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Review

Promiscuity and diversity in 3-ketosteroid reductases

Trevor M. Penning *, Mo Chen, Yi Jin

Center of Excellence in Environmental Toxicology, Department of Systems Pharmacology & Translational Therapeutics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104-6160, USA

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ABSTRACT

Many steroid hormones contain a Δ^4-3-ketosteroid functionality that undergoes sequential reduction by 5α- or 5β- steroid reductases to produce 5α- or 5β-dihydrosteroids; and a subsequent 3-keto-reduction to produce a series of isomeric tetrahydrosteroids. Apart from steroid 5α-reductase all the remaining enzymes involved in the two step reduction process in humans belong to the aldo-keto reductase (AKR) superfamily. The enzymes involved in 3-ketosteroid reduction are AKR1C1–AKR1C4. These enzymes are promiscuous and also catalyze 20-keto- and 17-keto-steroid reduction. Interest in these reactions exist since they regulate steroid hormone metabolism in the liver, and in steroid target tissues, they may regulate steroid hormone receptor occupancy. In addition many of the dihydrosteroids are not biologically inert. The same enzymes are also involved in the metabolism of synthetic steroids *e.g.*, hormone replacement therapeutics, contraceptive agents and inhaled glucocorticoids, and may regulate drug efficacy at their cognate receptors. This article reviews these reactions and the structural basis for substrate diversity in AKR1C1–AKR1C4, ketosteroid reductases.

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Contents

1. Introduction

The majority of steroid hormones and their synthetic derivatives contain a Δ^4-3-ketosteroid functionality in their A-ring. Since the early work of Tomkins [1,2], it has been recognized that when this group is present it undergoes 5α- or 5β-reduction catalyzed by either 5α-reductase enzymes (SRD5A1, SRD5A2 and SRD5A3) [3,4] or by steroid 5β-reductase [5,6], respectively to produce the

* Corresponding author at: Department of Systems Pharmacology & Translational Therapeutics, 42 Curie Blvd., 1315 BRBII/III, Philadelphia, PA 19104-6160, USA. Tel.: +1 215 898 9445; fax: +1 215 573 0200.
E-mail address: penning@upenn.edu (T.M. Penning).

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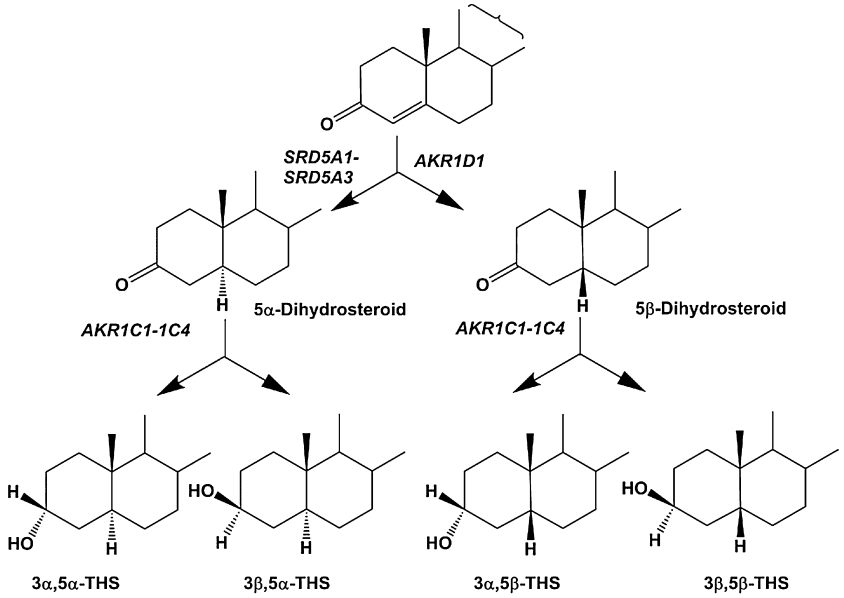

Fig. 1. Metabolism of Δ^4-3-ketosteroids to isomeric tetrahydrosteroids in humans. Enzymes are listed as gene names which are italicized. THS: tetrahydrosteroid.

