REVIEW

17β-Hydroxysteroid dehydrogenase (HSD)/17-ketosteroid reductase (KSR) family; nomenclature and main characteristics of the 17HSD/KSR enzymes

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ABSTRACT

A number of enzymes possessing 17β-hydroxysteroid dehydrogenase/17-ketosteroid reductase (17HSD/KSR) activities have been described and cloned, but their nomenclature needs specification. To clarify the present situation, descriptions of the eight cloned 17HSD/KSRs are given and guidelines for the classification of novel 17HSD/KSR enzymes are presented.

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INTRODUCTION

Since the 1950s (Ryan & Engel 1953), 17β-hydroxysteroid dehydrogenase/17-ketosteroid reductase (17HSD/KSR) activities have been characterized, and 17HSD/KSR enzymes have been purified from a large number of tissues of several species (see Jarabak 1969, Nicolas & Harris 1973, Bogovich & Payne 1980, Milewich et al. 1985, Inano & Tamaoki 1986, Murdock et al. 1986, Tait et al. 1989, Martel et al. 1992, Blomquist 1995, for example). Eight enzymes named HSD types 1–8, hereafter called 17HSD/KSR1–8, have so far been cloned (see Table 1). Kinetic data available suggest that more enzymes with 17HSD/KSR-activities will be cloned in the future. Before the cloning of the different types, 17HSD/KSRs had been successfully characterized based on their enzymatic properties and tissue and subcellular localization. However, the activities described generally reflected the sum of activities of several enzymes and not the characterization of an individual protein. On the other hand, cloning of the 17HSD/KSR enzymes has revealed that several of them possess further enzymatic activities, which has also complicated the definition of them. During the past decades, the names of the 17HSD/KSRs have become diverse and impractical, and therefore we attempt here to clarify the nomenclature and specification of them.

A brief description of individual and common features of the known 17HSD/KSR enzymes is given, enough to identify each enzyme discussed.

WHAT ARE 17HSD/17KSRs

17HSD/KSRs are NAD(H)- and/or NADP(H)-dependent enzymes that catalyze the oxidation and reduction of 17β-hydroxy- and 17-ketosteroids respectively. Both estrogens and androgens have the highest affinity for their receptors in the 17β-hydroxy form and hence 17HSD/KSR enzymes regulate the biological activity of the sex hormones. Certain 17HSD/KSRs are also involved in catabolic cascades of sex steroids. 17KSR activities are essential for estradiol (1,3,5(10)-estratriene-3,17β-diol) and testosterone (4-androsten-17β-ol-3-one) biosynthesis in the gonads, but they are also present
<table>
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<th>Type/protein family</th>
<th>Species cloned</th>
<th>References for cloning</th>
<th>Accession number</th>
<th>Subcellular localization</th>
<th>Tissue distribution&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Other names used/in use</th>
<th>Other references</th>
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</thead>
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<td>Type/protein family</td>
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<td>References for cloning</td>
<td>Accession number</td>
<td>Subcellular localization</td>
<td>Tissue distribution*</td>
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</tr>
<tr>
<td>Human</td>
<td>Qin et al. (1993), Lin et al. (1997)</td>
<td>S68288</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6/SDR Rat</td>
<td>Biswas &amp; Russell (1997)</td>
<td>U89280</td>
<td>Membrane-bound</td>
<td>Prostate, liver</td>
<td></td>
<td></td>
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<tr>
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<td>Duan et al. (1996)</td>
<td>U44803</td>
<td>Membrane-bound/associated</td>
<td>Ovary</td>
<td>PRAP</td>
<td>Duan et al. (1997)</td>
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<tr>
<td>Mouse</td>
<td>Nokelainen et al. (1998)</td>
<td>Y15733</td>
<td>Membrane-bound/associated</td>
<td>Ovary, placenta, mammary gland</td>
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<td>Mouse</td>
<td>Aziz et al. (1993)</td>
<td>U34072</td>
<td>Unknown</td>
<td>Kidney, liver, ovary, testis, spleen</td>
<td>Ke 6</td>
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</tbody>
</table>

*aThe list is not all-inclusive, but the tissues in which each enzyme is most commonly expressed are mentioned.
in certain extragonadal tissues and can convert low-activity precursors to their more potent forms in peripheral tissues. Instead, 17HSD activities tend to decrease the potency of estrogens and androgens and consequently may protect tissues from excessive hormone action (Table 1).

