REVIEW

17 β -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 17 β -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), 17 β -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 17 β -hydroxy- and 17-ketosteroids respectively. Both estrogens and androgens have the highest affinity for their receptors in the 17 β -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-3,17 β -diol) and testosterone (4-androsten-17 β -ol-3-one) biosynthesis in the gonads, but they are also present

TABLE 1. List of the cloned 17HSD/KSR enzymes

	Species cloned	References for cloning	Accession number	Subcellular localization	Tissue distribution ^a	Other names used/in use	Other references
Type/protein family							
1/SDR	Human	Peltoketo <i>et al.</i> (1988), Luu The <i>et al.</i> (1989)	X13440	Cytosolic	Ovary, placenta, breast	Placental 17HSD, 17β, 20α-HSD, estradiol 17HSD, estradiol-17β-dehydrogenase/oxidoreductase	Fournet-Dulguerov <i>et al.</i> (1987), Tremblay <i>et al.</i> (1989), Dupont <i>et al.</i> (1991), Ghersevich <i>et al.</i> (1994 <i>b,c</i>), Sawetawan <i>et al.</i> (1994), Sasano <i>et al.</i> (1996), Puranen <i>et al.</i> (1997), Ghosh <i>et al.</i> (1995), Azzi <i>et al.</i> (1996), Breton <i>et al.</i> (1996)
	Rat	Ghersevich <i>et al.</i> (1994 <i>a</i>), Akinola <i>et al.</i> (1996)	X78811, X97754	Membrane-associated?	Ovary	17β-Hydroxysteroid oxidoreductase, estrogenic 17KSR	
	Mouse	Nokelainen <i>et al.</i> (1996)	X89627				
2/SDR	Human	Wu <i>et al.</i> (1993)	L11708	Microsomal	Placenta, liver, gastrointestinal tract, kidney, uterus, breast, prostate		Casey <i>et al.</i> (1994), Elo <i>et al.</i> (1996), Moghrabi <i>et al.</i> (1997), Mustonen <i>et al.</i> (1997 <i>a</i> , 1998 <i>a,b</i>)
	Rat	Akinola <i>et al.</i> (1996)	X91234		Placenta, liver, gastrointestinal and urinary tracts		
	Mouse	Mustonen <i>et al</i> (1997 <i>b</i>)	Y09517				
3/SDR	Human	Geissler <i>et al.</i> (1994)	U05659	Microsomal	Testis	Testicular 17KSR/17β-hydroxysteroid oxidoreductase	Luu-The <i>et al.</i> (1995)
	Mouse	Sha <i>et al.</i> (1997)	U66827				
4/SDR/MFE	Porcine	Leenders <i>et al.</i> (1994)	X78201	Peroxisomal	Widely distributed	Peroxisomal multifunctional enzyme II, MFP2, 2-enoyl-CoA hydratase 2 D-specific hydroxyacyl dehydrogenase	Novikov <i>et al.</i> (1994), Markus <i>et al.</i> (1995)
	Human	Adamski <i>et al.</i> (1995)	X87176				
	Mouse	Normand <i>et al.</i> (1995)	X89998				
	Rat	Corton <i>et al.</i> (1996), Dieuaide-Noubhani <i>et al.</i> (1996), Qin <i>et al.</i> (1997)	X94978				
	Chicken	Kobayashi <i>et al.</i> (1997)	U77911				
	Guinea pig	Caira <i>et al.</i> (1998)	Y13623				