corresponding 5α/5β-dihydrosteroids, Fig. 1. These 5α/5β-dihydrosteroids are then reduced by NADPH-dependent 3α/3β-hydroxysteroid dehydrogenases to produce one of four stereoisomeric tetrahydrosteroids. Once formed the tetrahydrosteroids undergo conjugation reactions with either SULTs (sulfotransferases) or UGTs (uridine glucuronosyl transferases). The functionalization of the A-ring to yield the four isomeric tetrahydrosteroids is catalyzed by phase 1 enzymes whereas the conjugation reactions are catalyzed by phase 2 enzymes. Interest in these reactions exists because the 5α/5β-dihydrosteroids and their tetrahydrosteroids are not always biologically inert, they control steroid hormone metabolism, and inhibitors of these reactions may regulate steroid hormone action. In addition, many synthetic steroids also contain the Δ^4-3-ketosteroid functionality, and the same enzymes may regulate the duration and efficacy of these drugs which include: steroid contraceptives; anabolic steroids; and inhaled/replacement glucocorticoids. Natural inhibitors of the transformation of these drugs may also cause idiosyncratic drug reactions. This article will focus on the human 3-ketosteroid reductases that are responsible for the formation of the tetrahydrosteroids, and their promiscuity and diversity to act as 17-keto- and 20-keto-steroid reductases that influence the metabolism of androgens, estrogens and progestins.

2. Human ketosteroid reductases (aldo-keto reductases)

Of the human enzymes shown in Fig. 1, all are members of the aldo-keto reductase (AKR) superfamily except SRD5A1–SRD5A3. The AKRs involved include steroid 5β-reductase or AKR1D1[7,8] and the four 3-ketosteroid reductases [9–12]: AKR1C1, 3α(20α)-hydroxysteroid dehydrogenase; AKR1C2, type 3 3α-hydroxysterod dehydrogenase or bile-acid binding protein; AKR1C3, type 2 3α hydroxysteroid dehydrogenase/type 5 17β-hydroxysteroid dehydrogenase; and AKR1C4, type 1 3α-hydroxysteroid dehydrogenase or chlordecone reductase. AKR1C1–AKR1C4 are located on the same chromosome (10p15-p14), they share more than 86% sequence identity, they are available in recombinant form for study, and X-ray crystal structures exist for ternary complexes of AKR1D1 [8,13] and AKR1C1–AKR1C3 [14–17]. Each AKR enzyme adopts the typical $(\alpha/\beta)_8$ barrel structure of the AKR superfamily in which an α-helix and β-strand repeats itself eight times so that the β-strands coalesce in the center of the structure to make up the staves of the barrel. At the back of the barrel there are three large loops that help determine substrate specificity/promiscuity. The NADPH cofactor and steroid substrate lie perpendicular to each other so that the nicotinamide head group is in close proximity to the acceptor carbonyl that will be reduced. Steady state kinetic constants k_{cat},K_m and k_{cat}/K_m have been obtained for a large number of steroid substrates [9,11,12], and radiochromatogaphy in combination with liquid chromatography mass spectrometry have identified the products of these reactions [18–21]. Product identification has been an important component of assigning function to these enzymes since if there were reliance solely on changes in absorption or fluorescence of NAD(P)(H), reactions would have been mis-assigned.

Original *in vitro* characterization of recombinant AKR1C1–AKR1C4 used radiochromatography to identify the reaction products [12]: all enzymes catalyzed the NAD(P)H dependent reduction of [^{14}C]-5α-dihydrotestosterone (5α-DHT) to yield 5α-androstane-3α,17β-diol (3α-diol); the NAD(P)H dependent reduction of [^{14}C]-Δ^4-androstene-3,17-dione to yield testosterone; the NAD(P)H dependent reduction of [^{14}C]-estrone to yield 17β-estradiol; and the NAD(P)H dependent reduction of [^{14}C]-progesterone to yield 20α-hydroxyprogesterone. In addition, all enzymes catalyze the corresponding reverse reactions involving the NAD(P)$^+$ dependent oxidation of [^{14}C]-3α-diol to yield 5α-DHT and/or androsterone; the NAD(P)$^+$ dependent oxidation of [^{14}C]-testosterone to yield Δ^4-androstene-3,17-dione; the NAD(P)$^+$ dependent oxidation of [^{14}C]-17β-estradiol to yield estrone; and the NAD(P)$^+$ dependent oxidation of [^{14}C]-20α-hydroxyprogesterone to yield progesterone. Steady state kinetic parameters indicated that each of these enzymes had 3α/3β-, 17β- and 20α-hydroxysteroid dehydrogenase (HSD) activities to different extents. These studies suggested that AKR1C1 preferred to function as a 20α-HSD, AKR1C2 and AKR1C4 preferred to function as a 3α-HSD; and AKR1C3 preferred to function as a 17β-HSD. However, the function of these enzymes will be dictated by their preference for NADP(H) over NAD(H) and expression levels in hepatic, extrahepatic and steroid hormone target tissues.

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