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THE GENETICS, PATHOPHYSIOLOGY, AND MANAGEMENT OF HUMAN DEFICIENCIES OF P450c17

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P450c17 commands a central role in human steroidogenesis as the qualitative regulator of steroid hormone flux (Fig. 1). Analysis of P450c17 deficiencies in humans illustrates many aspects of the physiology of steroid biosynthesis and demonstrates poignant features of the genetics and biochemistry of P450c17. 17-Hydroxylase deficiency was first described in patients with sexual infantilism and hypertension.[10] It is now recognized to occur in partial and selective forms with variable phenotypes. This article reviews the genetics and biochemistry of P450c17 as a prelude for understanding the pathophysiology of such deficiencies and approaches to their diagnosis and management.

P450c17 AND *CYP17*

Patients who carry the diagnosis of 17-hydroxylase deficiency harbor alterations in the *CYP17* gene that encodes the P450c17 enzyme. P450c17 actually performs multiple chemical transformations. Human P450c17 17α-hydroxylates Δ^5-pregnenolone and Δ^4-progesterone with roughly equal catalytic efficiency,[3, 35] whereas all other reactions show prominent differences between Δ^5 and Δ^4 substrates. The 17,20-lyase activity is roughly 50 times more efficient for the 17α-hydroxypregneno-

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Figure 1. *See legend on opposite page.*

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lone-to-dehydroepiandrosterone (DHEA) reaction than for the 17α-hydroxyprogesterone-to-androstenedione reaction.[3, 35] Although the rate of the lyase reaction can be increased more than 10-fold by the addition of cytochrome b_5,[3, 31, 35] the Δ^5 preference persists, and the lyase rate never quite achieves the rate of the hydroxylase reactions. In addition, human P450c17 16α-hydroxylates progesterone but not pregnenolone.[3, 37, 62] In the presence of cytochrome b_5, P450c17 converts approximately 10% of pregnenolone substrate to a Δ^{16} andiene product,[35] which is also formed by porcine P450c17 and acts as a pheromone precursor in pigs.[48] Although experiments to study the chemistry of P450c17 often require certain conditions, such as detergent solubilization that could be considered nonphysiologic, the remarkable consistency of substrate preferences and kinetic constants observed for the modified solubilized P450c17 expressed in *Escherichia coli*,[31, 35] the native P450c17 expressed in yeast microsomes[3] or intact COS-1 cells,[37, 38] and that obtained from human tissues and cells[3, 62] strengthens these conclusions.

One consequence of this Δ^5 preference of human P450c17 for the 17,20-lyase reaction is that the vast majority of sex steroids in humans derive from DHEA as an intermediate. This Δ^5 preference also allows the phenomenon of adrenarche to occur in humans, an event that is characterized by a dramatic rise in adrenal DHEA production that occurs at about age 8 to 10 years,[12, 60] whereas cortisol production remains relatively constant. Adrenarche is an exemplary manifestation of the biochemistry of P450c17, in which the 17α-hydroxylase and 17,20-lyase activities are differentially regulated. In fact, this dichotomy between adrenal 17α-hydroxylase activity, reflected by relatively constant cortisol production, and 17,20-lyase activity, reflected by drastically age-dependent changes in DHEA production, previously suggested that distinct enzymes performed the two transformations; however, later copurification of the 17α-hydroxylase and 17,20-lyase activities of neonatal pig testes suggests otherwise.[47] This controversy was settled when the cDNA for bovine P450c17 was expressed in COS-1 cells, conferring 17α-hydroxylase and 17,20-lyase activities to these nonsteroidogenic cells[77] and proving genetically that the 17α-hydroxylase and 17,20-lyase enzymes

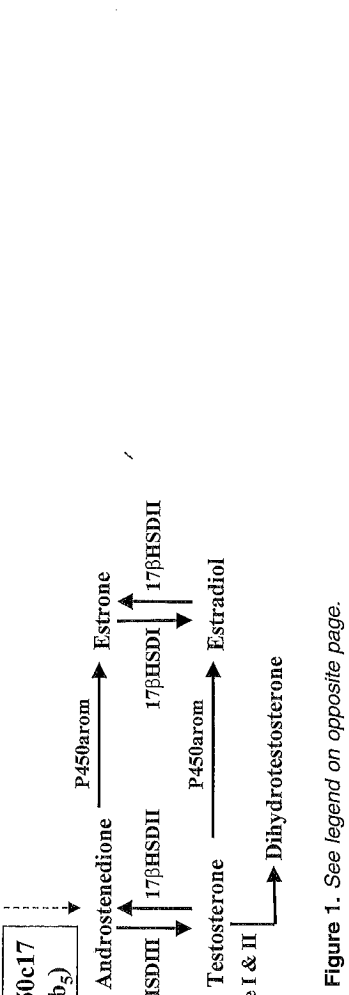

Figure 1. *See legend on opposite page.*

Figure 1. Major steroidogenesis pathways in humans and feedback loops controlling glucocorticoid and mineralocorticoid production. Ordinarily, cortisol is the major glucocorticoid produced by the adrenal zona fasciculata/reticularis, and cortisol exerts negative feedback inhibition *(double vertical bars)* to regulate pituitary adrenocorticotropic hormone (ACTH) production. Aldosterone is the principal mineralocorticoid of the adrenal zona glomerulosa, and aldosterone synthase (P450c11AS) expression is stimulated by volume depletion, which activates the renin-angiotensin (AII) system, and to a lesser extent, by ACTH. Aldosterone acts to stimulate kaluresis and salt and water retention, which feeds back on the kidney to suppress renin production. The production of corticosterone, a weak glucocorticoid, and of 11-deoxycorticosterone (DOC), a potent mineralocorticoid, is relatively low and unimportant in healthy individuals with intact feedback systems. Note that P450c11β in the zona fasciculata also 18-hydroxylates (18OH) DOC and corticosterone as minor products.

