treatment of classic 21-hydroxylase deficiency consists of glucocorticoid and mineralocorticoid replacement, and for both classic and nonclassic disease, sufficient glucocorticoid is administered to correct the androgen excess.
- Patients with 21-hydroxylase deficiency are prone to developing adrenal cortical adenomas and myelolipomas as well as adrenal rest tumors in the testis or elsewhere.

ADRENAL STEROIDOGENESIS

Adrenal steroidogenesis is a dynamic process, reliant on de novo synthesis, with no presynthesized hormones stored for immediate release. Cholesterol is the common precursor for all steroids and is efficiently converted along a series of steps to the final product. To initiate steroidogenesis, cholesterol is mobilized from a pool in the outer

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mitochondrial membrane (OMM),[1] which is replenished from cytosolic storage droplets of cholesterol esters. The steroidogenic acute regulatory (StAR) protein enables cholesterol transfer from the OMM to the inner mitochondrial membrane,[2] where the sidechain cleavage enzyme (CYP11A1, P450scc) catalyzes the first and rate-limiting step of steroidogenesis: the conversion of cholesterol to pregnenolone (**Fig. 1**A).[1,3]

Aldosterone Biosynthesis

Mineralocorticoid synthesis occurs in the zona glomerulosa (ZG) and requires the subsequent action of 3 enzymes: (1) 3β-hydroxysteroid dehydrogenase type 2 (HSD3B2), which performs the irreversible conversion of the hydroxyl group to a keto group on carbon 3 and simultaneous isomerization of the double bond from the Δ^5 to the Δ^4 position[4]; (2) 21-hydroxylase (CYP21A2, P450c21), which converts progesterone into 11-deoxycosticosterone; (3) aldosterone synthase (CYP11B2, P450c11AS), which catalyzes the final 3 steps of aldosterone synthesis: 11β-hydroxylation, 18-hydroxylation, and 18-methyl oxidation. The 18-aldehyde group, from which the name "aldosterone" derives, forms an intramolecular cyclic hemiacetal using the 11β-hydroxyl group, with loss of water.

The ZG is optimized for aldosterone synthesis: it is the only zone that has CYP11B2 and, in contrast, has little 17α-hydroxylase/17,20-lyase (CYP17A1, P450c17), an enzyme that directs steroids substrates toward cortisol and androgens synthesis (see **Fig. 1**B).[5] Angiotensin 2 and high extracellular potassium are the main stimulators of aldosterone synthesis, via increased intracellular calcium.[6]

Cortisol Biosynthesis

The glucocorticoid cortisol is synthesized in the zona fasciculata (ZF) under the regulation of adrenocorticotropin (ACTH). CYP17A1 catalyzes the 17α-hydroxylation of pregnenolone and progesterone with roughly equal efficiency, and this reaction leads to cortisol production. In addition, CYP17A1 subsequently cleaves the C17-C20 bond of 17-hydroxypregnenolone and to a much lesser degree of 17-hydroxyprogesterone (17OHP), which leads to 19-carbon (C_{19}) steroids (see **Fig. 1**A). Both reactions occur in a single active site, but with different regulation, as discussed later. With the activities of HDS3B2 and CYP21A2, which perform reactions similar to those on the mineralocorticoid pathway, 17-hydroxysteroids are converted to 11-deoxycortisol. Last, 11β-hydroxylase (CYP11B1, P450c11β), an enzyme closely related to CYP11B2, completes the synthesis of cortisol. In rodents and many small animals, the ZF lacks CYP17A1. Consequently, nascent progesterone is 21-hydroxylated and 11β-hydroxylated to yield corticosterone, which is the dominant glucocorticoid in these species, but it is ordinarily a minor product of the human adrenal.

Adrenal Androgen Biosynthesis

Adrenal C_{19} steroids are synthesized in the zona reticularis (ZR). Dehydroepiandrosterone (DHEA) is converted to its sulfate (DHEAS), which is the most abundant adrenal steroid. CYP17A1 is the only enzyme required for DHEA synthesis from pregnenolone and for androstenedione (AD) synthesis from progesterone. Although CYP17A1 is present in both ZF and ZR, its 17,20-lyase reaction is enhanced approximately 10 times by the cofactor cytochrome b_5 (CYB5A), which is absent in the ZF (see **Fig. 1**B).[7] Sulfotransferase SULT2A1 conjugates DHEA to DHEAS, a steroid with an important role in the regulation of adrenal androgen synthesis.[8] The adrenal synthesizes small amounts of testosterone, by the action of 17β-hydroxysteroid dehydrogenase type 5 (17βHSD5, AKR1C3) on AD (see **Fig. 1**A).