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Adrenal androgens and androgen precursors: definition, synthesis, regulation and physiologic actions

Adina Turcu^{1,*}, Joshua M. Smith^{2,*}, Richard Auchus¹, and William E. Rainey^{1,3}

¹Dept. of Internal Medicine, Division of Metabolism Endocrinology and Diabetes, University of Michigan, Ann Arbor, MI. 48109

²Dept. of Pediatrics, Division of Pediatric Endocrinology, University of Texas Southwestern Medical Center, Dallas, TX 75390-9032, USA

³Dept. of Molecular and Integrative Physiology, University of Michigan, Ann Arbor, MI. 48109

Abstract

The human adrenal produces more 19 carbon (C₁₉) steroids, by mass, than either glucocorticoids or mineralocorticoids. However, the mechanisms regulating adrenal C₁₉ steroid biosynthesis continue to represent one of the most intriguing mysteries of endocrine physiology. This review will discuss the C₁₉ steroids produced in the human adrenal and the features within the adrenal that allow production of these steroids. Finally, we consider the effects of these steroids in normal physiology and disorders of adrenal C₁₉ steroid excess.

Keywords

adrenal; 19 carbon steroid; dehydroepiandrosterone; adrenarche; zona reticularis; sulfotransferase (SULT2A1); cytochrome *b*₅; 17 α -hydroxylase/17,20-lyase (CYP17A1); 17 β -hydroxysteroid dehydrogenase type 5 (AKR1C3); 3 β -hydroxysteroid dehydrogenase type 2 (HSD3B2); androgen

Introduction

The human adrenal produces a variety of 19 carbon (C₁₉) steroids, such as dehydroepiandrosterone (DHEA), DHEA sulfate (DHEAS), androstenedione (A4), androstenediol and 11 β -hydroxyandrostenedione (11OHA) (135) (Figure 1). These steroids have little androgenic activity, but they provide a pool of circulating precursor for peripheral conversion to more potent androgens (e.g. testosterone, T) and estrogens, (e.g. estradiol) (79, 100, 128, 134, 141). The adrenal gland contributes ~1% to the total circulating T in males and up to 30–50% in females (84), and roughly half of circulating A4 is of adrenal origin (1); conversely, DHEA and DHEAS derive predominantly from the adrenal (1). In addition, synthesis of 11OHA and 11 β -hydroxytestosterone (11OHT) requires the adrenal specific enzyme 11 β -hydroxylase (CYP11B1) (Figure 1) (16, 135). Thus, because these steroids are mainly derived from the adrenal, DHEA, DHEAS, 11OHA and 11OHT are commonly

*These authors contributed equally to the writing of this manuscript.

referred to as “adrenal androgens” and DHEA and DHEAS have been used as biomarkers to help determine the adrenal contribution to diseases of androgen excess.

However, it is likely that the adrenal produces an even wider array of C₁₉ steroids. This concept is supported by a recent study where liquid chromatography/tandem mass spectrometry (LC-MS/MS) was utilized to measure C₁₉ steroids in adrenal vein (AV) samples from women with hyperaldosteronism, before and after cosyntropin stimulation (135). AV levels of DHEAS were the highest among the nine C₁₉ steroids that were measured. The most abundant unconjugated C₁₉ steroids in AV samples were 11OHA, DHEA and A4. Based on this study, the adrenal glands produce more C₁₉ steroids (sulfated and unconjugated) than cortisol. In addition, although secreted in smaller amounts, AV levels of T and 11OHT also increased following cosyntropin infusion. This study supports the concept that the human adrenal produces a broad set of androgens and precursor C₁₉ steroids, whose production is stimulated by adrenocorticotropin (ACTH).

C₁₉ steroidogenic pathways

Steroidogenic acute regulatory (StAR) protein

Steroid secretion is directly dependent on *de novo* steroid production, as there are no pre-synthesized hormone reservoirs in the adrenal cortex. Cholesterol, the common precursor of all steroids, is stored in cytoplasmic lipid droplets and must be transported to the outer mitochondrial membrane (OMM) to initiate steroid production (108). The initial enzymatic step for steroidogenesis, however, occurs deeper within the mitochondria. The steroidogenic acute regulatory (StAR) protein facilitates the transfer of cholesterol from the OMM to inner mitochondrial membrane (IMM), where it is then cleaved by the cholesterol side chain enzyme (CYP11A1) (32, 162). The human StAR gene is located on chromosome 8q11 and encodes primarily a 1.6 kb mRNA that produces the 37 kDa precursor protein (165). Upon entry into the mitochondria, StAR is cleaved to a 30 kDa form (5, 60). StAR is a member of a family of proteins containing a START (StAR-related lipid transfer)-domain, which consists of a β -sheet rich sterol-binding pocket (173). A single molecule of cholesterol fits into this pocket, and it has been suggested that StAR recirculates across the mitochondrial membranes several times before being inactivated following proteolytic cleavage. StAR appears to play a crucial role in steroid production, not only in the adrenal, but in the ovary and testis as well. In addition, the expression of StAR in many non-steroid producing tissues suggests a role in other cellular processes (4).

Mouse studies have shown that deletion of StAR leads to blockade of adrenal steroidogenesis and induces a life-threatening condition similar to lipid congenital adrenal hyperplasia (LCAH) (29) that is seen in human neonates with inactivating StAR gene mutations (20, 97). In the absence of StAR, adrenal steroidogenic capacity declines to only about 14% of the StAR-induced rate, although the mechanisms that, at least partially, maintain steroidogenesis have not clearly been defined. There is strong support for a role of two additional proteins, MLN64 and peripheral benzodiazepine receptor (also known as translocator protein or TSPO). The cholesterol transport activities of these proteins might account for the remaining 14% of steroid production in LCAH. For example, in the human placenta, which does not express StAR, MLN64 is believed to facilitate cholesterol

movement into the IMM to initiate pregnenolone biosynthesis (22, 178). Deficiency of StAR causes massively enlarged, lipid-laden adrenal glands that make minimal quantities of steroids and leads to eventual cellular apoptosis and organ dysfunction (21, 29, 83, 148). In addition, genetically male (XY) fetuses with LCAH have phenotypically female external genitalia due to the absence of *in utero* T production from lack of steroidogenesis in the developing testes (20, 83). The condition is lethal unless promptly recognized at birth and treated with corticosteroids (52, 63, 83). Affected fetuses have decreased adrenal C₁₉ steroids (including 16 α DHEAS) that normally enter the maternal circulation and act as precursors for placental conversion to estriol (134). Fetal LCAH is among the causes of low estriol in the maternal circulation throughout pregnancy.

Cholesterol Side-Chain Cleavage Enzyme (CYP11A1)

Cholesterol side-chain cleavage enzyme (CYP11A1, P450_{scc}) catalyzes the initial and rate limiting enzymatic reaction of steroidogenesis: the conversion of cholesterol to pregnenolone (85, 108, 149). Encoded by one gene on chromosome 15q23-q24 (158), this single P450 enzyme performs three serial reactions: 20-hydroxylation, 22-hydroxylation, and scission of the C20–C22 bond of cholesterol (150). Each of these three reactions requires a pair of electrons from reduced nicotinamide adenine dinucleotide phosphate (NADPH) and one molecule of oxygen. A type I P450 enzyme, CYP11A1 is located in the mitochondria and receives electrons from NADPH via an iron-sulfur protein, named ferredoxin (116). During this process, NADPH first reduces a flavoprotein called ferredoxin reductase, which in turn passes electrons to ferredoxin. Ferredoxin reductase and ferredoxin are electron transfer proteins that donate electrons to all of the various mitochondrial P450 enzymes (175).

The human *CYP11A1* gene encodes a 2 kb mRNA, which is translated into a 521 amino acid precursor (30). The leading 39-amino acids that introduce CYP11A1 into the mitochondria are lost during this process (104). The mitochondrial environment is required for CYP11A1 activity, as engineered forms missing the targeting peptide are inactive (15). Rabbit and mouse studies show that deletion of the gene for CYP11A1 (67, 183) drastically reduces steroidogenesis, which demonstrates that CYP11A1 is the only enzyme that can convert significant amounts of cholesterol to pregnenolone. Similar to StAR deficiency, partial deficiency of CYP11A1 activity has been observed in humans and resembles incomplete or “nonclassic” LCAH (145, 147).

CYP11A1 is needed for the production of all steroids, including those produced by the adrenal. Adrenal gland expression of CYP11A1 is mainly regulated by ACTH (74). The enzyme is expressed in all adrenal cortex zones, and although its expression is obligatory for the synthesis of C₁₉ steroids (Figure 2), it is the presence of downstream enzymes that determines whether these cells produce corticosteroids or C₁₉ steroids.

17 α -hydroxylase/17,20-lyase (CYP17A1)

CYP17A1 mediates the two steps involved in the conversion of pregnenolone to DHEA: the 17 α -hydroxylation of pregnenolone, followed by the scission of the C17–C20 bond of 17-hydroxypregnenolone (17OHP5). These two distinct reactions were long thought to be

catalyzed by separate enzymes. However, the cloning of bovine cDNA for CYP17A1 and its expression in non-steroidogenic COS-1 cells yielded both 17 α -hydroxylase and 17,20-lyase activities, proving that a single enzyme catalyzed both reactions (187). Similarly, the human CYP17A1 is encoded by a single gene, located on chromosome 10 and a single 2.1-kb mRNA is expressed and translated into a 57-kDa protein in both the adrenals and gonads (31, 75).

CYP17A1 is a type II P450, being located in the endoplasmic reticulum, where it receives electrons from NADPH via a flavoprotein called P450-oxidoreductase (POR) (184). Within this redox system, electrons are initially transferred from NADPH to the flavin adenine dinucleotide (FAD), then to the flavin mononucleotide within distinct domains of POR, and lastly to the P450.

Human CYP17A1 has similar affinities and activities for both pregnenolone and progesterone 17 α -hydroxylation; in contrast, 17,20-lyase reaction preferentially uses 17 α -hydroxypregnenolone as substrate, yielding an approximately 50-fold more efficient catalytic activity on the ⁵ pathway to DHEA than the ⁴ pathway to androstenedione (50, 70). Furthermore, the 17,20-lyase reaction is enhanced approximately 10 times by the cofactor cytochrome *b*₅ (CYB5A) (10, 78, 94, 120) in both pathways. The mechanism by which CYB5A regulates 17,20-lyase activity is not well understood; experimental data suggest that CYB5A is an allosteric activator of 17,20-lyase, promoting the interaction between the enzyme and POR, rather than acting alone, as an electron donor (10).

Various forms of CYP17A1 deficiency have been described, and their severity tends to correlate with the severity of the mutation (9, 182). The initial case was reported in 1966 and described a patient with combined, complete 17 α -hydroxylase/17,20-lyase deficiency, who presented with amenorrhea, sexual infantilism and hypertension (14). Deficiency of 17 α -hydroxylase results in decreased cortisol synthesis; the ensuing ACTH elevation stimulates the accumulation of metabolites proximal to the enzymatic defect, all on the mineralocorticoid pathway—primarily 11-deoxycorticosterone (DOC)—causing hypertension and hypokalemia. Despite not being able to produce normal amounts of the important steroid cortisol, these patients rarely show symptoms of adrenal insufficiency, due to the enhanced production of corticosterone, which also has glucocorticoid activity. Similarly, mice and rats normally lack Cyp17a1 in their adrenals and use corticosterone as their major glucocorticoid (80).

