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Review

The diverse chemistry of cytochrome P450 17A1 (P450c17, CYP17A1)

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ABSTRACT

The steroid hydroxylation and carbon–carbon bond cleavage activities of cytochrome P450 17A1 (CYP17A1) are responsible for the production of glucocorticoids and androgens, respectively. The inhibition of androgen synthesis is an important strategy to treat androgen-dependent prostate cancer. We discuss the different enzymatic activities towards the various substrates of CYP17A1, demonstrating its promiscuity. Additionally, a novel interhelical interaction is proposed between the F–G loop and the B'-helix to explain the 16α-hydroxylase activity of human CYP17A1 with progesterone as the substrate. The techniques used by biochemists to study this important enzyme are also summarized.

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Contents

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1. Cytochrome P450 enzymes

Microsomal human cytochrome P450 17A1 (CYP17A1, 17α-hydroxylase, 17,20-lyase) belongs to the cytochrome P450 super

family that contains a conserved cysteine residue, which provides the axial sulfur ligand attached to a heme prosthetic group. The P450 class of enzymes conducts a myriad of chemical transformations including oxidation, reduction, and non-redox reactions [1]. The prototypical reaction catalyzed by this family of enzymes is the oxygenation of C—H bonds to afford alcohol products. This process involves the two-electron reduction of a molecule of oxygen where one of the oxygen atoms goes to water and the other is incorporated into the alkane substrate [2]. The oxoiron active intermediate (compound I) responsible for C—H activation has been characterized by Mossbauer and UV–vis spectroscopy [3]. The compound I intermediate was isolated through stopped flow by mixing CYP119 in one syringe and m-chloroperoxybenzoic acid in the other syringe (2:1 ratio) followed by freeze quenching with liquid ethane. Most P450 enzymes share a common 3-dimensional structure. Deisenhoefer and co-workers compared the crystal structures of the soluble bacterial enzymes $P450_{cam}$ (CYP101), $P450_{terp}$ and $P450_{BM-3}$ and observed structural similarities in the three different proteins: 13 α-helices (A, B, B', C–L), and 5 β-sheets (β1–β5) [4]. The X-ray crystal structures of several eukaryotic, membrane-bound P450 enzymes reveal the same basic fold with some variable areas. There are 57 human cytochrome P450 genes that metabolize small molecules including fatty acids, xenobiotics, and steroids. Six of these (CYP11A, CYP11B1, CYP11B2, CYP17A1, CYP19A1, CYP21A2) are found in the steroid hormone biosynthesis pathway [5]. Crystal structures of CYP17A1 with azole inhibitors bound have been recently elucidated, and these structures can be used to increase our understanding of this enzyme [6]. This report will focus on the hydroxylation activity of CYP17A1, although the carbon–carbon (C—C) bond cleavage activity is also important and a topic of intense study [7]. The use of steroid analogs to show the diverse reactivity of this enzyme can enhance our understanding of the function of this important enzyme in human physiology and disease. The goal of this review is to educate the reader of the different approaches to study the enzymology of CYP17A1. The function of this enzyme may be elucidated with the information gained from biochemical studies.

2. CYP17A1: gene, physiology, and disease

The human *CYP17A1* gene is localized to chromosome 10q24.3 [8]. This gene is expressed in the adrenals and gonads, with minor amounts in the brain, placenta, and heart [9]. The same mRNA and protein is expressed in the adrenal and gonad. The 17-hydroxylase activity of CYP17A1 is required for the production of the

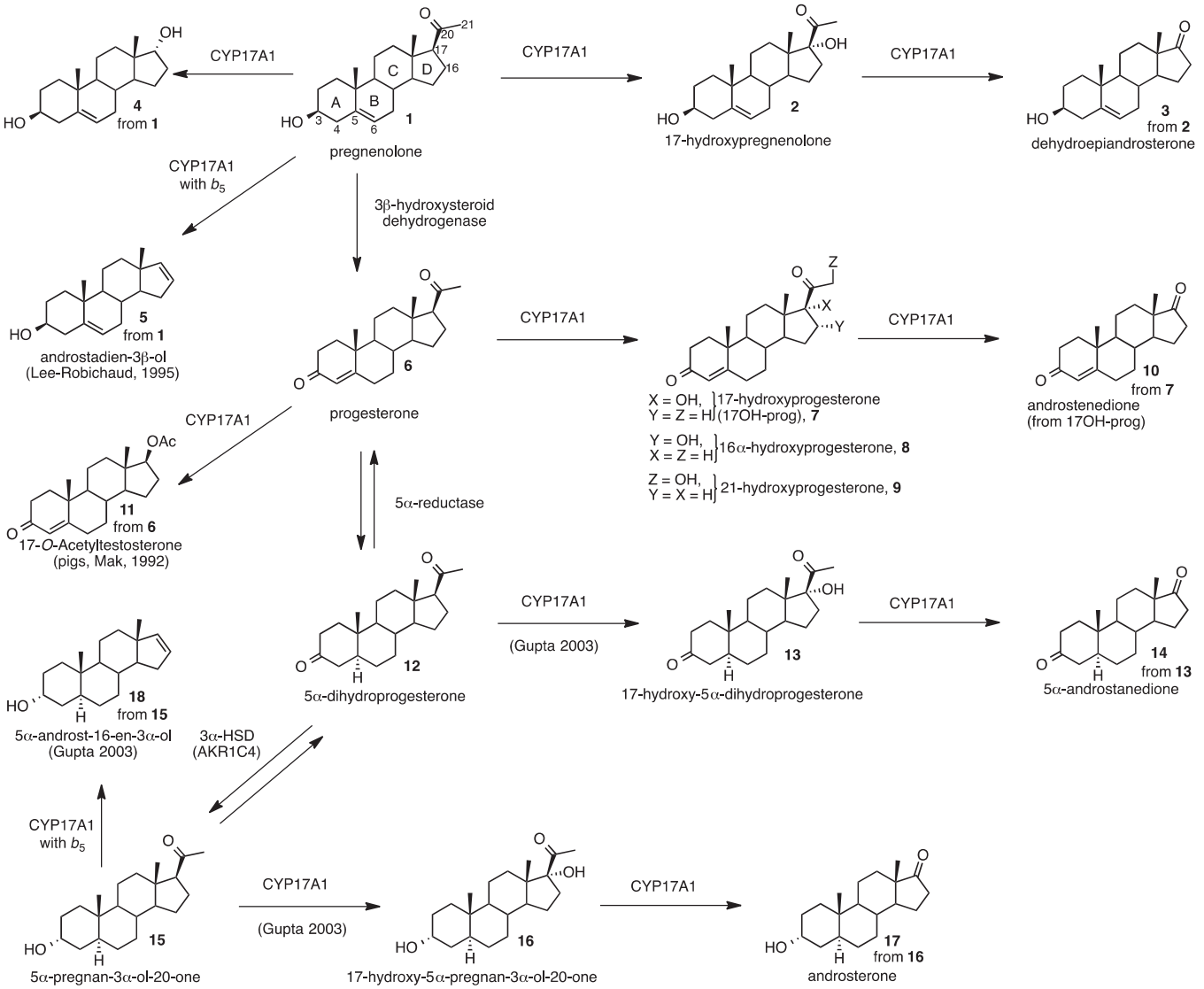

Fig. 1. The substrates and products of CYP17A1.