17HSD/KSRs differ from the majority of other steroidogenic enzymes, because most of them are able to catalyze, at least to some extent, reverse reactions under in vitro conditions. In the presence of a substantial excess of a suitable cofactor and/or in the absence of the preferred cofactor, 17HSD/KSRs can be compelled to catalyze both oxidative and reductive reactions. However, in cultured cells that better reflect in vivo conditions, the cloned 17HSD/KSRs are exclusively or mainly either 17HSDs or 17KSRs (see Table 2). Therefore we suggest that, in addition to kinetic characterization with partially purified protein or cell extracts, enzymatic properties of each new 17HSD/KSR are tested without additional cofactors, using cultured cells transfected with the novel cDNA. The physiological role of each enzyme in steroidogenesis can thus be estimated more reliably than by comparing solely kinetic values for different substrates. To avoid more confusion, we also prefer to maintain the current and fixed numbering for the cloned type 1–8 enzymes, and do not consider it practicable to divide 17HSD/KSRs further into 17HSD and 17KSR families.

SIMILARITY/DIVERSITY OF 17HSD/KSRs

Although the eight types of 17HSD/KSRs possess the same site of action on the steroid nucleus, and some of them catalyze the same substrates, the primary structures of the enzymes are not very similar. The 17HSD/KSR5 is a member of the aldoketoreductase (AKR) protein family (Deyashiki et al. 1995, Zhang et al. 1995), while the rest of the cloned 17HSD/KSRs (types 1–4 and 6–8) belong to the short-chain dehydrogenase/reductase (SDR) protein family (Jörnvall et al. 1995), sharing also an identity of less than 30%. In fact, 17HSD/KSRs are commonly more similar to other SDR members than to other 17HSD/KSRs, and thus they are connected by their enzymatic rather than primary structure similarities. On the other hand, several SDR members have a similar kind of secondary structure, and consequently are similarly folded (Duax & Ghosh 1997).

Due to the dissimilarity of the primary structures of 17HSD/KSRs, the 17HSD/KSR types in different species have easily been able to be separated from each other. Consequently, we recommend that new 17HSD/KSRs are numbered in the order in which they are cloned, regardless of the species the cDNA/gene is cloned from. The corresponding enzymes from other species are then labeled with the same number, although all types would not exist in some species. Such a procedure is suitable for the 17HSD/KSR family that possesses low sequence homology, and thus avoids confusing situations in which enzymes in different species have been assigned the same type number but actually are enzymatically distinct. For example, for the members of the 3β-HSD family that share high identity and diversity between species (Penning 1997), a similar procedure could not be applied.

There are two types of human 3β-HSD having 93.5% amino acid identity and similar substrate specificity, and up to six rodent types of 3β-HSD. The rodent forms show variable patterns of substrate specificity, but their DNA sequences are not dissimilar enough to allow identification of inter-species counterparts by sequence homology.

17HSD/KSR enzymes are expressed in distinct, though in some cases, overlapping patterns. 17HSD/KSRs also differ in their substrate and cofactor specificities. Certain 17HSD/KSRs catalyze primarily estrogens or androgens, whereas some of them accept both phenolic and neutral steroids as substrate. There are also species-specific differences in substrate specificities, such as in the case of 17HSD/KSR1 (Nokelainen et al. 1996, Puranen et al. 1997). Finally, some 17HSD/KSRs also catalyze several other reactions, such as oxidation of xenobiotics and progestins and β-oxidation of fatty acids, as the type 2, 4 and 5 enzymes do (Wu et al. 1993, Deyashiki et al. 1995, Leenders et al. 1996a, Dieuaide-Noubhani et al. 1997, Qin et al. 1997) (for details, see Tables 1 and 2).