Mutations that cause isolated deficiency of 17,20-lyase deficiency are more rare, and most involve attenuation of positive charges in the redox partner-binding site, thus altering the capacity of CYP17A1 to interact with its electron donor POR and with CYB5A (56). Clinically, these patients are deficient of both androgens and estrogens, as both adrenal and gonadal steroidogenesis is impaired. Subsequent to the cloning of the *CYP17A1* gene, ~100 mutations have been identified, the majority of which are clustered in specific populations, such as Brazilians of Spanish and Portuguese ancestry (W406R and R362C mutations, respectively) (35), descendants of Dutch Frieslanders (duplication of four nucleotides causing a frameshift) (71), and Southeast Asians (in-frame deletion of residues 487–489) (48, 92).

CYP17A1 is needed for the production of adrenal cortisol as well as C₁₉ steroids. As such, this enzyme is expressed at high levels in the fasciculata and reticularis zones (Figure 2). While the 17,20-lyase activity of CYP17A1 increases significantly in the inner reticularis, it does not appear to be due to increased CYP17A1 expression, but to the high expression of CYB5A in this zone (103, 166). Adrenal gland expression of CYP17A1 is mainly regulated by ACTH (154, 186). In addition, a number of growth factors, including insulin like growth factor I and II, enhance adrenal cell CYP17A1 expression, while transforming growth factor β inhibits CYP17A1 expression (87, 93, 129). What regulates CYB5A expression remains unknown.

SULT2A1

At least 44 distinct isoforms, grouped in five families, of steroid sulfotransferases (SULT) have been identified (47, 164). SULT2A1 is predominantly expressed in the cytoplasm of adrenocortical cells in zona reticularis, where it sulfates the 3 β -hydroxyl group of Δ^5 steroids (pregnenolone, 17 α -hydroxypregnenolone, DHEA, and androsta-5-ene-3 β ,17 β -diol). During fetal development, each of these steroids is used as SULT2A1 substrates, while in adults DHEA is preferentially utilized, resulting in DHEAS. The SULT2A1 gene has been mapped to 19q13.3 and spans at least 17kb with 6 exons (122). The resultant 1.9kb mRNA is translated into a 33.7-kDa SULT2A1 protein.

Conjugation of DHEA to its sulfated form, DHEAS, plays an important role in the regulation of adrenal androgen synthesis. In pregnancy, the fetal adrenal provides large amounts of DHEAS as precursor for placental estradiol synthesis (134). In contrast, DHEAS acts postnatally as a buffer to prevent excessive adrenal androgen production. Defects in DHEAS sulfation result in excessive amounts of DHEA, a substrate for HSD3B2 to yield A4, which is further converted to T (117). A SULT2A1 polymorphism found in African Americans might correlate with the risk of prostate and other cancers (118); however, a definitive link has not been established. No human mutations in SULT2A1 causing DHEAS deficiency have been yet identified. Instead, the process of DHEA sulfation can be impaired by defects in the enzyme that synthesizes the obligatory sulfate donor of SULT2A1, 3'-phosphoadenosine 5'-phosphosulfate (PAPS) (117, 164, 180). In humans, PAPS synthase (PAPSS) exists in two isoforms, PAPSS1, which is ubiquitously expressed, and PAPSS2, highly expressed in the major sites of DHEA sulfation: the adrenal and liver (164). Deficiency of PAPSS2 prevents DHEA sulfation, as described in a girl who presented with premature pubarche and advanced bone age, followed by acne, hirsutism, and secondary amenorrhea in adolescence (117).

As noted above, SULT2A1 is needed for sulfation of DHEA but can also efficiently sulfate pregnenolone and 17-hydroxypregnenolone. SULT2A1 expression, however, is limited to the adrenal zona reticularis (Figure 2), and therefore selective expression of this enzyme plays an important role in defining which cells produce DHEAS and the repertoire of steroid sulfates emerging from the adrenal. The expression of SULT2A1 also increases in the adrenal during adrenarche (114, 166).

3 β -hydroxysteroid dehydrogenase/ 5 α -isomerase type 2 (HSD3B2)

HSD3B2 is a key enzyme for the synthesis of mineralocorticoids, glucocorticoids and androgens. HSD3B2 catalyzes the conversion of the hydroxyl group to a keto group on carbon 3 and the isomerization of the double bond from the B ring (5 steroids) to the A ring (4 steroids) (90, 99, 168). Pregnenolone, 17 α -hydroxypregnenolone, DHEA and androstenediol are all substrates for HSD3B2 (95, 169), which are irreversibly converted to progesterone, 17 α -hydroxyprogesterone, A4 and T, respectively. While rodents have multiple HSD3B2 isoforms, the human genome has only two active genes and several pseudogenes (89). HSD3B2 is the principal isoform in the adrenals and gonads. The *HSD3B2* gene on chromosome 1p12 is transcribed to give a 1.7kb mRNA, which is translated to a 42-kDa protein (91, 101).

Mutations in HSD3B2 cause a rare form of congenital adrenal hyperplasia, in which circulating concentrations of 5-steroids, particularly 17 α -hydroxypregnenolone, are elevated (19, 110, 113, 138, 153). The production of some 4-steroids (not cortisol) is partially compensated (109) by type 1 isoform of HSD3B2, which is present in extra-adrenal tissues, such as breast, liver, brain, and placenta. The spectrum of HSD3B2 deficiency ranges from complete or “classic” to mild or “partial”, the latter of which is extremely rare but is often misdiagnosed due to former incorrect criteria. In classic HSD3B2 deficiency, the glucocorticoid and mineralocorticoid deficiencies are life-threatening in early infancy (18, 123, 152). Genetic males are unable to synthesize sufficient androgens to completely virilize their external genitalia, while genetic females have clitoromegaly and mild virilization due to overproduction of DHEA and peripheral conversion to active androgens (110, 113, 139).

The adrenal reticularis has substantially lower levels of HSD3B2 compared to the adjacent fasciculata (Figure 2). The relative lack of HSD3B2 expression facilitates DHEAS synthesis by decreasing competition with CYP17A1 for pregnenolone and 17OHP5 (33, 133). In adrenarche, the characteristic expansion of a zona reticularis with low HSD3B2 expression occurs, which contributes to the increased synthesis of adrenal DHEAS through the transition from prepubertal period to adult life (54, 55, 68, 166). The phenomenon of increased androgen production as a result of decreased HSD3B2 activity was also demonstrated by McCartin et al. when they reported the presence of premature adrenarche in an 11-year-old subject with a profound loss in HSD3B2 activity owing to a compound heterozygous mutation in the *HSD3B2* gene (105).

Type 5 17 β -Hydroxysteroid dehydrogenase (AKR1C3)

The conversion of androstendione to T requires 17 β -hydroxysteroid dehydrogenase activity. In the testis, the type 3 17 β HSD (HSD17B3) catalyzes this reaction (53). This enzyme is not expressed in the adrenal (115). Instead, the human adrenal expresses AKR1C3, also known as 17 β -hydroxysteroid dehydrogenase type 5 (115), a member of the aldo-keto reductase (AKR) family that is also found in non-steroidogenic tissues (39, 46). This enzyme has an array of substrates and activities, including the ability to catalyze the reduction of A4 to T (46, 98). AKR1C3 was originally cloned as a 3 α -HSD (39, 98) and found to reduce DHT to 3 α -androstenediol (39). This protein was later recognized to also have 17 β HSD activity and to be accountable for much of the extra-testicular and peripheral conversion of A4 to T,

although with poor catalytic efficiency (131). The postnatal adrenal also expresses AKR1C3 in the zona reticularis, and AKR1C3 appears to be the enzyme responsible for the small amount of T produced directly by the adrenal glands (115), and is likely responsible for the larger amounts of androgens produced in congenital adrenal hyperplasia.

AKR1C3 is a 37-kDa protein, encoded on chromosome 10p15.1 and transcribed to give an mRNA of 1200–1400 nucleotides (82). Little is known about the regulation of AKR1C3, but ACTH is believed to play a stimulatory role in the adrenal. The *AKR1C3* gene is found in a cluster with 3 other AKR1C genes, whose proteins have overlapping activities. Although no human deficiencies in AKR1C3 have been reported, a polymorphism in the *AKR1C3* gene (pGlu77Gly in exon 2) has been associated with lower T in men (73). The promoter region of this gene has become of interest, as a few studies indicate an increase in AKR1C3 transcription contributing to the hyperandrogenism in PCOS (44, 132).

Mechanisms regulating adrenal C₁₉ steroid production

Progress in defining the mechanisms that regulate adrenal C₁₉ steroid production has been hampered by the fact that research has focused adrenal DHEAS, which is abundant only in some large mammals (36). To date, there has been little progress in defining an adrenal androgen-stimulating hormone that might specifically regulate adrenal DHEA(S) production. Although the regulation of adrenal C₁₉ steroid biosynthesis is incompletely understood, ACTH remains the most widely accepted primary mediator of C₁₉ steroid production (136, 142). As is seen for cortisol, dexamethasone suppression of ACTH levels decreases circulating adrenal androgens, suggesting a primary regulatory role for ACTH (140). C₁₉ steroids also exhibit a diurnal pattern of expression that mimics circulating levels of ACTH, although the diurnal fluctuation in DHEAS is small due to its long half-life (126). Moreover, children with ACTH receptor defects fail to experience adrenarche and the increase of adrenal C₁₉ steroids (2, 179), thereby supporting a requirement for ACTH in this phenomenon. However, it is also clear that DHEAS levels increase at the time of adrenarche in a manner that appears independent of the cortisol and ACTH levels, which maintain a constant pattern (81). This discrepancy is in part due to cortisol's tight regulatory feedback control of ACTH and highlights the fact that DHEAS and other C₁₉ steroids do not appear to exert negative feedback on ACTH production. This clear age-related separation of circulating levels of cortisol and DHEAS has led many researchers to pursue a so-called adrenal androgen stimulating hormone (AASH). Most research has focused on the pituitary as the source of a potential AASH. Indeed, plasma levels of pro-opiomelanocortin (POMC) related peptides, including β -lipotropin and β -endorphin, correlate with the rise in DHEAS seen at the time of adrenarche (57, 58, 119). In addition, there was a brief period of support for AASH being the proximal 18-amino acid hinge region (amino acids 79–96) of POMC, but the initial studies were not confirmed by additional *in vitro* studies (106, 125, 130). Other pituitary and non-pituitary derived hormones [prolactin, insulin, insulin-like growth factor-I (IGF-I)] have been studied but have been found not to show a selective correlation with circulating DHEAS levels seen during adrenarche or to selectively stimulate C₁₉ steroid production in human adrenocortical cells (7, 62, 127, 157). Corticotropin releasing hormone (CRH) appears to regulate DHEAS production in fetal adrenal (155); however evidence to support a similar role in adults is lacking. Thus, determination of the role of a

non-ACTH controlling hormonal factor for adrenal C₁₉ steroids still needs more investigation.

