Steroid hormone

Overview: Steroid hormone receptors (nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, see Dahlman-Wright *et al*., 2006; Lu *et al*., 2006) are nuclear hormone receptors of the NR3 class, with endogenous agonists that include 5α-dihydrotestosterone (DHT), aldosterone, cortisol, corticosterone, progesterone, testosterone and estradiol. These receptors exist as dimers coupled with chaperone molecules (such as HSP90 and immunophilin HSP65), which are shed on binding the steroid hormone. Although rapid signalling phenomena are observed (see Levin, 2008; Prossnitz and Maggiolini, 2009), the principal signalling cascade appears to involve binding of the activated receptors to nuclear hormone response elements of the genome, with a 15-nucleotide consensus sequence AGAACAnnnTGTTCT (i.e. an inverted palindrome) as homo- or heterodimers. They also affect transcription by protein–protein interactions with other transcription factors, such as activator protein 1 and nuclear factor κB. Splice variants of each of these receptors can form functional or non-functional monomers that can dimerize to form functional or non-functional receptors. For example, alternative splicing of PR mRNA produces A and B monomers that combine to produce functional AA, AB and BB receptors with distinct characteristics (Vegeto *et al*., 1993).

A 7TM receptor responsive to oestrogen (GPER, also known as GPR30, ENSG00000164850, see Prossnitz *et al*., 2008) has been described. Human orthologues of 7TM 'membrane progestin receptors' (ENSG00000182749, ENSG00000170915 and ENSG00000137819), initially discovered in fish (Zhu *et al*., 2003a,b), appear to localize to intracellular membranes and appear to respond to 'non-genomic' progesterone analogues independently of G proteins (Smith *et al*., 2008).

Nomenclature	Glucocorticoid	Mineralocorticoid	Progesterone	Androgen
Preferred abbreviation	GR	MR	PR	AR
Systematic nomenclature	NR3C1	NR3C2	NR3C3	NR3C4
Other names	Type II glucocorticoid receptor	Type I glucocorticoid receptor, aldosterone receptor	–	dihydrotestosterone receptor
Ensembl ID	ENSG00000113580	ENSG00000151623	ENSG00000082175	ENSG00000169083
Rank order of potency	Cortisol, corticosterone >> aldosterone, deoxycortisone (Rupprecht *et al*., 1993)	Corticosterone, cortisol, aldosterone, progesterone (Rupprecht *et al*., 1993)	Progesterone	DHT>testosterone
Selective agonists	RU28362, RU26988	Aldosterone	ORG2058, progesterone	DHT, mibolerone, R1881
Selective antagonists	Mifepristone, ZK112993, onapristone	RU28318, ZK112993, onapristone	Mifepristone, ZK112993, onapristone	Hydroxyflutamide, nilutamide
Probes	[^{3}H]-Dexamethasone	[^{3}H]-Aldosterone	[^{3}H]-ORG2058	[^{3}H]-DHT, [^{3}H]-mibolerone, [^{3}H]-R1881

[^{3}H]-Dexamethasone also binds to MR *in vitro*. PR antagonists have been suggested to subdivide into Type I (e.g. onapristone) and Type II (e.g. ZK112993) groups. These groups appear to promote binding of PR to DNA with different efficacies and evoke distinct conformational changes in the receptor, leading to a transcription-neutral complex (Gass *et al*., 1998; Leonhardt *et al*., 1998). Mutations in AR underlie testicular feminization and androgen insensibility syndromes, spinal and bulbar muscular atrophy (Kennedy's disease).

Nomenclature	Oestrogen α	Oestrogen β
Preferred abbreviation	ERα	ERβ
Systematic nomenclature	NR3A1	NR3A2
Other names	Estradiol	Estradiol
Ensembl ID	ENSG00000091831	ENSG00000140009
Selective agonists	PPT (Kraichely *et al*., 2000; Stauffer *et al*., 2000)	DPN (Meyers *et al*., 2001)
Selective antagonists	MPP (Sun *et al*., 2002)	PHTPP (Compton *et al*., 2004), *R,R*-THC (Meyers *et al*., 1999; Sun *et al*., 1999)

R,R-THC exhibits partial agonist activity at ERα (Meyers *et al*., 1999; Sun *et al*., 1999). Oestrogen receptors may be blocked non-selectively by tamoxifen and raloxifene and labelled by [^{3}H]-estradiol and [^{3}H]-tamoxifen. Many agents thought initially to be antagonists at oestrogen receptors appear to have tissue-specific efficacy (e.g. tamoxifen is an antagonist at oestrogen receptors in the breast, but is an agonist at oestrogen receptors in the uterus), hence the descriptor SERM (selective oestrogen receptor modulator) or SnuRM (selective nuclear receptor modulator). Y134 has been suggested to be an ERα-selective oestrogen receptor modulator (Ning *et al*., 2007).

Additional 'orphan' oestrogen receptor-related proteins have been described (ERRα ENSG00000173153; ERRβ ENSG00000119715; ERRγ ENSG00000057103); DY131 is an agonist with selectivity for ERRβ and ERRγ compared with ERRα, ERα and ERβ (Yu and Forman, 2005).

Abbreviations: **DHT**, 5α-dihydrotestosterone; **DPN**, 2,3-*bis*(4-hydroxyphenyl)propionitrile; **DY131**,*N'*-([1E]-[4-(diethylamino)phenyl] methylene)-4-hydroxybenzohydrazide; **MPP**, 1,3-*bis*(4-hydroxyphenyl)-4-methyl-5-(4-[2-piperidinylethoxy]phenol)-1*H*-pyrazole; **ORG2058**, 16-α-ethyl-21-hydroxy-19-norpregn-4-ene-3,20-dione; **PPT**, 4,4',4''-(4-propyl-[1*H*]-pyrazole-1,3,5-triyl)trisphenol; **PHTPP**, 4-(2-phenyl-5,7-bis[trifluoromethyl]pyrazolo[1,5-a]pyrimidin-3-yl)phenol; **R1881**, 17β-hydroxy-17α-methyl-estra-4,9,11-triene-3-one, also known as methyltrienolone; ***R,R*-THC**, *R,R*-tetrahydrochrysene; **RU26988**, 11β,17β-dihydroxy-21-methyl-17α-pregna-1,4,6-trien-20-yl-3-on; **RU28318**, 3-oxo-7-propyl-17-hydroxy-androstan-4-en-17-yl; **RU28362**, 11β,17β-dihydroxy-6-methyl-17-(1-propionyl)androsta-1,4,6-triene-3-one; **Y134**, (6-hydroxy-2-[4-hydroxyphenyl]-benzo[b]thiophen-3-yl)-(4-[4-isopropylpiperazin-1-yl]-phenyl)methanone; **ZK112993**, 11β-(4-acetylphenyl)-17β-hydroxyl-17α-(1-propinyl)-4,8-estradiene-3-one

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