A BRIEF DESCRIPTION OF THE MAIN PROPERTIES OF 17HSD/KSR1–8

17HSD/KSR1

17HSD/KSR1 is predominantly an enzyme of estradiol biosynthesis. It is abundantly expressed in granulosa cells of developing follicles, in which it catalyzes the conversion of 3-hydroxy-1,3,5(10)-estratrien-17-one (estrone) to estradiol (Tremblay et al. 1989, Ghersevich et al. 1994a, Sawetawan et al. 1994). In addition to the ovary, 17HSD/KSR1 participates in estradiol biosynthesis in the human (Fournet-Dulguerov et al. 1987) but not in the rodent placenta (Nokelainen et al. 1996, Akinola et al. 1997). Variable amounts of the type I enzyme are also expressed in human breast epithelial cells.
### Table 2. Catalytic characterization of 17HSD/KSR enzymes

<table>
<thead>
<tr>
<th>Type/protein family</th>
<th>Species cloned</th>
<th>Preferred cofactor</th>
<th>17HSD/KSR activity in vitro</th>
<th>17HSD/KSR activity in vivo&lt;sup&gt;b&lt;/sup&gt; / catalytic preference</th>
<th>Substrate specificity</th>
<th>Putative function</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/SDR</td>
<td>Human</td>
<td>NADH, NADPH</td>
<td>Dehydrogenase&lt;</td>
<td>Reductase</td>
<td>Estrogens</td>
<td>E2 production</td>
<td>Miettinen et al. (1996), Nokelainen et al. (1996), Puranen et al. (1997)</td>
</tr>
<tr>
<td></td>
<td>Rat</td>
<td></td>
<td>Dehydrogenase&gt;</td>
<td>Dehydrogenase</td>
<td>Estrogens, (androgens)</td>
<td>E2, T production</td>
<td>Wu et al. (1993), Miettinen et al. (1996)</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td></td>
<td>Only reductase activity measured</td>
<td>Not tested/ reductase</td>
<td>Androgens, estrogens</td>
<td>T production</td>
<td>Geissler et al. (1994)</td>
</tr>
<tr>
<td>2/SDR</td>
<td>Human</td>
<td>NAD&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Dehydrogenase&lt;</td>
<td>Reductase</td>
<td>Estrogens, (androgens)</td>
<td>E2, T production (20αP activation)</td>
<td>Wu et al. (1993), Miettinen et al. (1996)</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td></td>
<td>Dehydrogenase&gt;</td>
<td>Dehydrogenase</td>
<td>Estrogens, (androgens)</td>
<td>E2, T production</td>
<td>Wu et al. (1993), Miettinen et al. (1996)</td>
</tr>
<tr>
<td>3/SDR</td>
<td>Human</td>
<td>NADPH</td>
<td>Only reductase activity measured</td>
<td>Not tested/ reductase</td>
<td>Androgens, estrogens</td>
<td>T production</td>
<td>Geissler et al. (1994)</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td></td>
<td>Dehydrogenase&lt;</td>
<td>Reductase</td>
<td>Estrogens, (androgens)</td>
<td>E2 production</td>
<td>Nokelainen et al. (1998)</td>
</tr>
<tr>
<td>4/SDR/MFE</td>
<td>Porcine</td>
<td>NAD&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Dehydrogenase&lt;</td>
<td>Reductase</td>
<td>Estrogens</td>
<td>T production, detoxification</td>
<td>Leenders et al. (1996a), Qin et al. (1997)</td>
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<td></td>
<td>Human</td>
<td></td>
<td>Dehydrogenase&gt;</td>
<td>Dehydrogenase</td>
<td>Fatty acyl-CoA, estrogens</td>
<td>β-oxidation of fatty acids, E2 inactivation</td>
<td>Leenders et al. (1996a), Qin et al. (1997)</td>
</tr>
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<td>6/SDR</td>
<td>Rat</td>
<td>NAD&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Only dehydrogenase activity measured</td>
<td>Dehydrogenase</td>
<td>Androgens, (estrogens)</td>
<td>E2 production</td>
<td>Nokelainen et al. (1998)</td>
</tr>
<tr>
<td>7/SDR</td>
<td>Mouse</td>
<td>NADPH</td>
<td>Dehydrogenase&lt;</td>
<td>Reductase</td>
<td>Estrogens</td>
<td>E2 production</td>
<td>Nokelainen et al. (1998)</td>
</tr>
<tr>
<td>8/SDR</td>
<td>Human</td>
<td>NAD&lt;sup&gt;+&lt;/sup&gt;/ NADH</td>
<td>Dehydrogenase&gt;</td>
<td>Not tested/ dehydrogenase</td>
<td>Estrogens, (androgens)</td>
<td>E2 inactivation (E2 production), androgen inactivation</td>
<td>Fomitcheva et al. (1998)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Activities have been measured using purified protein or an enzyme-rich cell lysate to which an appropriate substrate and cofactor have been added.

