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Structure and function of human 17β-hydroxysteroid dehydrogenases

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Abstract

17β-Hydroxysteroid dehydrogenases (17β-HSDs) catalyze the NAD(P)(H) dependent oxidoreduction at C17 oxo/β-hydroxyl groups of androgen and estrogen hormones. This reversible reaction constitutes an important pre-receptor control mechanism for nuclear receptor ligands, since the conversion "switches" between the 17β–OH receptor ligands and their inactive 17-oxo metabolites. At present, 14 mammalian 17β-HSDs are described, of which at least 11 exist within the human genome, encoded by different genes. The enzymes differ in their expression pattern, nucleotide cofactor preference, steroid substrate specificity and subcellular localization, and thus constitute a complex system ensuring cell-specific adaptation and regulation of sex steroid hormone levels. Broad and overlapping substrate specificities with enzymes involved in lipid metabolism suggest interactions of several 17β-HSDs with other metabolic pathways. Several 17β-HSDs enzymes constitute promising drug targets, of particular importance in cancer, metabolic diseases, neurodegeneration and possibly immunity.
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Keywords: Hydroxysteroid dehydrogenase; Steroid metabolism; 17β-Hydroxysteroid dehydrogenase; Pre-receptor control; Short-chain dehydrogenase/reductase

1. Introduction

The 17β-hydroxysteroid dehydrogenase enzymes (17β-HSDs, EC1.1.1.62) catalyze the NAD(P)(H) dependent oxidoreduction of hydroxyl/keto groups at position C17 of androgens and estrogens and in this manner regulate intracellular availability of steroid hormone ligands to their nuclear receptors. This pathway constitutes a pre-receptor control mechanism, since androgen and estrogen receptors transactivate their target genes by binding the 17β-hydroxylated steroids with much higher affinity than the 17-oxo steroids (Labrie et al., 2000a,b; Luu-The, 2001; Nobel et al., 2001; Peltoketo et al., 1999). The enzyme-activity was described well over 40 years ago (Ghraf et al., 1977, 1973; Jarabak et al., 1962) in eukaryotic and prokaryotic species and since then a large number of detailed analyses have added to the wealth of information available for these diverse enzymes (Labrie et al., 2000b; Peltoketo et al., 1999). At present, 14 different mammalian 17β-HSDs have been characterized and with the exception of 17β-HSD5, which is an aldo-keto reductase (AKR), all are members of the short-chain dehydrogenase/reductase (SDR) family (Labrie et al., 2000b; Peltoketo et al., 1999) (Lukacik et al., in preparation, submitted for publication). Human 17β-HSDs differ in nucleotide cofactor and substrate specificities, subcellular compartmentalization and tissue-specific expression patterns. Accordingly, 17β-HSDs are largely grouped into in vivo oxidative enzymes (17β-HSD types 2, 4, 6, 8, 9, 10, 11, 14) catalyzing the NAD^+ dependent inactivation of receptor ligands, and in vivo reductive enzymes (17β-HSD types 1, 3, 5, 7) which are NADPH dependent and whose reactions lead to steroid receptor ligands (Labrie et al., 2000b; Peltoketo et al., 1999) (Table 1). This review article aims to summarize the main structural and functional features currently described for human 17β-HSDs.

2. Physiological importance and substrate specificities of human 17β-HSDs

Primates differ from other mammals by their unique ability to synthesize sex steroids independently from gonadal sources by secreting large amounts of the adrenal steroids dehydroepiandrosterone (DHEA) and its sulfated derivative dehydroepiandrosterone sulfate (DHEA-S), which are then locally metabolized to the active hormones (Labrie et al., 2003, 2000a,b, and references therein). The importance in humans is highlighted by the fact that gonadectomy does not abolish occurrence of sex steroids, which are then locally produced and act on their target tissues (Labrie et al., 2000b). Likewise, in post-menopausal