were, in fact, both embodied in a single enzyme, P450c17. Differential regulation of the two principal activities of P450c17 is possible because the abundance of P450-oxidoreductase[37] and the addition[31, 35, 50] or coexpression[3] of cytochrome b_5 preferentially augments the 17,20-lyase activity, and phosphorylation[7, 76] also selectively enhances 17,20-lyase activity. Recent data showing high expression of b_5 in the zona reticularis of monkeys[40] and humans[71] suggest that the developmentally regulated expression of b_5 might be a key event in the genesis of adrenarche in higher primates.

PATHOPHYSIOLOGY

P450c17 deficiencies are a form of congenital adrenal hyperplasia in which not only adrenal but also gonadal steroidogenesis is impaired. In humans, one gene for P450c17 is expressed in the adrenals and gonads[11] instead of two tissue-specific isozymes. A single 2.1-kb mRNA species yields a 57-kd protein in these tissues, and mutations in this gene produce a spectrum of deficiencies in 17-hydroxysteroids and C_{19} steroids. Loss of P450c17 in the adrenal gland impairs cortisol and DHEA production, whereas gonadal deficiency of P450c17 abrogates sex steroid production. The initial description of 17-hydroxylase deficiency was a case in which both 17α-hydroxylase and 17,20-lyase products were absent.[10] When the gene for human P450c17 was cloned,[54] patients with 17-hydroxylase deficiency were found to harbor mutations in the *CYP17* gene,[4, 67] but molecular techniques and subsequent clinical evaluations failed to implicate *CYP17* mutations as the cause of isolated 17,20-lyase deficiency.[73] Recently, three cases of isolated 17,20-lyase deficiency have been confirmed by molecular genetics,[8, 20] demonstrating that amino acid substitution mutations in P450c17 can cause an isolated loss of 17,20-lyase activity.

Combined 17α-Hydroxylase/17, 20-Lyase Deficiency

Loss of P450c17 in the human adrenal gland prohibits the biosynthesis of cortisol and C_{19} steroids. Curiously, the adrenal glands of patients with 17-hydroxylase deficiency are similar to those of rodents, which do not express P450c17,[63] such that rodents rely on corticosterone as their principal glucocorticoid, and their adrenal glands cannot make C_{19} steroids. Patients with 17-hydroxylase deficiency rarely[26] manifest symptoms of adrenal insufficiency owing to sustained corticosterone production. Because corticosterone is a weaker glucocorticoid than cortisol, abnormally high corticosterone production is necessary before feedback inhibition on pituitary corticotropin (ACTH) secretion occurs,[45] establishing a new steady state (Fig. 2). To produce sufficient corticosterone to make up for the absence of cortisol, dramatically elevated quantities of intermediate steroids, such as progesterone and 11-deoxycorticosterone

(DOC), must accumulate, as w
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(DOC), must accumulate, as well as unusual metabolites, such as 18-hydroxycorticosterone[33] and 19-nor-deoxycorticosterone.[23] This ACTH-driven overproduction of mineralocorticoids leads to hypertension, a characteristic presenting feature of this disease. The hypertension usually develops in early adulthood[9] but can present in infancy[15] and can be severe.[46] As is true in other hypertensive disorders caused by mineralocorticoid excess,[39] the hypertension can become fixed if the disease is not treated for many years.[52]

Although the general description given herein is true for most patients with this disorder, considerable variation in phenotype and laboratory findings has been described. These variables include the degree of genital virilization in 46,XY subjects and the capacity for menstruation in 46,XX subjects; the severity of the hypertension and hypokalemia; the aldosterone secretion rate; the type and amount of adrenocortical hyperplasia; the gonadal morphology and histology; and the coexistence of additional disorders, such as 21-hydroxylase deficiency[53] or maternal androgen excess.[14] This heterogeneity has not been completely explained, but many factors, including the severity of the P450c17 deficiency, variations in genes regulating hormone responsiveness, diet (sodium consumption), and environment, undoubtedly contribute. The reader is referred to a detailed discussion of case reports,[72] which is beyond the scope of this article.

Isolated 17, 20-Lyase Deficiency

This disoder is extremely rare because mutations that cause this phenotype must not only destroy most 17,20-lyase activity but preserve most 17α-hydroxylase activity. Patients who are 46,XY present with ambiguous genitalia at birth or with inguinal hernias with or without pubertal delay as adolescents[72] (Table 1). Patients do not show the consequences of mineralocorticoid excess because preserved cortisol production prevents excessive DOC and corticosterone accumulation. Clinical laboratory findings vary considerably owing to the age of diagnosis, the severity of the disease, and the discrepancy between the 17α-hydroxylase and 17,20-lyase activities in a given individual. Nonetheless, C_{19} steroid production is severely, although not completely, impaired, whereas 17-hydroxylated steroid production is nearly or completely normal.

DIAGNOSIS

Unlike forms of congenital adrenal hyperplasia, such as the lipoid type and 21-hydroxylase deficiency, in which glucocorticoid and mineralocorticoid production are impaired, patients with 17-hydroxylase deficiency do not have an adrenal crisis in the postnatal period. Consequently, the diagnosis is often not entertained until hypertension, hypokalemia, or pubertal delay is evaluated during adolescence or early

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