<sup>b</sup>Activities have been measured in cultured cells transfected with a cDNA in question. A substrate has been added to the media from which a product formed has been collected and measured at certain time points.

<sup>c</sup>Substrates or functions presented in parenthesis are not the primary substrates or activities of an enzyme.

DHT, 5α-dihydrotestosterone; E2, estradiol; P, progesterone; 20αP, 20α-dihydroprogesterone; T, testosterone.
17HSD/KSR2

17HSD/KSR2 converts estradiol, testosterone and 5α-androstan-17β-ol-3-one (5α-dihydrotestosterone) to their less active forms estrone, 4-androstene-3,17-dione (androstenedione) and 5α-androstan-3,17-dione (5α-androstane-dione) respectively, and it also possesses 20α-HSD activity (Wu et al. 1993). The type 2 enzyme is widely and abundantly expressed in both adult and fetal tissues such as placenta, uterus, liver and the gastrointestinal and urinary tracts (Casey et al. 1994, Moghrabi et al. 1997, Mustonen et al. 1997a, 1998a). Due to its expression pattern and enzymatic characteristics, it has been suggested that the type 2 enzyme protects tissues from excessive steroid actions.

17HSD/KSR3

17HSD/KSR3 is almost exclusively expressed in the testis, in which it is essential for testosterone biosynthesis (Geissler et al. 1994). Deficiency of the active enzyme results in male pseudohermaphroditism (Geissler et al. 1994, Andersson et al. 1995). In addition to the conversion of androstenedione to testosterone, the enzyme is capable of catalyzing conversion of 5α-androstanedione to 5α-dihydrotestosterone and estrone to estradiol.

17HSD/KSR4

Among 17HSD/KSRs, type 4 is an unique multifunctional enzyme (MFE) consisting of 17HSD/KSR-, hydrotase- and sterol carrier 2-like domains (Adamski et al. 1992, Leenders et al. 1996a, Qin et al. 1997). This peroxisomal enzyme (Markus et al. 1995) is cleaved to a 32 kDa N-terminal fragment, and both the full-length (80 kDa) and the 32 kDa peptide catalyze D-specific dehydrogenase reaction of 3-hydroxyacyl-CoA, estradiol and Δ5-3α,17β-androstene-diol. The central part of the full-length enzyme catalyzes the 2-enoyl-acyl-CoA hydrotase reaction, while the C-terminus of the 17HSD/KSR can facilitate the transfer of 7-dehydrocholesterol and phosphatidylcholine between membranes in vitro (Novikov et al. 1994, Leenders et al. 1996a, Qin et al. 1997). 17HSD/KSR4 is ubiquitously expressed, but in some tissues it shows cell-specific expression. In brain it is present only in Purkinje cells, in the lung only in bronchial epithelium and in the uterus in luminal and glandular epithelium (Kaufmann et al. 1995, Möller et al. 1999). Deficiency of 17HSD/KSR4 leads to the disease known as Zellweger syndrome (Novikov et al. 1997, van Grunsven et al. 1998).