An alternative hypothesis has revolved around a role for intra-adrenal steroids in regulating adrenal C₁₉ steroid production, as well as adrenarche (3). Several studies have demonstrated an age-dependent increase in intra-adrenal C₁₉ and C₂₁ steroid levels to the range needed to act as competitive inhibitors of HSD3B2 (24, 25, 42). In this manner, steroid precursors would influence C₁₉ steroid synthesis by promoting 17OHP metabolism to DHEA at adrenarche. Recent *in vitro* studies by Topor et al also established that cortisol inhibits HSD3B2 and stimulates the biosynthesis of DHEA at concentrations above 50 μ M (170). The exact role of cortisol inhibition of HSD3B2 during adrenarche is not clear. For example, several C₁₉ steroids levels are high in pre-pubertal children with under-treated classic congenital adrenal hyperplasia (CAH), in whom intra-adrenal cortisol levels are low (23). In addition, as noted earlier, the adrenal reticularis appears to have very low levels of HSD3B2 expression. An alternative role of cortisol inhibition of HSD3B2 may be through its action within the zona fasciculata, where an inhibition of HSD3B2 could influence its production of 11OHA and androstenedione.

Adrenal C₁₉ steroid production during the process of aging

The fetal adrenal glands are large compared to those of adults and consist of 80% of the so-called “fetal zone”. Until birth, the fetal zone secretes remarkable quantities of DHEA and DHEAS, which are used by the placenta as precursors for estrogen production (17, 51, 134, 151). After birth, the fetal zone involutes, which accounts for the rapid decline in DHEAS synthesis in the first months of life. The zona reticularis is indistinct during infancy but has been shown to expand starting around 4–5 years of age and continue to grow throughout the first two decades of life (38, 40). This process is followed by a rise in circulating concentrations of DHEAS (38, 45, 121). A marked increase in circulating DHEAS is easily detectable during the process of adrenarche (41, 68, 166), and most studies support a primary role for peripheral conversion of adrenal derived C₁₉ steroids to more potent androgens underlying the growth of axillary and pubic hair in children of both genders (11, 79). The adrenarche-associated rise in DHEAS is a phenomenon specific to human beings and some Old World primates, such as the chimpanzee and gorilla (26, 34, 36, 156). The physiologic significance of adrenarche remains somewhat unclear. Most researchers have focused on the use of adrenal-derived C₁₉ steroids by peripheral tissues, which have enzymes that can convert the precursors to more active androgens (Figure 3). Some evidence suggests that DHEAS has a neuromodulatory effect, which might serve to protect certain parts of the prepubertal brain that are more active metabolically (26). Another theory is that adrenarche supports an evolutionary role of “juvenility”, which might have helped human ancestors adapt their body composition to environmental factors during the transition to adulthood (65, 66).

Pathophysiology of adrenal C₁₉ steroids

Premature Adrenarche—Normally, adrenarche in humans is a gradual process that precedes the onset of puberty. Premature adrenarche (PA) refers to the early increase in adrenal androgen production and the subsequent early appearance of pubic or axillary hair

before age 8 years in girls and 9 years in boys (premature pubarche), without the presence of other secondary sex characteristics (69, 167). However, the age of adrenarche (based on premature pubarche vs. normal pubarche) appears to differ between ethnic populations, as does the onset of puberty (64). Children with PA exhibit elevated serum levels of DHEA, DHEAS, A4, and T, as well as of their urinary metabolites (43, 69, 86, 96, 143, 144, 176). Steroid profiles of infants with fine genital hair studied by LC–MS/MS show a mild elevation of DHEAS when compared with healthy pre-adrenarchal children, suggesting that pubic hair in infancy might represent a mild and early-onset variant of PA (77). Toscano *et al.* observed that PA was associated with increases in plasma levels of C₂₁ steroids like pregnenolone and 17-hydroxypregnenolone, along with the C₁₉ steroids DHEA, DHEAS, and A4 but with no change in cortisol or 11-deoxycortisol (171). These findings imply that children with PA have an early expansion of the reticularis (that has low HSD3B2 and high CYP17A1 and CYB5A activity) (114) that is seen in later years for children without premature pubarche.

Castration-resistant prostate cancer—While the prostate does not have the ability to produce steroids from cholesterol, it does have enzymes needed to metabolize circulating adrenal C₁₉ steroids to active androgens (88, 100). This appears to include the ability to convert the 11 hydroxylated adrenal C₁₉ steroids to active androgens (16, 163). The ability of the fetal Müllerian structures to metabolize circulating androgens and precursors has long been known. Formation of the male external genitalia during embryogenesis, as well as sexual maturation at puberty, are mediated by the action of DHT the more potent 5 α -reduced metabolite of T (61) (Fig. 3). This conversion is catalyzed predominantly by type 2 5 α -reductase (SRD5A2) and occurs in the target androgen tissues, including the prostate (72). DHT contributes to excessive prostate tissue expansion, as in benign prostatic hypertrophy and prostate cancer. Initial therapy for prostate cancer has involved removing sources of DHT through castration (both surgical and pharmaceutical), androgen receptor antagonists, and 5 α -reductase inhibitors. Progressive disease despite castration is termed castration-resistant prostate cancer (CRPC) and is uniformly fatal. Recent evidence has suggested that CRPC continues to be stimulated by intracellular DHT, which is formed without going through the canonical pathway. This pathway was initially described a decade ago in tammar wallabies (181), whose testes produce 5 α -androstane-3 α ,17 β -diol (5 α Adiol) rather than T. In this pathway, the 17-hydroxyprogesterone (17OHP4) is first 5 α -, then 3 α -reduced, and only subsequently undergoes 17, 20-lyase cleavage, to form androsterone. After 17 α -reduction to 5 α -androstanediol, circulating 5 α -androstanediol is 3 α -oxidized to produce DHT in target tissues such as genital skin and prostate, thus bypassing the conventional androgens as intermediates. While the prostate uses SRD5A2 for conversion of T to DHT, SRD5A1 has a greater affinity for some of these precursors and completely bypasses T as an intermediate step. New drugs targeting CYP17A1 (like abiraterone acetate) block this “backdoor pathway” and prolong survival for men with CRPC with or without prior docetaxel treatment (37, 146). However, evidence suggests that the blockade is incomplete,(6) and further work is needed to find other treatments for this cancer.

Congenital adrenal hyperplasia—CAH refers to a group of autosomal recessive genetic defects in cortisol biosynthesis. The most common form of CAH is 21-hydroxylase

(CYP21A2) deficiency (21OHD), and when the nonclassic form is included, 21OHD is one of the most common genetic diseases in human beings (159). Ordinarily, the zonation of the normal adrenal gland segregates key enzymes to prevent efficient active androgen synthesis. In contrast, a hallmark of 21OHD is excessive adrenal androgen production. Females with classic 21OHD are born with masculinized ambiguous genitalia from intrauterine androgen excess, while adult women with nonclassic 21OHD might present with hirsutism, irregular menses, and subfertility (159).

The excess 17OHP4 resulting from CYP21A2 deficiency is diverted through the pathways left accessible, to form potent androgens, such as T (Fig. 4). The catalytic efficiency of the 17,20-lyase reaction for human CYP17A1, which is ~50 times greater for the Δ^5 reaction as compared with the Δ^4 reaction (49), explains the enormous 17OHP4 accumulation in 21OHD. Significant A4 synthesis might still occur via the Δ^4 pathway in the presence of very high intra-adrenal 17OHP4 that is seen in patients with 21OHD. Emerging evidence has demonstrated that the excessive 17OHP4 of patients with 21OHD may also be metabolized via the “backdoor pathway” (76), as described in CRPC. Interestingly, DHEAS, the dominant ACTH-dependent C₁₉ steroid product of the adrenal, is often paradoxically low or low-normal in 21OHD patients even when control is poor (137). This might be due to the disrupted adrenal zonation seen in patients with 21OHD (107), such that the zona reticularis (which lacks HSD3B2, and thus favors DHEA synthesis) is replaced by areas that co-express HSD3B2 along with CYB5A. The backdoor pathway to DHT has been proposed to contribute to the virilization of female fetuses with CAH (8). In addition, the adrenal glands might also produce other active androgens, such as 11OHT. While small amounts of these androgens were documented in AV samples obtained from normal adrenals (135), patients with 21OHD might directly secrete sufficient quantities to play a role in the virilization of female subjects. The androgen activity of 11OHT was tested using a cell-based androgen-responsive reporter assay, and found to be 30 times higher than that of AD. Given the abundance of intra-adrenal androgen precursors in 21OHD and the biosynthetic pathways required, the 11-oxygenated androgens might be prominent products of the 21OHD adrenal (Fig 4).

Polycystic ovary syndrome (PCOS)—PCOS is the most common endocrine disorder observed in women of reproductive age (28, 59, 172). PCOS is usually defined as hyperandrogenic anovulation with or without polycystic-appearing ovaries. Patients present with elevated serum androgen levels and/or abnormal hair growth (hirsutism), and they have 8 or fewer menses per year (indicating oligo-/anovulation) (12). The endocrine imbalance seen in women presenting with PCOS is also variable. However, one feature present in the majority of women with PCOS is androgen excess. The elevated androgens have a variety of actions in these patients, including dysregulation of LH and FSH, which impacts the normal ovarian and menstrual cycles, as well as direct ovarian disruption of normal follicular development. Finally, the elevated androgens have additional phenotypic effects in women with PCOS that include growth of facial and body hair, acne, and in the more severe cases, male-pattern baldness.

Several androgens, in various combinations, may be elevated in women with PCOS (13), with great individual variability between patients, again supporting the concept that the

disorder may have multiple causes. Most studies suggest that the ovary exhibits abnormally high T production in the majority of PCOS women. However, there is considerable support that the adrenal can contribute to the hyperandrogenism seen in PCOS. Some fifty years ago it was demonstrated that suppression of the hypothalamic pituitary adrenal (HPA) axis reduced the urinary androgen excretion in 1/3 of hirsute women (102). In follow-up studies by the same group, ovarian and adrenal vein sampling showed that T in PCOS patients could arise from the adrenal and/or ovary (124, 160, 161). Since these original observations, numerous studies have better defined the contribution of the ovary versus the adrenal to the androgen excess in women with PCOS (27, 59, 111, 112, 174, 177, 185). While there remains some controversy as to the relative impact of the adrenal versus ovary to PCOS androgen profiles, most authorities agree that, like the symptoms seen in PCOS, the source(s) of androgen excess is/are also variable.

Conclusions

The adrenal glands synthesize an assortment of C₁₉ steroids, of which DHEA and DHEAS have been the major focus and biomarkers of adrenal androgen excess. Recent quantitation of steroids by LC-MS/MS in samples obtained directly from the adrenal veins demonstrate that, indeed, DHEAS is the most abundant C₁₉ steroid secreted by the adrenal glands; however, this study also documents that the adrenal gland is the source of other C₁₉ steroids, including A4, 11OHA and 11OHT. Although the mechanisms that regulate the synthesis of adrenal C₁₉ steroid have not yet been fully elucidated, ACTH appears to be the primary mediator.

Unlike the testis, which is an efficient androgen producer, the adrenal gland plays only a secondary role in active androgen in men. However, in women and pre-pubertal children, the adrenal gland is an important source of androgen and androgen precursors that play both physiologic and pathologic roles. The role of the adrenal glands in pathologic androgen production becomes important in several conditions, including PA, CRPC, CAH and PCOS. Future studies are needed to explore the mechanisms regulating normal and pathologic production of adrenal C₁₉ steroidogenesis regulation and dysregulation.

