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Review

Androgen-metabolizing enzymes: A structural perspective

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ABSTRACT

Androgen-metabolizing enzymes convert cholesterol, a relatively inert molecule, into some of the most potent chemical messengers in vertebrates. This conversion involves thermodynamically challenging reactions catalyzed by P450 enzymes and redox reactions catalyzed by Aldo-Keto Reductases (AKRs). This review covers the structures of these enzymes with a focus on active site interactions and proposed mechanisms. Due to their role in a number of diseases, particularly in cancer, androgen-metabolizing enzymes have been targets of drug design. Hence we will also highlight how existing knowledge of structure is being used to this end.

Contents

Abbreviations: 3β-DIOL, 5α-androstane-3β,17β-diol; 17OHD, 17α-hydroxylase/17,20-lyase deficiency; 20,22-DHC, 20,22-dihydroxycholesterol; 20-HC, 20-hydroxycholesterol; 22-HC, 22-hydroxycholesterol; ABAD, amyloid beta-binding alcohol dehydrogenase; AcO^-, acetate; Adx, adrenodoxin; AI, aromatase inhibitor; AKR, aldo/keto reductase; ANZ, anastrozole; AR, androgen receptor; AEXS, aromatase excess syndrome; AROD, aromatase deficiency; ASD, androstenedione or androst-4-ene-3,17-dione; CPR, cytochrome P450 reductase; DBD, DNA-binding domain; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; DSO, disordered sexual development; E1, estrone; E2, estradiol; ER, estrogen receptor; EXM, exemestane; FDA, US Food and Drug Administration; GPER, G-protein-coupled estrogen receptor; HADH2, type II hydroxyacyl-CoA dehydrogenase; HRE, hormone response element; HSD, hydroxysteroid dehydrogenase; K_d, dissociation constant; LBD, ligand-binding domain; LTZ, letrozole; MR, mineralocorticoid receptor; NAD(P), nicotinamide adenosine dinucleotide (phosphate); NMR, nuclear magnetic resonance; P450, cytochrome P450; PCOS, polycystic ovary syndrome; PDB, protein data bank; R.M.S.D., root-mean-square deviation; SDR, short-chain dehydrogenases/reductase; TAF, transcription-activation-factor.

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1. Introduction

Steroid hormones are crucial substances for the vital coordination of various metabolic and physiological processes in the human body [1]. They include androgens, estrogens, progestins, mineralocorticoids and glucocorticoids. Androgens and estrogens are responsible for the development of primary and secondary sexual characteristics and coordinate physiological and behavioral changes at different stages of development, particularly during puberty, pregnancy and menopause [2].

Progestins are important for reproduction [3] and may have effects on reward, conditioning and motivation that may influence vulnerability to drug abuse [4]. Mineralocorticoids and their antagonists regulate salt/water balance by counteracting actions. Mineralocorticoids act to increase salt appetite, sympathetic drive and vasopressin release, potentially leading to hypertension, which is offset by the infusion of mineralocorticoid receptor (MR) antagonists [5]. Glucocorticoids effect stimulating and repressing actions to the ultimate goal of self-preservation. These include the stimulation of gluconeogenesis to provide energy for "flight or fight" response and the suppression of the reproductive axis as a stress response prioritizing the individual over the species [6]. Furthermore glucocorticoids help avoid sepsis by limiting the production of pro-inflammatory elements by dendritic cells in response to invading bacteria [7].

Testosterone is the most abundant androgen in the serum of healthy adult men and its deficiency predisposes men to type-2 diabetes. On the other hand, androgen excess predisposes women to insulin resistant diabetes [8]. In young healthy humans adrenal cortex and testis are the major organs of androgen hormone production [9,10]. Limited steroid hormone synthesis is also reported in peripheral tissues such as liver, prostate, brain, etc. [11–14]. Synthesis of androgen occurs with the successive modifications, mostly on peripheral groups, of cholesterol whose backbone ring-system remains intact all along the biosynthetic pathway (Fig. 1) [15,16]. Due to their masculinizing effects and