17HSD/KSR5

17HSD/KSR5 is also known as type 2 3α-HSD (also known as AKR1C3), and differently from other 17HSD/KSRs it belongs to the AKR family. With other members of the AKR family, type 1 3α-HSD, type 3 3α-HSD and 20α-HSD, 17HSD/KSR5 shares 84, 86 and 88% identity respectively. Two human allele variants of the type 5 enzyme have been cloned (Qin et al. 1993, Khanna et al. 1995a, Lin et al. 1997), and they share 99-4% amino acid sequence identity and similar enzymatic characteristics (Dufort et al. 1999).

Both human and mouse 17HSD/KSR5 catalyze the conversion of androstenedione to testosterone, and additionally possess 3α-HSD and dihydrodiol dehydrogenase activity to some extent (Deyashiki et al. 1995, Khanna et al. 1995a, Lin et al. 1997, Dufort et al. 1999). Because the 17HSD/KSR activity of the human type 5 enzyme is highly labile and destroyed upon homogenization of the cells or tissue (Dufort et al. 1999), human 17HSD/KSR5 has previously been identified predominantly as 3α-HSD (Khanna et al. 1995a, Lin et al. 1997). In intact cells, however, human 17HSD/KSR5 catalyzes 17HSD/KSR reactions several times more efficiently than 3α-HSD reactions (Dufort et al. 1999). Human, but not mouse, 17HSD/KSR5 also converts 4-pregnene-3,20-dione (progesterone) to 20α-hydroxy-4-pregnen-3-one (20α-dihydroprogesterone) effectively (Dufort et al. 1999). 17HSD/KSR5 appears to be involved in formation of androgens in the testis and several peripheral tissues. Using specific probes and antibodies for human 17HSD/KSR5, the type 5 enzyme has been localized in the liver, adrenal, testis, the basal cells of the prostate, and in prostatic carcinoma cell lines, DU-145 and LNCaP, as well as in the osteosarcoma cells MG-63 (Dufort et al. 1999, El-Alfy et al. 1999).

17HSD/KSR6

17HSD/KSR6 converts 5α-androstan-3α,17β-diol to 5α-androstan-3α-ol-17-one and thus it is part of the catalytic cascade of 5α-dihydrotestosterone (Biswa & Russell 1997). 17HSD/KSR6 also shows low dehydrogenase activity with
<table>
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<th>17HSD type (species)</th>
<th>Gene</th>
<th>References for cloning</th>
<th>Accession number</th>
<th>Estimated size (kb)</th>
<th>Size of mRNAs (kb)</th>
<th>Number of exons</th>
<th>Chromosomal localization</th>
<th>Deficiency/mutations found</th>
<th>Other references</th>
</tr>
</thead>
<tbody>
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<td>Human</td>
<td>HSD17B1 (EDH17B2)</td>
<td>Luu-The et al. (1990), Peltoketo et al. (1992)</td>
<td>M27136, M27138, M84472</td>
<td>3.2</td>
<td>1.3, 2.2</td>
<td>6</td>
<td>17q21</td>
<td>Luu The et al. (1989), Rommens et al. (1995)</td>
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</tr>
<tr>
<td>Human</td>
<td>HSD17BP1 (EDH17B1) (17β-HSD I)</td>
<td></td>
<td>M29037</td>
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<td>Hsd17b1</td>
<td>Akinola et al. (1998)</td>
<td>X98038</td>
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<td>1.4, 1.7</td>
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<td>HSD17B3</td>
<td>Geissler et al. (1994)</td>
<td>U05659</td>
<td>&gt;60</td>
<td>1.3</td>
<td>11</td>
<td>9q22</td>
<td>Male pseudo-hermaphroditism</td>
<td>Andersson et al. (1996), Takeyama et al. (1998)</td>
</tr>
<tr>
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<td>HSD17B4</td>
<td>Leenders et al. (1999)</td>
<td>AF057720–AF057740</td>
<td>&gt;100</td>
<td>3.0</td>
<td>24</td>
<td>5q2-3</td>
<td>Zellweger syndrome</td>
<td>Leenders et al. (1996b), Novikov et al. (1997), van Grunsven et al. (1998)</td>
</tr>
<tr>
<td>Mouse</td>
<td>Hsd17B5</td>
<td>Rheault et al. (1999)</td>
<td>AF110408–AF110414</td>
<td>16</td>
<td>1.2</td>
<td>9</td>
<td>13 region A2</td>
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<td>Ke6</td>
<td>Maxwell et al. (1995)</td>
<td>U34072</td>
<td>2.2 kb</td>
<td>1.0, 1.2</td>
<td>9</td>
<td></td>
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</table>

*Previous names are given in parenthesis.

bTwo splicing variants are of same size.

