Ovarian and Adrenal Androgen Biosynthesis and Metabolism

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SUMMARY

The pathways of adrenal and ovarian steroid biosynthesis use the same enzymes for the initial steps of steroidogenesis but express different enzymes that convert steroid precursors to the final active products. Both the adrenal and ovary produce dehydroepiandrosterone (DHEA), the principal precursor of androgens and estrogens. The key enzyme in DHEA production is P450c17, which catalyzes both 17α-hydroxylation and 17,20-lyase activities. The 17,20-lyase activity of human P450c17 strongly favors 17-hydroxypregnenolone rather than 17-hydroxyprogesterone (17-OHP) as a substrate, producing abundant DHEA, so that most human androgens and estrogens derive from DHEA. Understanding the biochemistry of P450c17 is central to understanding the hyperandrogenism of polycystic ovary syndrome (PCOS). Rare genetic disorders of steroidogenesis provide human genetic knockout experiments of nature, yielding important information about the biosynthesis and physiological roles of steroids.

Key Words: Androgens; steroidogenesis; ovary; adrenal; 17,20-lyase; 17-hydroxylase; CYP21; P450c17; StAR; 3β-hydroxysteroid dehydrogenase; 17β-hydroxysteroid dehydrogenase; 5α-reductase; 11β-hydroxylase.

1. INTRODUCTION

The pathways of steroidogenesis employ a relatively small number of steroidogenic enzymes, but variations in their tissue specificity of expression and in the availability of substrates and cofactors result in the widely varying patterns of steroid production in each steroidogenic tissue (1). Although no cell type expresses all the steroidogenic enzymes, their interrelationships can be seen in the idealized integrated pathway shown in Fig. 1. Cholesterol is the precursor for all steroid hormones. The human adrenal and ovary can synthesize cholesterol de novo from acetate, but most cholesterol is provided by plasma low-density lipoproteins (LDLs) derived from dietary cholesterol. The presence of adequate LDL suppresses 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting step in cholesterol synthesis. HMG-CoA reductase, as well as LDL receptor number and uptake of LDL cholesterol, are stimulated by adrenocorticotropic hormone (ACTH) in the adrenal and by follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in the ovary. Steroidogenic cells take up LDL cholesterol esters by receptor-mediated endocytosis to be either stored or immediately converted to free cholesterol for use as substrate in steroidogenesis. Storage of cholesterol esters in lipid droplets is under the control of two opposing enzymes, cholesterol esterase (cholesterol ester hydrolase) and cholesterol synthetase. LH and ACTH stimulate esterase to increase the availability of free cholesterol for steroidogenesis while inhibiting synthetase.
2. BACKGROUND

2.1. The Steroidogenic Enzymes

2.1.1. Early Steps: From Cholesterol to DHEA

2.1.1.1. THE STEROIDOGENIC ACUTE REGULATORY PROTEIN

Chronic regulation of steroidogenesis by LH or ACTH occurs at the level of gene transcription (1), whereas more acute regulation leading to steroid secretion following an LH surge is controlled by cholesterol access to the rate-limiting enzyme P450scc (2). This acute regulation is mediated by the steroidogenic acute regulatory protein (StAR), which facilitates the movement of cholesterol into the mitochondrion, where it becomes the substrate for the cholesterol side-chain cleavage enzyme, P450scc, the first steroid biosynthetic enzyme. StAR was first identified as short-lived 30- and 37-kDa phosphoproteins rapidly synthesized by steroidogenic cells in response to trophic hormone stimulation (2).