References

1. Abraham GE. Ovarian and adrenal contribution to peripheral androgens during the menstrual cycle. *The Journal of clinical endocrinology and metabolism*. 1974; 39:340–346. [PubMed: 4278727]
2. Akin L, Kurtoglu S, Kendirici M, Akin MA. Familial glucocorticoid deficiency type 2: a case report. *Journal of clinical research in pediatric endocrinology*. 2010; 2:122–125. [PubMed: 21274326]
3. Anderson DC. The adrenal androgen-stimulating hormone does not exist. *Lancet*. 1980; 2:454–456. [PubMed: 6106101]
4. Anuka E, Gal M, Stocco DM, Orly J. Expression and roles of steroidogenic acute regulatory (StAR) protein in ‘non-classical’, extra-adrenal and extra-gonadal cells and tissues. *Molecular and cellular endocrinology*. 2013; 371:47–61. [PubMed: 23415713]
5. Artemenko IP, Zhao D, Hales DB, Hales KH, Jefcoate CR. Mitochondrial processing of newly synthesized steroidogenic acute regulatory protein (StAR), but not total StAR, mediates cholesterol transfer to cytochrome P450 side chain cleavage enzyme in adrenal cells. *The Journal of biological chemistry*. 2001; 276:46583–46596. [PubMed: 11579102]

6. Attard G, Reid AH, Auchus RJ, Hughes BA, Cassidy AM, Thompson E, Oommen NB, Folkert E, Dowsett M, Arlt W, de Bono JS. Clinical and biochemical consequences of CYP17A1 inhibition with abiraterone given with and without exogenous glucocorticoids in castrate men with advanced prostate cancer. *The Journal of clinical endocrinology and metabolism*. 2012; 97:507–516. [PubMed: 22170708]
7. Aubert ML, Grumbach MM, Kaplan SL. Heterologous radioimmunoassay for plasma human prolactin (hPRL); values in normal subjects, puberty, pregnancy and in pituitary disorders. *Acta endocrinologica*. 1974; 77:460–476. [PubMed: 4479135]
8. Auchus RJ. The backdoor pathway to dihydrotestosterone. *Trends Endocrinol Metab*. 2004; 15:432–438. [PubMed: 15519890]
9. Auchus RJ. The genetics, pathophysiology, and management of human deficiencies of P450c17. *Endocrinol Metab Clin North Am*. 2001; 30:101–119. [PubMed: 11344930]
10. Auchus RJ, Lee TC, Miller WL. Cytochrome b₅ augments the 17,20 lyase activity of human P450c17 without direct electron transfer. *The Journal of biological chemistry*. 1998; 273:3158–3165. [PubMed: 9452426]
11. Auchus RJ, Rainey WE. Adrenarche - physiology, biochemistry and human disease. *Clinical endocrinology*. 2004; 60:288–296. [PubMed: 15008992]
12. Azziz R. Diagnosing the diagnosis: why we must standardize the defining features of polycystic ovary syndrome. *Ann Clin Biochem*. 2008; 45:3–5. [PubMed: 18275667]
13. Azziz RWK, Reyna R, Key TJ, Knochauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. *The Journal of clinical endocrinology and metabolism*. 2004; 89:2745–2749. [PubMed: 15181052]
14. Biglieri EG, Herron MA, Brust N. 17 α -hydroxylation deficiency in man. *The Journal of clinical investigation*. 1966; 15:1945–1954.
15. Black SM, Harikrishna JA, Szklarz GD, Miller WL. The mitochondrial environment is required for activity of the cholesterol side-chain cleavage enzyme, cytochrome P450scc. *Proc Natl Acad Sci USA*. 1994; 91:7247–7251. [PubMed: 8041774]
16. Bloem LM, Storbeck KH, Schloms L, Swart AC. 11 β -hydroxyandrostenedione returns to the steroid arena: biosynthesis, metabolism and function. *Molecules*. 2013; 18:13228–13244. [PubMed: 24165582]
17. Bolte E, Wiqvist N, Diczfalussy E. Metabolism of dehydroepiandrosterone and dehydroepiandrosterone sulphate by the human foetus at midpregnancy. *Acta endocrinologica*. 1966; 52:583–597. [PubMed: 4223662]
18. Bongiovanni AM. The adrenogenital syndrome with deficiency of 3 β -hydroxysteroid dehydrogenase. *The Journal of clinical investigation*. 1962; 41:2086–2092. [PubMed: 13968789]
19. Bongiovanni AM. The adrenogenital syndrome with deficiency of 3 β -hydroxysteroid dehydrogenase. *The Journal of clinical investigation*. 1962; 41:2086. [PubMed: 13968789]
20. Bose HS, Sugawara T, Strauss JF 3rd, Miller WL. International Congenital Lipoid Adrenal Hyperplasia C. The pathophysiology and genetics of congenital lipoid adrenal hyperplasia. *The New England journal of medicine*. 1996; 335:1870–1878. [PubMed: 8948562]
21. Bose HS, Sugawara T, Strauss JF III, Miller WL. The pathophysiology and genetics of congenital lipoid adrenal hyperplasia. *The New England journal of medicine*. 1996; 335:1870–1878. [PubMed: 8948562]
22. Bose HS, Whittall RM, Huang MC, Baldwin MA, Miller WL. N-218 MLN64, a protein with StAR-like steroidogenic activity, is folded and cleaved similarly to StAR. *Biochemistry*. 2000; 39:11722–11731. [PubMed: 10995240]
23. Brunelli VL, Chiumello G, David M, Forest MG. Adrenarche does not occur in treated patients with congenital adrenal hyperplasia resulting from 21-hydroxylase deficiency. *Clinical endocrinology*. 1995; 42:461–466. [PubMed: 7621563]
24. Byrne GC, Perry YS, Winter JS. Kinetic analysis of adrenal 3 β -hydroxysteroid dehydrogenase activity during human development. *The Journal of clinical endocrinology and metabolism*. 1985; 60:934–939. [PubMed: 3156870]

25. Byrne GC, Perry YS, Winter JS. Steroid inhibitory effects upon human adrenal 3 beta-hydroxysteroid dehydrogenase activity. *The Journal of clinical endocrinology and metabolism*. 1986; 62:413–418. [PubMed: 3455692]
26. Campbell B. Adrenarche in comparative perspective. *Am J Hum Biol*. 2011; 23:44–52. [PubMed: 21140467]
27. Carmina E. Ovarian and Adrenal Hyperandrogenism. *Annals of the New York Academy of Sciences*. 2006; 1092:130–137. [PubMed: 17308139]
28. Carmina E, Azziz R. Diagnosis, phenotype, and prevalence of polycystic ovary syndrome. *Fertility and sterility*. 2006; 86 (Suppl 1):S7–8. [PubMed: 16798288]
29. Caron K, Soo S-C, Wetsel W, Stocco D, Clark B, Parker K. Targeted disruption of the mouse gene encoding steroidogenic acute regulatory protein provides insights into congenital lipid adrenal hyperplasia. *Proc Natl Acad Sci USA*. 1997; 94:11540–11545. [PubMed: 9326645]
30. Chung B, Matteson KJ, Voutilainen R, Mohandas TK, Miller WL. Human cholesterol side-chain cleavage enzyme, P450_{scc}: cDNA cloning, assignment of the gene to chromosome 15, and expression in the placenta. *Proc Natl Acad Sci USA*. 1986; 83:8962–8966. [PubMed: 3024157]
31. Chung BC, Picado-Leonard J, Haniu M, Bienkowski M, Hall PF, Shively JE, Miller WL. Cytochrome P450c17 (steroid 17 α -hydroxylase/17,20 lyase): cloning of human adrenal and testis cDNAs indicates the same gene is expressed in both tissues. *Proceedings of the National Academy of Sciences of the United States of America*. 1987; 84:407–411. [PubMed: 3025870]
32. Clark BJ, Wells J, King SR, Stocco DM. The purification, cloning and expression of a novel luteinizing hormone-induced mitochondrial protein in MA-10 mouse Leydig tumor cells. Characterization of the steroidogenic acute regulatory protein (StAR). *The Journal of biological chemistry*. 1994; 269:28314–28322. [PubMed: 7961770]
33. Conley AJ, Bird IM. The role of cytochrome P450 17 alpha-hydroxylase and 3 beta-hydroxysteroid dehydrogenase in the integration of gonadal and adrenal steroidogenesis via the delta 5 and delta 4 pathways of steroidogenesis in mammals. *Biol Reprod*. 1997; 56:789–799. [PubMed: 9096858]
34. Conley AJ, Pattison JC, Bird IM. Variations in adrenal androgen production among (nonhuman) primates. *Seminars in reproductive medicine*. 2004; 22:311–326. [PubMed: 15635499]
35. Costa-Santos M, Kater CE, Auchus RJ. Two Prevalent CYP17 Mutations and Genotype-Phenotype Correlations in 24 Brazilian Patients with 17-Hydroxylase Deficiency. *The Journal of clinical endocrinology and metabolism*. 2004; 89:49–60. [PubMed: 14715827]
36. Cutler GB Jr, Glenn M, Bush M, Hodgen GD, Graham CE, Loriaux DL. Adrenarche: a survey of rodents, domestic animals, and primates. *Endocrinology*. 1978; 103:2112–2118. [PubMed: 155005]
37. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, Chi KN, Jones RJ, Goodman OB, Saad F, Staffurth JN, Mainwaring P, Harland S, Flaig TW, Hutson TE, Cheng T, Patterson H, Hainsworth JD, Ryan CJ, Sternberg CN, Ellard SL, Fléchon A, Saleh M, Scholz M, Efstathiou E, Zivi A, Bianchini D, Loriot Y, Chieffo N, Kheoh T, Haqq CM, Scher HI. Investigators C-A. Abiraterone and increased survival in metastatic prostate cancer. *The New England journal of medicine*. 2011; 364:1995–2005. [PubMed: 21612468]
38. de Peretti E, Forest MG. Unconjugated dehydroepiandrosterone plasma levels in normal subjects from birth to adolescence in human: the use of a sensitive radioimmunoassay. *The Journal of clinical endocrinology and metabolism*. 1976; 43:982–991. [PubMed: 186482]
39. Deyashiki Y, Ogasawara A, Nakayama T, Nakanishi M, Miyabe Y, Sato K, Hara A. Molecular cloning of two human liver 3 alpha-hydroxysteroid/dihydrodiol dehydrogenase isoenzymes that are identical with chlordecone reductase and bile-acid binder. *The Biochemical journal*. 1994; 299 (Pt 2):545–552. [PubMed: 8172617]
40. Dhom G. The prepuberal and puberal growth of the adrenal (adrenarche). *Beitr Pathol*. 1973; 150:357–377. [PubMed: 4785066]
41. Dhom G. The Prepuberal and Puberal Growth of the Adrenal (Adrenarche). *Beiträge zur Pathologie*. 1973; 150:357–377. [PubMed: 4785066]