TABLE 1. *Continued*

	Species cloned	References for cloning	Accession number	Subcellular localization	Tissue distribution ^a	Other names used/in use	Other references
Type/protein family							
5/AKR	Mouse	Deyashiki <i>et al.</i> (1995)	D45850	Cytosolic	Liver, kidney, testis, prostate, adrenal, bone	HAKRb, AKR1C3, type 2 3 α HSD, mouse estradiol 17 β -dehydrogenase	Lin <i>et al.</i> (1992), Labrie <i>et al.</i> (1997), Dufort <i>et al.</i> (1999), El-Alfy <i>et al.</i> (1999)
	Human	Qin <i>et al.</i> (1993), Lin <i>et al.</i> (1997)	S68288				
6/SDR	Rat	Biswas & Russell (1997)	U89280	Membrane-bound	Prostate, liver		
7/SDR	Rat	Duan <i>et al.</i> (1996)	U44803	Membrane-bound/ associated	Ovary	PRAP	Duan <i>et al.</i> (1997)
	Mouse	Nokelainen <i>et al.</i> (1998)	Y15733		Ovary, placenta, mammary gland		
8/SDR	Human	Ando <i>et al.</i> (1996)	D82061	Unknown	Liver, pancreas, kidney, skeletal muscle	HKE6	Kikuti <i>et al.</i> (1997), Fomitcheva <i>et al.</i> (1998)
	Mouse	Aziz <i>et al.</i> (1993)	U34072		Kidney, liver, ovary, testis, spleen	Ke 6	

^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 β -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 β -HSD having 93.5% amino acid identity and similar substrate specificity, and up to six rodent types of β -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 1 enzyme are also expressed in human breast epithelial cells

TABLE 2. Catalytic characterization of 17HSD/KSR enzymes

Type/protein family	Species cloned	Preferred cofactor	17HSD/KSR activity <i>in vitro</i> ^a	17HSD/KSR activity <i>in vivo</i> ^b /catalytic preference	Substrate specificity	Putative function	References
1/SDR	Human Rat Mouse	NADH, NADPH	Dehydrogenase < reductase	Reductase	Estrogens Estrogens, androgens	E2 production E2, T production	Miettinen <i>et al.</i> (1996), Nokelainen <i>et al.</i> (1996), Puranen <i>et al.</i> (1997)
2/SDR	Human Rat Mouse	NAD ⁺	Dehydrogenase > reductase	Dehydrogenase	Estrogens, androgens, (progestins) ^c	E2, T inactivation (20αP activation)	Wu <i>et al.</i> (1993), Miettinen <i>et al.</i> (1996)
3/SDR	Human Mouse	NADPH	Only reductase activity measured	Not tested/reductase	Androgens, estrogens	T production	Geissler <i>et al.</i> (1994)
4/SDR/MFE	Porcine Human Mouse Rat Chicken Guinea pig Mouse	NAD ⁺	Dehydrogenase >> reductase	Dehydrogenase	Fatty acyl-CoA, estrogens	β-oxidation of fatty acids, E2 inactivation	Leenders <i>et al.</i> (1996a), Qin <i>et al.</i> (1997)
5/AKR	Human Mouse	NADPH	Dehydrogenase < reductase	Reductase	Steroids, cholic acids, xenobiotics	T production, detoxification T production, 20αP activation, bile acid production, detoxification DHT inactivation	Deyashiki <i>et al.</i> (1995), Khanna <i>et al.</i> (1995a), Lin <i>et al.</i> (1997), Dufort <i>et al.</i> (1999) Biswas & Russell (1997)
6/SDR	Rat	NAD ⁺	Only dehydrogenase activity measured	Dehydrogenase	Androgens, (estrogens)		
7/SDR	Mouse Rat	NADPH	Dehydrogenase < reductase	Reductase	Estrogens	E2 production	Nokelainen <i>et al.</i> (1998)
8/SDR	Mouse Human	NAD ⁺ /NADH	Dehydrogenase > reductase	Not tested/dehydrogenase	Estrogens, androgens	E2 inactivation (E2 production), androgen inactivation	Fomitcheva <i>et al.</i> (1998)

^aActivities have been measured using purified protein or an enzyme-rich cell lysate to which an appropriate substrate and cofactor have been added.^bActivities 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.^cSubstrates 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.

(Miettinen *et al.* 1996, Sasano *et al.* 1996). The human 17HSD/KSR1 clearly prefers phenolic substrates over neutral ones, while rodent type 1 enzymes catalyze effectively both estrogenic and androgenic substrates (Nokelainen *et al.* 1996, Puranen *et al.* 1997).

17HSD/KSR2

17HSD/KSR2 converts estradiol, testosterone and 5 α -androstane-17 β -ol-3-one (5 α -dihydrotestosterone) to their less active forms estrone, 4-androstene-3,17-dione (androstenedione) and 5 α -androstane-3,17-dione (5 α -androstenedione) respectively, and it also possesses 20 α -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.* 1996). In addition to the conversion of androstenedione to testosterone, the enzyme is capable of catalyzing conversion of 5 α -androstenedione to 5 α -dihydrotestosterone and estrone to estradiol.