*Generic name AKR1C3 is used as well but was not registered at HUGO Nomenclature Committee.

dDeficiency is due to the abnormal regulation of Ke 6 and not because of the mutations in the gene.
5α-dihydrotestosterone, testosterone and estradiol and possesses a weak oxidative 3α-HSD activity. The type 6 enzyme shares 65% sequence identity with retinol dehydrogenase type 1 and is most abundantly expressed in liver and prostate, at least in rodent tissues.

17HSD/KSR7

While 17HSD/KSR1 is expressed in the developing follicles, 17HSD/KSR7 is the enzyme of ovarian estradiol biosynthesis in luteinized cells (Nokelainen et al. 1998). Both rat and mouse type 7 enzymes catalyze exclusively estrone to estradiol, and 17HSD/KSR7 is abundantly expressed in the corpus luteum during the second half of rodent pregnancy, in particular. 17HSD/KSR7 mRNA has also been detected in placental, mammary gland and kidney samples. Rat 17HSD/KSR7 was first cloned as prolactin receptor associated protein (PRAP) based on its capability to bind the short form of prolactin receptor (Duan et al. 1996).

17HSD/KSR8

The Ke 6 gene product has been characterized as a protein whose abnormal regulation is linked to the development of recessive polycystic kidney disease in mice (Aziz et al. 1993). Recently it was found to be a 17HSD/KSR (Fomitcheva et al. 1998), and we suggest that it is named 17HSD/KSR8. In in vitro conditions, this novel 17HSD/KSR8 converts most efficiently estradiol to estrone and, to some extent, it also catalyses oxidative reactions of androgens and the reduction from estrone to estradiol. The Ke 6 gene gives rise to two splicing variants, a and b, and consequently to two protein species. In addition to the kidney, the Ke 6a (17HSD/KSR8a) protein is abundant in liver and gonads, while the Ke 6b (17HSD/KSR8b) form is spleen specific. Interestingly, in the ovary, 17HSD/KSR8 is present in cumulus cells and not in granulosa or luteal cells like 17HSD/KSR1 and -7 respectively.

17HSD/KSR genes

Up to the present, genes for 17HSD/KSR types 1–5 and 8 have been characterized and the first four of them have been named HSD17B1–4 as recommended by the HUGO Nomenclature Committee. Genes for 17HSD/KSR5 and 8 were discovered before their 17β-hydroxysteroid converting activity was established, and therefore they have been named divergently. It is also worthy of note that human HSD17B1 is situated in tandem with a gene that has been named HSD17BP1 and whose function is not known. These two genes were previously called EDH17B2 and 17β-HSD II (HSD17B1), and EDH17B1 and 17β-HSD I (HSD17BP1) (Table 3).

Due to alternative splicing and selective use of promoter and polyadenylation signals, 17HSD/KSR genes are expressed in several mRNA species (Table 3). Two splicing variants have been characterized for the HSD17B2 (Labrie et al. 1995) and mouse Ke 6 genes (Maxwell et al. 1995), and the latter, at least, is also translated to two different proteins. Two human HSD17B1 promoters result in two 17HSD/KSR1 mRNA forms (Luu-The et al. 1990), but apparently only the shorter mRNA type (1·3 kb) is efficiently translated to 17HSD/KSR1 protein (Miettinen et al. 1996). Alternative use of polyadenylation signals, in turn, leads to two rat 17HSD/KSR1 transcripts (Akinola et al. 1996, 1998). Instead, HSD17B4 is expressed as a single mRNA species and the protein product is later split to three different functional parts (Leenders et al. 1996a).

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