42. Dickerman Z, Grant DR, Faiman C, Winter JS. Intraadrenal steroid concentrations in man: zonal differences and developmental changes. *The Journal of clinical endocrinology and metabolism*. 1984; 59:1031–1036. [PubMed: 6593324]
43. Doberne Y, Levine LS, New MI. Elevated urinary testosterone and androstanediol in precocious adrenarche. *Pediatr Res*. 1975; 9:794–797. [PubMed: 171616]
44. Du X, Rosenfield RL, Qin K. KLF15 Is a transcriptional regulator of the human 17 β -hydroxysteroid dehydrogenase type 5 gene. A potential link between regulation of testosterone production and fat stores in women. *The Journal of clinical endocrinology and metabolism*. 2009; 94:2594–2601. [PubMed: 19366843]
45. Ducharme JR, Forest MG, De Peretti E, Sempe M, Collu R, Bertrand J. Plasma adrenal and gonadal sex steroids in human pubertal development. *The Journal of clinical endocrinology and metabolism*. 1976; 42:468–476. [PubMed: 130382]
46. Dufort I, Rheault P, Huang XF, Soucy P, Luu-The V. Characteristics of a highly labile human type 5 17 β -hydroxysteroid dehydrogenase. *Endocrinology*. 1999; 140:568–574. [PubMed: 9927279]
47. Falany CN. Enzymology of human cytosolic sulfotransferases. *FASEB journal: official publication of the Federation of American Societies for Experimental Biology*. 1997; 11:206–216. [PubMed: 9068609]
48. Fardella CE, Zhang LH, Mahachoklertwattana P, Lin D, Miller WL. Deletion of amino acids Asp487-Ser488-Phe489 in human cytochrome P450c17 causes severe 17 α -hydroxylase deficiency. *The Journal of clinical endocrinology and metabolism*. 1993; 77:489–493. [PubMed: 8345056]
49. Fluck CE, Miller WL, Auchus RJ. The 17, 20-lyase activity of cytochrome p450c17 from human fetal testis favors the Δ^5 steroidogenic pathway. *The Journal of clinical endocrinology and metabolism*. 2003; 88:3762–3766. [PubMed: 12915666]
50. Flück CE, Miller WL, Auchus RJ. The 17, 20-lyase activity of cytochrome P450c17 from human fetal testis favors the Δ^5 steroidogenic pathway. *The Journal of clinical endocrinology and metabolism*. 2003; 88:3762–3766. [PubMed: 12915666]
51. Frandsen VA, Stakemann G. The Site of Production of Oestrogenic Hormones in Human Pregnancy. 3. Further Observations on the Hormone Excretion in Pregnancy with Anencephalic Foetus. *Acta endocrinologica*. 1964; 47:265–276. [PubMed: 14218830]
52. Gassner HL, Toppari J, Quinteiro Gonzalez S, Miller WL. Near-miss apparent SIDS from adrenal crisis. *The Journal of pediatrics*. 2004; 145:178–183. [PubMed: 15289763]
53. Geissler WM, Davis DL, Wu L, Bradshaw KD, Patel S, Mendonca BB, Elliston KO, Wilson JD, Russell DW, Andersson S. Male pseudohermaphroditism caused by mutations of testicular 17 β -hydroxysteroid dehydrogenase 3. *Nature genetics*. 1994; 7:34–39. [PubMed: 8075637]
54. Gell JS, Atkins B, Margraf L, Mason JI, Sasano H, Rainey WE, Carr BR. Adrenarche is associated with decreased 3 β -hydroxysteroid dehydrogenase expression in the adrenal reticularis. *Endocrine research*. 1996; 22:723–728. [PubMed: 8969933]
55. Gell JS, Carr BR, Sasano H, Atkins B, Margraf L, Mason JI, Rainey WE. Adrenarche results from development of a 3 β -hydroxysteroid dehydrogenase-deficient adrenal reticularis. *The Journal of clinical endocrinology and metabolism*. 1998; 83:3695–3701. [PubMed: 9768686]
56. Geller DH, Auchus RJ, Miller WL. P450c17 mutations R347H and R358Q selectively disrupt 17,20-lyase activity by disrupting interactions with P450 oxidoreductase and cytochrome b5. *Molecular endocrinology*. 1999; 13:167–175. [PubMed: 9892022]
57. Genazzani AR, Facchinetti F, Petraglia F, Pintor C, Bagnoli F, Puggioni R, Corda R. Correlations between plasma levels of opioid peptides and adrenal androgens in prepuberty and puberty. *Journal of steroid biochemistry*. 1983; 19:891–895. [PubMed: 6310259]
58. Genazzani AR, Facchinetti F, Pintor C, Puggioni R, Parrini D, Petraglia F, Bagnoli F, Corda R. Proopiomelanocortin-related peptide plasma levels throughout prepuberty and puberty. *The Journal of clinical endocrinology and metabolism*. 1983; 57:56–61. [PubMed: 6304136]
59. Goodarzi MO, Azziz R. Diagnosis, epidemiology, and genetics of the polycystic ovary syndrome. *Best practice & research Clinical endocrinology & metabolism*. 2006; 20:193–205. [PubMed: 16772151]

60. Granot Z, Geiss-Friedlander R, Melamed-Book N, Eimerl S, Timberg R, Weiss AM, Hales KH, Hales DB, Stocco DM, Orly J. Proteolysis of normal and mutated steroidogenic acute regulatory proteins in the mitochondria: the fate of unwanted proteins. *Molecular endocrinology*. 2003; 17:2461–2476. [PubMed: 12958217]
61. Griffin JE. Androgen resistance--the clinical and molecular spectrum. *The New England journal of medicine*. 1992; 326:611–618. [PubMed: 1734252]
62. Guercio G, Rivarola MA, Chaler E, Maceiras M, Belgorosky A. Relationship between the GH/IGF-I axis, insulin sensitivity, and adrenal androgens in normal prepubertal and pubertal boys. *The Journal of clinical endocrinology and metabolism*. 2002; 87:1162–1169. [PubMed: 11889181]
63. Hauffa BP, Miller WL, Grumbach MM, Conte FA, Kaplan SL. Congenital adrenal hyperplasia due to deficient cholesterol side-chain cleavage activity (20, 22-desmolase) in a patient treated for 18 years. *Clinical endocrinology*. 1985; 23:481–493. [PubMed: 3841304]
64. Herman-Giddens ME, Slora EJ, Wasserman RC, Bourdony CJ, Bhapkar MV, Koch GG, Hasemeier CM. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. *Pediatrics*. 1997; 99:505–512. [PubMed: 9093289]
65. Hochberg Z. Evo-Devo of child growth III: premature juvenility as an evolutionary trade-off. *Horm Res Paediatr*. 2010; 73:430–437. [PubMed: 20395652]
66. Hochberg Z. Juvenility in the context of life history theory. *Archives of disease in childhood*. 2008; 93:534–539. [PubMed: 18337281]
67. Hu MC, Hsu NC, El Hadj NB, Pai CI, Chu HP, Wang CK, Chung BC. Steroid deficiency syndromes in mice with targeted disruption of Cyp11a1. *Molecular endocrinology*. 2002; 16:1943–1950. [PubMed: 12145347]
68. Hui XG, Akahira J, Suzuki T, Nio M, Nakamura Y, Suzuki H, Rainey WE, Sasano H. Development of the human adrenal zona reticularis: morphometric and immunohistochemical studies from birth to adolescence. *The Journal of endocrinology*. 2009; 203:241–252. [PubMed: 19723922]
69. Ibanez L, Dimartino-Nardi J, Potau N, Saenger P. Premature adrenarche--normal variant or forerunner of adult disease? *Endocrine reviews*. 2000; 21:671–696. [PubMed: 11133068]
70. Imai T, Globerman H, Gertner JM, Kagawa N, Waterman MR. Expression and purification of functional human 17 alpha-hydroxylase/17,20-lyase (P450c17) in *Escherichia coli*. Use of this system for study of a novel form of combined 17 alpha-hydroxylase/17,20-lyase deficiency. *The Journal of biological chemistry*. 1993; 268:19681–19689. [PubMed: 8396144]
71. Imai T, Yanase T, Waterman MR, Simpson ER, Pratt JJ. Canadian Mennonites and individuals residing in the Friesland region of The Netherlands share the same molecular basis of 17 alpha-hydroxylase deficiency. *Human genetics*. 1992; 89:95–96. [PubMed: 1577471]
72. Imperato-McGinley J, Guerrero L, Gautier T, Peterson RE. Steroid 5alpha-reductase deficiency in man: an inherited form of male pseudohermaphroditism. *Science*. 1974; 186:1213–1215. [PubMed: 4432067]
73. Jakobsson J, Palonek E, Lorentzon M, Ohlsson C, Rane A, Ekstrom L. A novel polymorphism in the 17beta-hydroxysteroid dehydrogenase type 5 (aldo-keto reductase 1C3) gene is associated with lower serum testosterone levels in caucasian men. *Pharmacogenomics J*. 2007; 7:282–289. [PubMed: 16983398]
74. John ME, John MC, Boggaram V, Simpson ER, Waterman MR. Transcriptional regulation of steroid hydroxylase genes by corticotropin. *Proceedings of the National Academy of Sciences of the United States of America*. 1986; 83:4715–4719. [PubMed: 3014507]
75. Kagimoto M, Winter JS, Kagimoto K, Simpson ER, Waterman MR. Structural characterization of normal and mutant human steroid 17 alpha-hydroxylase genes: molecular basis of one example of combined 17 alpha-hydroxylase/17,20 lyase deficiency. *Molecular endocrinology*. 1988; 2:564–570. [PubMed: 2843762]
76. Kamrath C, Hochberg Z, Hartmann MF, Remer T, Wudy SA. Increased activation of the alternative “backdoor” pathway in patients with 21-hydroxylase deficiency: evidence from urinary steroid hormone analysis. *The Journal of clinical endocrinology and metabolism*. 2012; 97:E367–375. [PubMed: 22170725]