17HSD/KSR4

Among 17HSD/KSRs, type 4 is an unique multifunctional enzyme (MFE) consisting of 17HSD/KSR-, hydratase- 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 Δ^5 -3 α ,17 β -androstene-diol. The central part of the full-length enzyme catalyses the 2-enoyl-acyl-CoA hydratase 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 3 α -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 3 α -HSD, type 3 3 α -HSD and 20 α -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 3 α -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 3 α -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 3 α -HSD reactions (Dufort *et al.* 1999). Human, but not mouse, 17HSD/KSR5 also converts 4-pregnene-3,20-dione (progesterone) to 20 α -hydroxy-4-pregnen-3-one (20 α -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 5 α -androstane-3 α ,17 β -diol to 5 α -androstane-3 α -ol-17-one and thus it is part of the catabolic cascade of 5 α -dihydrotestosterone (Biswas & Russell 1997). 17HSD/KSR6 also shows low dehydrogenase activity with

TABLE 3. Nomenclature and characterization of the cloned 17HSD/KSR genes

17HSD type (species)	Gene	References for cloning	Accession number	Estimated size (kb)	Size of mRNAs (kb)	Number of exons	Chromosomal localization	Deficiency/ mutations found	Other references
1									
Human	<i>HSD17B1</i> (<i>EDH17B2</i>) ^a (<i>17β-HSD II</i>)	Luu-The <i>et al.</i> (1990), Peltoketo <i>et al.</i> (1992)	M27136, M27138, M84472	3·2	1·3, 2·2	6	17q21		Luu The <i>et al.</i> (1989), Rommens <i>et al.</i> (1995)
Human	<i>HSD17BP1</i> (<i>EDH17B1</i>) (<i>17β-HSD I</i>)		M29037						
Rat	<i>Hsd17b1</i>	Akinola <i>et al.</i> (1998)	X98038	2·2	1·4, 1·7	6			
2									
Human	<i>HSD17B2</i>	Labrie <i>et al.</i> (1995)	L40796– L40802	>40	1·5 ^b	5	16q24·1–2		Casey <i>et al.</i> (1994), Durocher <i>et al.</i> (1995)
3									
Human	<i>HSD17B3</i>	Geissler <i>et al.</i> (1994)	U05659	>60	1·3	11	9q22	Male pseudo- hermaphroditism	Andersson <i>et al.</i> (1996), Takeyama <i>et al.</i> (1998)
4									
Human	<i>HSD17B4</i>	Leenders <i>et al.</i> (1999)	AF057720– AF057740	>100	3·0	24	5q2·3	Zellweger syndrome	Leenders <i>et al.</i> (1996b), Novikov <i>et al.</i> (1997), van Grunsven <i>et al.</i> (1998)
5									
Human	<i>HSD17B5</i> ^c	Khanna <i>et al.</i> (1995a)	L43831– L43839	15	1·2	9	10p14–15		Khanna <i>et al.</i> (1995b)
Mouse	<i>Hsd17b5</i>	Rheault <i>et al.</i> (1999)	AF110408– AF110414	16	1·2	9	13 region A2		
8									
Human	<i>HKE6</i>	Kikuti <i>et al.</i> (1997)	D84401	2·2 kb	1·0	9	6p21·3	Polycystic kidney disease ^d	Aziz <i>et al.</i> (1993), Fomitcheva <i>et al.</i> (1998), Ramirez <i>et al.</i> (1998)
Mouse	<i>Ke6</i>	Maxwell <i>et al.</i> (1995)	U34072	2·2 kb	1·0, 1·2	9	17		

^aPrevious names are given in parenthesis.^bTwo splicing variants are of same size.^cGeneric name *AKRIC3* 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.

5 α -dihydrotestosterone, testosterone and estradiol and possesses a weak oxidative 3 α -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 17 β -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 17 β -HSD II (*HSD17B1*), and EDH17B1 and 17 β -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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