Abbreviations: HSD, hydroxysteroid dehydrogenase; 17β-HSD, 17β-hydroxysteroid dehydrogenase; SDR, short-chain dehydrogenase/reductase; AKR, aldo-keto reductase

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Table 1
Properties of human 17β-HSDs

Human protein	Type	Chromosomal localization	Function	Human genetic disease	PDB code	Cofactor preference	Substrates	Subcellular localization	Expression pattern
17HSD1	SDR	17q21.2	E2 production	nd	1FDT, 1EQU, 1JTV	NADP(H)	Estrogens	Soluble	Widespread; gonads, breast, placenta, liver
17HSD2	SDR	16q23.3	E2, T inactivation	nd	nd	NAD(H)	Estrogens, androgens, progestins	ER	Widespread; prostate, liver, intestine
17HSD3	SDR	9q22.32	T production	Male pseudo-hermaphroditism	nd	NADP(H)	Androgens	ER	Mainly testis
17HSD4	SDR	5q23.1	β-Oxidation of FA, E2 inactivation	Zellweger-like syndrome	1ZBQ	NAD(H)	Estrogens, acyl CoAs	Peroxisomes	Widespread
17HSD5	AKR	10p15.1	T production, 20αP activation, bile acid production and detoxification, eicosanoid synthesis	nd	1RY0, 1SIP	NADP(H)	Androgens, eicosanoids	Soluble	Liver, prostate
17HSD7	SDR	Two genes: 95% i.d. 10p11.2; 1q23	Cholesterol synthesis and E2 production		nd	NADP(H)	Estrogens, cholesterol	ER	
17HSD8	SDR	6p21.32	E2 and androgen inactivaction, FA β-oxidation?	PKD?	nd	NAD(H)	Androgens	?	Widespread, liver, kidney
17HSD10	SDR	Xp11.22	Estrogen and androgen inactivation, β-oxidation of FA, bile acid isomerisation	MHBD deficiency	1SO8, 1UZT	NAD(H)	Estrogens, androgens, bile acids, progestins, branched/straight OH-acyl CoAs	Mitochondria	Widespread, liver, CNS, kidney, testis
17HSD11	SDR	4q22.1	Conversion of 5α-androstane-3α,17β-diol to androsterone	nd	1YB1	NAD(H)	Androgens?	ER	Steroidogenic tissues
17HSD12	SDR	11p11.2	3-Ketoacyl-CoA reductase; FA synthesis	nd	nd	NADP(H)	Steroids? acyl CoAs	?	?
17HSD14	SDR	19q13.33	E2, T inactivation; β-oxidation?	nd	1YDE	NAD(H)	Estrogens, androgens, fatty acyl CoAs?	Soluble	CNS, kidney

nd = not determined.

women nearly 100% of sex steroids are produced in extragonadal tissues from their adrenal precursors. Plasma levels of DHEA and DHEA-S in adult humans are two to four orders of magnitude higher than levels of androgens and estrogens (Labrie et al., 2000b), respectively. This provides a unique source for peripheral tissues to synthesize, regulate and adapt levels of sex hormones in a given physiological situation. In this context, 17β-HSDs operate together with other steroid metabolizing enzymes to create a system, which has been termed “intracrinology” by Labrie (1991). This mechanism describes the competence of peripheral cells to synthesize their own hormones which are not secreted but produced from adrenal steroids, and are distinct from classical endocrine, exocrine or paracrine mechanisms (Labrie, 1991). Besides 17β-HSDs, the enzyme components necessary to produce active steroids in an intracrine manner from DHEA and DHEA-S are steroid sulfatase, aromatase (CYPB19), 3α-HSDs and 5α-reductases, and the pathways involved are outlined in Fig. 1. The functions of these enzymes in inactivating the ligands of steroid recteptors are also important so that overall these reactions allow for specific substrate fluxes and highly regulated adaptations to physiological needs. Intrinsically bidirectional enzymes like 17β-HSDs usually display certain in vivo

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