77. Kaplowitz P, Soldin SJ. Steroid profiles in serum by liquid chromatography-tandem mass spectrometry in infants with genital hair. *J Pediatr Endocrinol Metab.* 2007; 20:597–605. [PubMed: 17642420]
78. Katagiri M, Kagawa N, Waterman MR. The role of cytochrome b₅ in the biosynthesis of androgens by human P450c17. *Arch Biochem Biophys.* 1995; 317:343–347. [PubMed: 7893148]
79. Kaufman FR, Stanczyk FZ, Matteri RK, Gentzschein E, Delgado C, Lobo RA. Dehydroepiandrosterone and dehydroepiandrosterone sulfate metabolism in human genital skin. *Fertility and sterility.* 1990; 54:251–254. [PubMed: 2143146]
80. Keeney DS, Jenkins CM, Waterman MR. Developmentally regulated expression of adrenal 17 alpha-hydroxylase cytochrome P450 in the mouse embryo. *Endocrinology.* 1995; 136:4872–4879. [PubMed: 7588219]
81. Kenny FM, Preeyasombat C, Migeon CJ. Cortisol production rate. II. Normal infants, children, and adults. *Pediatrics.* 1966; 37:34–42. [PubMed: 5323003]
82. Khanna M, Qin KN, Klisak I, Belkin S, Sparkes RS, Cheng KC. Localization of multiple human dihydrodiol dehydrogenase (DDH1 and DDH2) and chlordecone reductase (CHDR) genes in chromosome 10 by the polymerase chain reaction and fluorescence in situ hybridization. *Genomics.* 1995; 25:588–590. [PubMed: 7789999]
83. Kirkland RT, Kirkland JL, Johnson CM, Horning MG, Librik L, Clayton GW. Congenital lipoid adrenal hyperplasia in an eight-year-old phenotypic female. *The Journal of clinical endocrinology and metabolism.* 1973; 36:488–496. [PubMed: 4685387]
84. Kirschner MA, Bardin CW. Androgen production and metabolism in normal and virilized women. *Metabolism: clinical and experimental.* 1972; 21:667–688. [PubMed: 4562220]
85. Koritz SB, Kumar AM. On the mechanism of action of the adrenocorticotrophic hormone. The stimulation of the activity of enzymes involved in pregnenolone synthesis. *The Journal of biological chemistry.* 1970; 245:152–159. [PubMed: 4391541]
86. Korth-Schutz S, Levine LS, New MI. Dehydroepiandrosterone sulfate (DS) levels, a rapid test for abnormal adrenal androgen secretion. *The Journal of clinical endocrinology and metabolism.* 1976; 42:1005–1013. [PubMed: 180041]
87. Kristiansen SB, Endoh A, Casson PR, Buster JE, Hornsby PJ. Induction of steroidogenic enzyme genes by insulin and IGF-I in cultured adult human adrenocortical cells. *Steroids.* 1997; 62:258–265. [PubMed: 9055386]
88. Kumagai J, Hofland J, Erkens-Schulze S, Dits NF, Steenbergen J, Jenster G, Homma Y, de Jong FH, van Weerden WM. Intratumoral conversion of adrenal androgen precursors drives androgen receptor-activated cell growth in prostate cancer more potently than de novo steroidogenesis. *Prostate.* 2013; 73:1636–1650. [PubMed: 23996639]
89. Labrie F, Simard J, Luu-The V, Belanger A, Pelletier G. Structure, function and tissue-specific gene expression of 3beta-hydroxysteroid dehydrogenase/5-ene-4-ene isomerase enzymes in classical and peripheral intracrine steroidogenic tissues. *J Steroid Biochem Mol Biol.* 1992; 43:805–826. [PubMed: 22217825]
90. Lachance Y, Luu-The V, Labrie C, Simard J, Dumont M, de Launoit Y, Guerin S, Leblanc G, Labrie F. Characterization of human 3 beta-hydroxysteroid dehydrogenase/delta 5-delta 4-isomerase gene and its expression in mammalian cells. *The Journal of biological chemistry.* 1990; 265:20469–20475. [PubMed: 2243100]
91. Lachance Y, Luu-The V, Verreault H, Dumont M, Rheume E, Leblanc G, Labrie F. Structure of the human type II 3 beta-hydroxysteroid dehydrogenase/delta 5-delta 4 isomerase (3 beta-HSD) gene: adrenal and gonadal specificity. *DNA and cell biology.* 1991; 10:701–711. [PubMed: 1741954]
92. Lam CW, Arlt W, Chan CK, Honour JW, Lin CJ, Tong SF, Choy KW, Miller WL. Mutation of proline 409 to arginine in the meander region of cytochrome p450c17 causes severe 17 alpha-hydroxylase deficiency. *Molecular genetics and metabolism.* 2001; 72:254–259. [PubMed: 11243732]
93. Lebrethon MC, Jaillard C, Naville D, Begeot M, Saez JM. Effects of transforming growth factor-beta 1 on human adrenocortical fasciculata-reticularis cell differentiated functions. *The Journal of clinical endocrinology and metabolism.* 1994; 79:1033–1039. [PubMed: 7962271]

94. Lee-Robichaud P, Wright JN, Akhtar ME, Akhtar M. Modulation of the activity of human 17 α -hydroxylase-17,20-lyase (CYP17) by cytochrome b₅: endocrinological and mechanistic implications. *The Biochemical journal*. 1995; 308:901–908. [PubMed: 8948449]
95. Lee TC, Miller WL, Auchus RJ. Medroxyprogesterone acetate and dexamethasone are competitive inhibitors of different human steroidogenic enzymes. *The Journal of clinical endocrinology and metabolism*. 1999; 84:2104–2110. [PubMed: 10372718]
96. Likitmaskul S, Cowell CT, Donaghue K, Kreutzmann DJ, Howard NJ, Blades B, Silink M. ‘Exaggerated adrenarche’ in children presenting with premature adrenarche. *Clinical endocrinology*. 1995; 42:265–272. [PubMed: 7758231]
97. Lin D, Sugawara T, Strauss JF 3rd, Clark BJ, Stocco DM, Saenger P, Rogol A, Miller WL. Role of steroidogenic acute regulatory protein in adrenal and gonadal steroidogenesis. *Science*. 1995; 267:1828–1831. [PubMed: 7892608]
98. Lin HK, Jez JM, Schlegel BP, Peehl DM, Pachter JA, Penning TM. Expression and characterization of recombinant type 2 3 α -hydroxysteroid dehydrogenase (HSD) from human prostate: demonstration of bifunctional 3 α /17 β -HSD activity and cellular distribution. *Molecular endocrinology*. 1997; 11:1971–1984. [PubMed: 9415401]
99. Lorence MC, Murry BA, Trant JM, Mason JI. Human 3 β -hydroxysteroid dehydrogenase/delta 5----4 isomerase from placenta: expression in nonsteroidogenic cells of a protein that catalyzes the dehydrogenation/isomerization of C21 and C19 steroids. *Endocrinology*. 1990; 126:2493–2498. [PubMed: 2139411]
100. Luu-The V. Assessment of steroidogenesis and steroidogenic enzyme functions. *J Steroid Biochem Mol Biol*. 2013; 137:176–182. [PubMed: 23770321]
101. Luu The V, Lachance Y, Labrie C, Leblanc G, Thomas JL, Strickler RC, Labrie F. Full length cDNA structure and deduced amino acid sequence of human 3 β -hydroxy-5-ene steroid dehydrogenase. *Molecular endocrinology*. 1989; 3:1310–1312. [PubMed: 2779585]
102. Mahesh VB, Greenblatt RB, Aydar CK, Roy S, Puebla RA, Ellegood JO. Urinary Steroid Excretion Patterns in Hirsutism. I. Use of Adrenal and Ovarian Suppression Tests in the Study of Hirsutism. *The Journal of clinical endocrinology and metabolism*. 1964; 24:1283–1292. [PubMed: 14243172]
103. Mapes S, Corbin CJ, Tarantal A, Conley A. The primate adrenal zona reticularis is defined by expression of cytochrome b₅, 17 α -hydroxylase/17,20-lyase cytochrome P450 (P450c17) and NADPH-cytochrome P450 reductase (reductase) but not 3 β -hydroxysteroid dehydrogenase/delta5-4 isomerase (3 β -HSD). *The Journal of clinical endocrinology and metabolism*. 1999; 84:3382–3385. [PubMed: 10487714]
104. Matocha M, Waterman MR. Synthesis and processing of mitochondrial steroid hydroxylases. *In vivo* maturation of the precursor of cytochrome P450_{scc}, cytochrome P450 and adrenodoxin. *The Journal of biological chemistry*. 1985; 260:2259–2265.
105. McCartin S, Russell AJ, Fisher RA, Wallace AM, Arnhold IJ, Mason JI, Varley J, Mendonca BB, Sutcliffe RG. Phenotypic variability and origins of mutations in the gene encoding 3 β -hydroxysteroid dehydrogenase type II. *Journal of molecular endocrinology*. 2000; 24:75–82. [PubMed: 10656999]
106. Mellon SH, Shively JE, Miller WL. Human proopiomelanocortin-(79-96), a proposed androgen stimulatory hormone, does not affect steroidogenesis in cultured human fetal adrenal cells. *The Journal of clinical endocrinology and metabolism*. 1991; 72:19–22. [PubMed: 1846003]
107. Merke DP, Chrousos GP, Eisenhofer G, Weise M, Keil MF, Rogol AD, Van Wyk JJ, Bornstein SR. Adrenomedullary dysplasia and hypofunction in patients with classic 21-hydroxylase deficiency. *The New England journal of medicine*. 2000; 343:1362–1368. [PubMed: 11070100]
108. Miller WL, Auchus RJ. The molecular biology, biochemistry, and physiology of human steroidogenesis and its disorders. *Endocrine reviews*. 2011; 32:81–151. [PubMed: 21051590]
109. Moisan AM, Ricketts ML, Tardy V, Desrochers M, Mebarki F, Chaussain JL, Cabrol S, Raux-Demay MC, Forest MG, Sippell WG, Peter M, Morel Y, Simard J. New insight into the molecular basis of 3 β -hydroxysteroid dehydrogenase deficiency: identification of eight mutations in the HSD3B2 gene in eleven patients from seven new families and comparison of the functional properties of twenty-five mutant enzymes. *The Journal of clinical endocrinology and metabolism*. 1999; 84:4410–4425. [PubMed: 10599696]

110. Moisan AM, Ricketts ML, Tardy V, Desrochers M, Mebarki F, Chaussain JL, Cabrol S, Raux-Demay MC, Forest MG, Sippell WG, Peter M, Morel Y, Simard J. New insight into the molecular basis of 3 β -hydroxysteroid dehydrogenase deficiency: identification of eight mutations in the HSD3B2 gene eleven patients from seven new families and comparison of the functional properties of twenty-five mutant enzymes. *The Journal of clinical endocrinology and metabolism*. 1999; 84:4410–4425. [PubMed: 10599696]
111. Moran CAR. The role of the adrenal cortex in polycystic ovary syndrome. *Obstet Gynecol Clin North Am*. 2001; 28:63–75. [PubMed: 11293004]
112. Moran C, Reyna R, Boots LS, Azziz R. Adrenocortical hyperresponsiveness to corticotropin in polycystic ovary syndrome patients with adrenal androgen excess. *Fertility and sterility*. 2004; 81:126–131. [PubMed: 14711555]
113. Morel Y, Mebarki F, Rheume E, Sanchez R, Forest MG, Simard J. Structure-function relationships of 3 β -hydroxysteroid dehydrogenase: contribution made by the molecular genetics of 3 β -hydroxysteroid dehydrogenase deficiency. *Steroids*. 1997; 62:176–184. [PubMed: 9029734]
114. Nakamura Y, Gang HX, Suzuki T, Sasano H, Rainey WE. Adrenal changes associated with adrenarche. *Rev Endocr Metab Disord*. 2009; 10:19–26. [PubMed: 18821019]
115. Nakamura Y, Hornsby PJ, Casson P, Morimoto R, Satoh F, Xing Y, Kennedy MR, Sasano H, Rainey WE. Type 5 17 β -hydroxysteroid dehydrogenase (AKR1C3) contributes to testosterone production in the adrenal reticularis. *The Journal of clinical endocrinology and metabolism*. 2009; 94:2192–2198. [PubMed: 19336506]
116. Nelson DR, Kamataki T, Waxman DJ, Guengerich FP, Estabrook RW, Feyereisen R, Gonzalez FJ, Coon MJ, Gunsalus IC, Gotoh O, et al. The P450 superfamily: update on new sequences, gene mapping, accession numbers, early trivial names of enzymes, and nomenclature. *DNA and cell biology*. 1993; 12:1–51. [PubMed: 7678494]
117. Noordam C, Dhir V, McNelis JC, Schlereth F, Hanley NA, Krone N, Smeitink JA, Smeets R, Sweep FC, Claahsen-van der Grinten HL, Arlt W. Inactivating PAPSS2 mutations in a patient with premature pubarche. *The New England journal of medicine*. 2009; 360:2310–2318. [PubMed: 19474428]
118. Nowell S, Falany CN. Pharmacogenetics of human cytosolic sulfotransferases. *Oncogene*. 2006; 25:1673–1678. [PubMed: 16550167]
119. O'Connell Y, McKenna TJ, Cunningham SK. β -Lipotropin-stimulated adrenal steroid production. *Steroids*. 1996; 61:332–336. [PubMed: 8738840]
120. Onoda M, Hall PF. Cytochrome b₅ stimulates purified testicular microsomal cytochrome P450 (C₂₁ side-chain cleavage). *Biochem Biophys Res Commun*. 1982; 108:454–460. [PubMed: 7150304]
121. Orentreich N, Brind JL, Rizer RL, Vogelmann JH. Age changes and sex differences in serum dehydroepiandrosterone sulfate concentrations throughout adulthood. *The Journal of clinical endocrinology and metabolism*. 1984; 59:551–555. [PubMed: 6235241]
122. Otterness DM, Her C, Aksoy S, Kimura S, Wieben ED, Weinshilboum RM. Human dehydroepiandrosterone sulfotransferase gene: molecular cloning and structural characterization. *DNA and cell biology*. 1995; 14:331–341. [PubMed: 7710689]
123. Pang S. Congenital adrenal hyperplasia owing to 3 β -hydroxysteroid dehydrogenase deficiency. *Endocrinol Metab Clin North Am*. 2001; 30:81–99. vi–vii. [PubMed: 11344940]
124. Parker CR Jr, BD, Greenblatt RB, Mahesh VB. Peripheral, ovarian, and adrenal vein steroids in hirsute women: acute effects of human chorionic gonadotropin and adrenocorticotrophic hormone. *Fertility and sterility*. 1975; 26:877–888. [PubMed: 126875]
125. Parker, L.; Lifrak, E.; Shivley, J., et al. Human adrenal gland cortical androgen-stimulating hormone (CASH) is identical with a portion of the joining peptide of pituitary pro-opiomelanocortin (POMC). In. 71st Annual Meet of The Endocrine Society; 1989;
126. Parker, LN. Adrenal Androgens in Clinical Medicine. Academic Press, Inc; 1989. p. 615
127. Parker LN, Sack J, Fisher DA, Odell WD. The adrenarche: prolactin, gonadotropins, adrenal androgens, and cortisol. *The Journal of clinical endocrinology and metabolism*. 1978; 46:396–401. [PubMed: 156191]