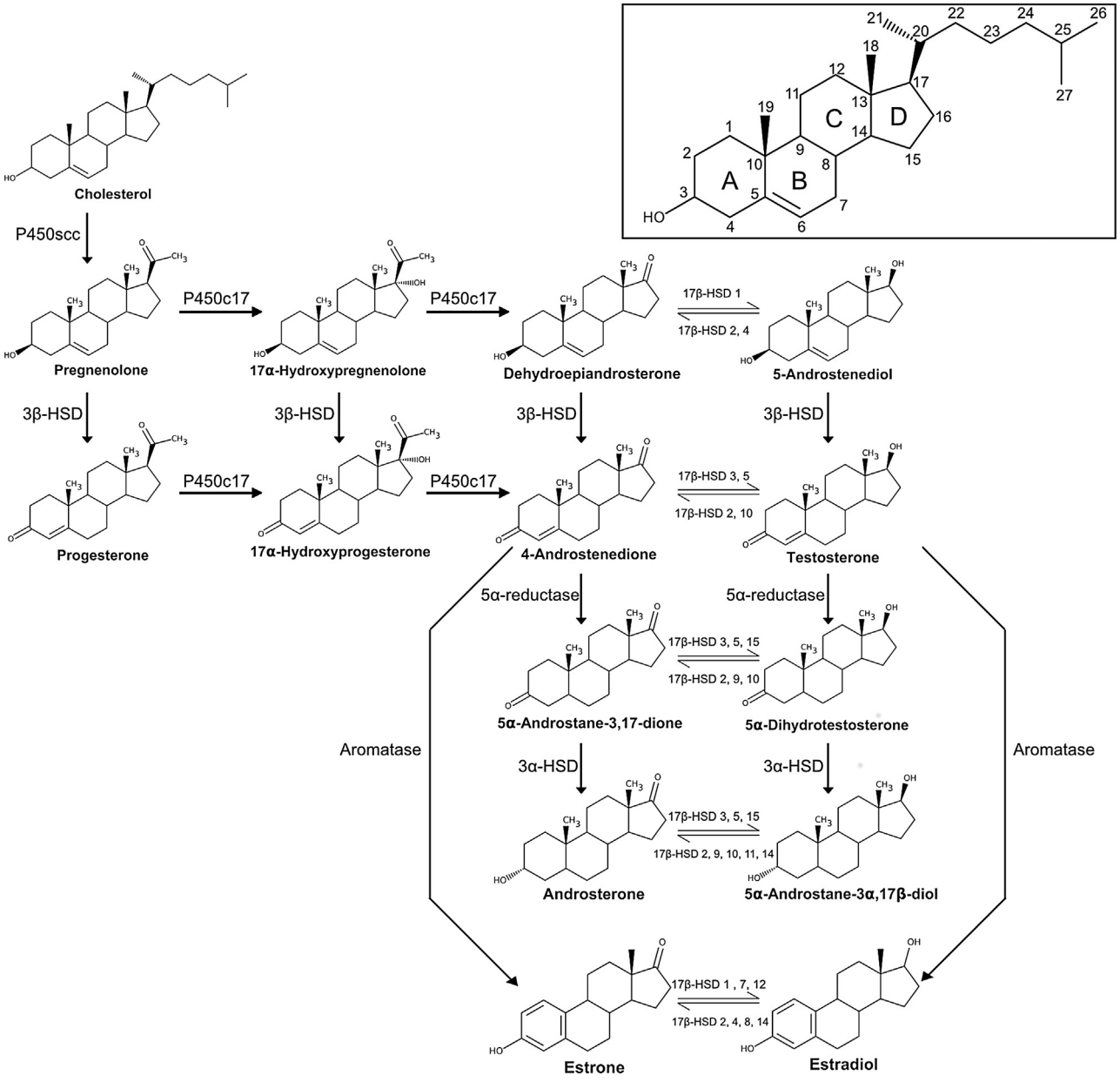

Fig. 1. The androgen metabolism pathway. The standard numbering of cholesterol carbons is shown in the insert.