128. Pelletier G. Expression of steroidogenic enzymes and sex-steroid receptors in human prostate. *Best practice & research Clinical endocrinology & metabolism*. 2008; 22:223–228. [PubMed: 18471781]
129. Penhoat A, Rainey WE, Viard I, Saez JM. Regulation of adrenal cell-differentiated functions by growth factors. *Hormone research*. 1994; 42:39–43. [PubMed: 7959633]
130. Penhoat A, Sanchez P, Jaillard C, Langlois D, Begeot M, Saez JM. Human proopiomelanocortin-(79-96), a proposed cortical androgen-stimulating hormone, does not affect steroidogenesis in cultured human adult adrenal cells. *The Journal of clinical endocrinology and metabolism*. 1991; 72:23–26. [PubMed: 1846004]
131. Penning TM, Burczynski ME, Jez JM, Hung CF, Lin HK, Ma H, Moore M, Palackal N, Ratnam K. Human 3 α -hydroxysteroid dehydrogenase isoforms (AKR1C1-AKR1C4) of the aldo-keto reductase superfamily: functional plasticity and tissue distribution reveals roles in the inactivation and formation of male and female sex hormones. *The Biochemical journal*. 2000; 351:67–77. [PubMed: 10998348]
132. Qin K, Ehrmann DA, Cox N, Refetoff S, Rosenfield RL. Identification of a functional polymorphism of the human type 5 17 β -hydroxysteroid dehydrogenase gene associated with polycystic ovary syndrome. *The Journal of clinical endocrinology and metabolism*. 2006; 91:270–276. [PubMed: 16263811]
133. Rainey WE, Carr BR, Sasano H, Suzuki T, Mason JI. Dissecting human adrenal androgen production. *Trends Endocrinol Metab*. 2002; 13:234–239. [PubMed: 12128283]
134. Rainey WE, Rehman KS, Carr BR. The human fetal adrenal: making adrenal androgens for placental estrogens. *Seminars in reproductive medicine*. 2004; 22:327–336. [PubMed: 15635500]
135. Rege J, Nakamura Y, Satoh F, Morimoto R, Kennedy MR, Layman LC, Honma S, Sasano H, Rainey WE. Liquid chromatography-tandem mass spectrometry analysis of human adrenal vein 19-carbon steroids before and after ACTH stimulation. *The Journal of clinical endocrinology and metabolism*. 2013; 98:1182–1188. [PubMed: 23386646]
136. Reiter EO, Fuldauer VG, Root AW. Secretion of the adrenal androgen, dehydroepiandrosterone sulfate, during normal infancy, childhood, and adolescence, in sick infants, and in children with endocrinologic abnormalities. *The Journal of pediatrics*. 1977; 90:766–770. [PubMed: 140222]
137. Rezvani I, Garibaldi LR, Digeorge AM, Artman HG. Disproportionate suppression of dehydroepiandrosterone sulfate (DHEAS) in treated patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Pediatric research*. 1983; 17:131–134. [PubMed: 6219334]
138. Rheaume E, Lachance Y, Zhao HF, Breton N, Dumont M, de Launoit Y, Trudel C, Luu-The V, Simard J, Labrie F. Structure and expression of a new complementary DNA encoding the almost exclusive 3 β -hydroxysteroid dehydrogenase/delta 5-delta 4-isomerase in human adrenals and gonads. *Molecular endocrinology*. 1991; 5:1147–1157. [PubMed: 1944309]
139. Rheaume E, Simard J, Morel Y, Mebarki F, Zachmann M, Forest MG, New MI, Labrie F. Congenital adrenal hyperplasia due to point mutations in the type II 3 β -hydroxysteroid dehydrogenase gene. *Nature genetics*. 1992; 1:239–245. [PubMed: 1363812]
140. Rich BH, Rosenfield RL, Lucky AW, Helke JC, Otto P. Adrenarche: changing adrenal response to adrenocorticotropin. *The Journal of clinical endocrinology and metabolism*. 1981; 52:1129–1136. [PubMed: 6262366]
141. Rosenfield RL. Hirsutism and the variable response of the pilosebaceous unit to androgen. *The journal of investigative dermatology Symposium proceedings/the Society for Investigative Dermatology, Inc [and] European Society for Dermatological Research*. 2005; 10:205–208.
142. Rosenfield RL, Grossman BJ, Ozoa N. Plasma 17-ketosteroids and testosterone in prepubertal children before and after ACTH administration. *The Journal of clinical endocrinology and metabolism*. 1971; 33:249–253. [PubMed: 4327687]
143. Rosenfield RL, Lucky AW. Acne, hirsutism, and alopecia in adolescent girls. Clinical expressions of androgen excess. *Endocrinol Metab Clin North Am*. 1993; 22:507–532. [PubMed: 8243445]
144. Rosenfield RL, Rich BH, Lucky AW. Adrenarche as a cause of benign pseudopuberty in boys. *The Journal of pediatrics*. 1982; 101:1005–1009. [PubMed: 6216332]
145. Rubtsov P, Karmanov M, Sverdlova P, Spirin P, Tiulpakov A. A novel homozygous mutation in CYP11A1 gene is associated with late-onset adrenal insufficiency and hypospadias in a 46, XY

- patient. *The Journal of clinical endocrinology and metabolism*. 2009; 94:936–939. [PubMed: 19116240]
146. Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, Fizazi K, Mainwaring P, Piulats JM, Ng S, Carles J, Mulders PF, Basch E, Small EJ, Saad F, Schrijvers D, Van Poppel H, Mukherjee SD, Suttman H, Gerritsen WR, Flaig TW, George DJ, Yu EY, Efsthathiou E, Pantuck A, Winkvist E, Higano CS, Taplin ME, Park Y, Kheoh T, Griffin T, Scher HI, Rathkopf DE. Investigators C-A. Abiraterone in metastatic prostate cancer without previous chemotherapy. *The New England journal of medicine*. 2013; 368:138–148. [PubMed: 23228172]
 147. Sahakitrunguang T, Tee MK, Blackett PR, Miller WL. Partial defect in the cholesterol side-chain cleavage enzyme P450_{scc} (CYP11A1) resembling nonclassic congenital lipid adrenal hyperplasia. *The Journal of clinical endocrinology and metabolism*. 2011; 96:792–798. [PubMed: 21159840]
 148. Sandison AT. A form of lipoidosis of the adrenal cortex in an infant. *Archives of disease in childhood*. 1955; 30:538–541. [PubMed: 13275986]
 149. Shikita M, Hall PF. The stoichiometry of the conversion of cholesterol and hydroxycholesterols to pregnenolone (3 β -hydroxypregn-5-en-20-one) catalysed by adrenal cytochrome P-450. *Proceedings of the National Academy of Sciences of the United States of America*. 1974; 71:1441–1445. [PubMed: 4151518]
 150. Shimizu K, Hayano M, Gut M, Dorfman RI. The transformation of 20 α -hydroxysterol to isocaproic acid and C₂₁ steroids. *The Journal of biological chemistry*. 1961; 236:695–699.
 151. Siiteri PK, MacDonald PC. The utilization of circulating dehydroisoandrosterone sulfate for estrogen synthesis during human pregnancy. *Steroids*. 1963; 2:713–730.
 152. Simard J, Durocher F, Mebarki F, Turgeon C, Sanchez R, Labrie Y, Couet J, Trudel C, Rheume E, Morel Y, Luu-The V, Labrie F. Molecular biology and genetics of the 3 β -hydroxysteroid dehydrogenase/delta5-delta4 isomerase gene family. *The Journal of endocrinology*. 1996; 150 (Suppl):S189–207. [PubMed: 8943802]
 153. Simard J, Ricketts ML, Gingras S, Soucy P, Feltus FA, Melner MH. Molecular biology of the 3 β -hydroxysteroid dehydrogenase/delta5-delta4 isomerase gene family. *Endocrine reviews*. 2005; 26:525–582. [PubMed: 15632317]
 154. Simpson ER, Mason JJ, John ME, Zuber MX, Rodgers RJ, Waterman MR. Regulation of the biosynthesis of steroidogenic enzymes. *Journal of steroid biochemistry*. 1987; 27:801–805. [PubMed: 2826909]
 155. Sirianni R, Rehman KS, Carr BR, Parker CR Jr, Rainey WE. Corticotropin-releasing hormone directly stimulates cortisol and the cortisol biosynthetic pathway in human fetal adrenal cells. *The Journal of clinical endocrinology and metabolism*. 2005; 90:279–285. [PubMed: 15494460]
 156. Smail PJ, Faiman C, Hobson WC, Fuller GB, Winter JSD. Further Studies on Adrenarche in Nonhuman Primates. *Endocrinology*. 1982; 111:844–848. [PubMed: 6213402]
 157. Smith CP, Dunger DB, Williams AJ, Taylor AM, Perry LA, Gale EA, Preece MA, Savage MO. Relationship between insulin, insulin-like growth factor I, and dehydroepiandrosterone sulfate concentrations during childhood, puberty, and adult life. *The Journal of clinical endocrinology and metabolism*. 1989; 68:932–937. [PubMed: 2523898]
 158. Sparkes RS, Klisak I, Miller WL. Regional mapping of genes encoding human steroidogenic enzymes: P450_{scc} to 15q23-q24, adrenodoxin to 11q22; adrenodoxin reductase to 17q24-q25; and P450_{c17} to 10q24-q25. *DNA and cell biology*. 1991; 10:359–365. [PubMed: 1863359]
 159. Speiser PW, White PC. Congenital adrenal hyperplasia. *The New England journal of medicine*. 2003; 349:776–788. [PubMed: 12930931]
 160. Stahl NLTC, Beauchamps G, Greenblatt RB. Serum testosterone levels in hirsute women: a comparison of adrenal, ovarian and peripheral vein values. *Obstet Gynecol*. 1973; 41:650–654. [PubMed: 4735317]
 161. Stahl NLTC, Greenblatt RB. Ovarian, adrenal, and peripheral testosterone levels in the polycystic ovary syndrome. *American Journal of Obstetrics and Gynecology*. 1973; 117:194–200. [PubMed: 4728868]
 162. Stocco DM, Clark BJ. Regulation of the acute production of steroids in steroidogenic cells. *Endocrine reviews*. 1996; 17:221–244. [PubMed: 8771357]

163. Storbeck KH, Bloem LM, Africander D, Schloms L, Swart P, Swart AC. 11beta-Hydroxydihydrotestosterone and 11-ketodihydrotestosterone, novel C19 steroids with androgenic activity: a putative role in castration resistant prostate cancer? *Molecular and cellular endocrinology*. 2013; 377:135–146. [PubMed: 23856005]
164. Strott CA. Sulfonation and molecular action. *Endocrine reviews*. 2002; 23:703–732. [PubMed: 12372849]
165. Sugawara T, Holt JA, Driscoll D, Strauss JF 3rd, Lin D, Miller WL, Patterson D, Clancy KP, Hart IM, Clark BJ, et al. Human steroidogenic acute regulatory protein: functional activity in COS-1 cells, tissue-specific expression, and mapping of the structural gene to 8p11.2 and a pseudogene to chromosome 13. *Proceedings of the National Academy of Sciences of the United States of America*. 1995; 92:4778–4782. [PubMed: 7761400]
166. Suzuki T, Sasano H, Takeyama J, Kaneko C, Freije WA, Carr BR, Rainey WE. Developmental changes in steroidogenic enzymes in human postnatal adrenal cortex: immunohistochemical studies. *Clinical endocrinology*. 2000; 53:739–747. [PubMed: 11155097]
167. Talbot NB, Butler AM, Maclachlan EA. The Effect of Testosterone and Allied Compounds on the Mineral, Nitrogen, and Carbohydrate Metabolism of a Girl with Addison's Disease. *The Journal of clinical investigation*. 1943; 22:583–593. [PubMed: 16695041]
168. Thomas JL, Myers RP, Strickler RC. Human placental 3 beta-hydroxy-5-ene-steroid dehydrogenase and steroid 5----4-ene-isomerase: purification from mitochondria and kinetic profiles, biophysical characterization of the purified mitochondrial and microsomal enzymes. *Journal of steroid biochemistry*. 1989; 33:209–217. [PubMed: 2770297]
169. Thomas JL, Myers RP, Strickler RC. Human placental 3 β -hydroxy-5-ene-steroid dehydrogenase and steroid 5/4-ene-isomerase: purification from mitochondria and kinetic profiles, biophysical characterization of the purified mitochondrial and microsomal enzymes. *Journal of steroid biochemistry*. 1989; 33:209–217. [PubMed: 2770297]
170. Topor LS, Asai M, Dunn J, Majzoub JA. Cortisol stimulates secretion of dehydroepiandrosterone in human adrenocortical cells through inhibition of 3 β HSD2. *The Journal of clinical endocrinology and metabolism*. 2011; 96:E31–39. [PubMed: 20943790]
171. Toscano V, Balducci R, Adamo MV, Mangiantini A, Cives C, Boscherini B. Changes in steroid pattern following acute and chronic adrenocorticotropin administration in premature adrenarche. *Journal of steroid biochemistry*. 1989; 32:321–326. [PubMed: 2537914]
172. Trivax B, Azziz R. Diagnosis of polycystic ovary syndrome. *Clin Obstet Gynecol*. 2007; 50:168–177. [PubMed: 17304034]
173. Tsujishita Y, Hurley JH. Structure and lipid transport mechanism of a StAR-related domain. *Nat Struct Biol*. 2000; 7:408–414. [PubMed: 10802740]
174. Tzingounis VAAM, Natrajan PK, Greenblatt RB. The significance of adrenal and ovarian catheterization in patients with polycystic ovary syndrome. *Int J Gynaecol Obstet*. 1978; 17:78–82. [PubMed: 39844]
175. Vickery LE. Molecular recognition and electron transfer in mitochondrial steroid hydroxylase systems. *Steroids*. 1997; 62:124–127. [PubMed: 9029726]
176. Voutilainen R, Perheentupa J, Apter D. Benign premature adrenarche: clinical features and serum steroid levels. *Acta Paediatr Scand*. 1983; 72:707–711. [PubMed: 6227200]
177. Wajchenberg BLAS, Okada H, Czeresnia CE, Peixoto S, Lima SS, Goldman J. Determination of the source(s) of androgen overproduction in hirsutism associated with polycystic ovary syndrome by simultaneous adrenal and ovarian venous catheterization. Comparison with the dexamethasone suppression test. *The Journal of clinical endocrinology and metabolism*. 1986; 63:1204–1210. [PubMed: 3760120]
178. Watari H, Arakane F, Moog-Lutz C, Kallen CB, Tomasetto C, Gerton GL, Rio MC, Baker ME, Strauss JF 3rd. MLN64 contains a domain with homology to the steroidogenic acute regulatory protein (StAR) that stimulates steroidogenesis. *Proceedings of the National Academy of Sciences of the United States of America*. 1997; 94:8462–8467. [PubMed: 9237999]
179. Weber A, Clark AJ, Perry LA, Honour JW, Savage MO. Diminished adrenal androgen secretion in familial glucocorticoid deficiency implicates a significant role for ACTH in the induction of adrenarche. *Clinical endocrinology*. 1997; 46:431–437. [PubMed: 9196605]

180. Weinshilboum RM, Otterness DM, Aksoy IA, Wood TC, Her C, Raftogianis RB. Sulfation and sulfotransferases 1: Sulfotransferase molecular biology: cDNAs and genes. *FASEB journal: official publication of the Federation of American Societies for Experimental Biology*. 1997; 11:3–14. [PubMed: 9034160]
181. Wilson JD, Auchus RJ, Leihy MW, Guryev OL, Estabrook RW, Osborn SM, Shaw G, Renfree MB. 5 α -androstane-3 α ,17 β -diol is formed in tammar wallaby pouch young testes by a pathway involving 5 α -pregnane-3 α ,17 α -diol-20-one as a key intermediate. *Endocrinology*. 2003; 144:575–580. [PubMed: 12538619]
182. Yanase T, Simpson ER, Waterman MR. 17 α -hydroxylase/17,20-lyase deficiency: from clinical investigation to molecular definition. *Endocrine reviews*. 1991; 12:91–108. [PubMed: 2026124]
183. Yang X, Iwamoto K, Wang M, Artwohl J, Mason JJ, Pang S. Inherited congenital adrenal hyperplasia in the rabbit is caused by a deletion in the gene encoding cytochrome P450 cholesterol side-chain cleavage enzyme. *Endocrinology*. 1993; 132:1977–1982. [PubMed: 7682938]
184. Yasukochi Y, Masters BS. Some properties of a detergent-solubilized NADPH-cytochrome c(cytochrome P-450) reductase purified by biospecific affinity chromatography. *The Journal of biological chemistry*. 1976; 251:5337–5344. [PubMed: 821951]
185. Yildiz BO, Azziz R. The adrenal and polycystic ovary syndrome. *Rev Endocr Metab Disord*. 2007; 8:331–342. [PubMed: 17932770]
186. Zuber MX, John ME, Okamura T, Simpson ER, Waterman MR. Bovine adrenocortical cytochrome P-450(17 α). Regulation of gene expression by ACTH and elucidation of primary sequence. *The Journal of biological chemistry*. 1986; 261:2475–2482. [PubMed: 3003117]
187. Zuber MX, Simpson ER, Waterman MR. Expression of bovine 17 α -hydroxylase cytochrome P450 cDNA in non-steroidogenic (COS-1) cells. *Science*. 1986; 234:1258–1261. [PubMed: 3535074]

Fig. 1.

Adrenal C₁₉ steroid biosynthetic pathways. The steroid secreted from the human adrenal at the highest levels have larger font. The more abundant steroids are graphically overemphasized. Abbreviations: DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate; StAR, steroidogenic acute regulatory protein; CYP11A1, cytochrome P450 cholesterol side-chain cleavage; HSD3B2, 3β-hydroxysteroid dehydrogenase type 2; CYB5A, cytochrome b5; AKR1C3, 17β-hydroxysteroid dehydrogenase type 5; SULT2A1, steroid sulfotransferase type 2A1, CYP11B1, 11β-hydroxylase.

Fig. 2. Adrenal steroidogenic enzymes and associated proteins that impact C₁₉ steroid production with their human adrenal zonal expression pattern. Abbreviations: ZG, zona glomerulosa; ZF, zona fasciculata; ZR, zona reticularis; CYP11A1, cytochrome P450 cholesterol side-chain cleavage; CYP17, 17 α -hydroxylase/17,20-lyase; CYB5, cytochrome b5; SULT2A1, steroid sulfotransferase type 2A1; AKR1C3, 17 β -hydroxysteroid dehydrogenase type 3; HSD3B2, 3 β -hydroxysteroid dehydrogenase type 2.

Fig. 3.

Adrenal-derived C₁₉ steroids act as precursors for the production of more potent androgens in peripheral tissues, including hair follicles, genital skin and prostate. The classical pathway for bioactive androgen synthesis, as well as a proposed alternative pathway using 11 β -hydroxyandrostenedione (11OHA) is shown. Abbreviations: A4, androstenedione; T, testosterone; DHT, dihydrotestosterone; 11OHT, 11 β -hydroxytestosterone; 11OHDHT, 11 β -hydroxyDHT; STS, sulfatase; HSD3B, 3 β -hydroxysteroid dehydrogenases; HSD17, 17 β -hydroxysteroid dehydrogenases; SRD5A, 5 α -reductase type A.

Fig. 4.

Pathways of steroid hormone synthesis in 21-hydroxylase deficiency. Abbreviations: A4, androstenedione; T, testosterone; DHT, dihydrotestosterone; 11OHA, 11 β -hydroxyandrostenedione; 11OHT, 11 β -hydroxytestosterone; SRDA1/2, 5 α -reductase types 1 or 2; AKR1C2/4, 3 α -hydroxysteroid dehydrogenases types 2 or 4; CYP17A1, 17 α -hydroxylase/17,20-lyase; HSD17B3/6, 17 β -hydroxysteroid dehydrogenase types 3 or 6; AKR1C3, 17 β -hydroxysteroid dehydrogenase types 5.