

NUCLEAR RECEPTORS

Steroid hormone

Overview: Steroid hormone receptors are nuclear hormone receptors of the NR3 class, with endogenous agonists that include 5 α -dihydrotestosterone, 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. The activated receptors then bind to nuclear hormone response elements of the genome, with a 15 nucleotide consensus sequence AGAACAnnnTGTCT (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- κ B. Splice variants of each of these receptors can form functional or nonfunctional monomers that can dimerize to form functional or nonfunctional 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).

Nomenclature	Mineralocorticoid	Glucocorticoid	Progesterone	Androgen
Preferred abbreviation	MR	GR	PR	AR
Other names	Type I glucocorticoid receptor, aldosterone receptor	Type II glucocorticoid receptor	—	Dihydrotestosterone receptor
Ensembl ID	ENSG00000151623	ENSG00000113580	ENSG00000082175	ENSG00000169083
Rank order of potency	Corticosterone = cortisol = aldosterone = progesterone (Rupprecht <i>et al.</i> , 1993)	Cortisol, corticosterone >> aldosterone, deoxycortisone (Rupprecht <i>et al.</i> , 1993)	Progesterone	DHT > testosterone
Selective agonists	Aldosterone	RU28362, RU26988	ORG2058, progesterone	DHT, mibolerone, R1881
Selective antagonists	RU28318, ZK112993, onapristone	Mifepristone, ZK112993, onapristone	Mifepristone, ZK112993, onapristone	Hydroxyflutamide
Radioligands	[³ H]-aldosterone	[³ H]-dexamethasone	[³ H]-ORG2058	[³ H]-DHT, [³ H]-mibolerone, [³ H]-R1881

[³H]-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 insensitivity syndromes, spinal and bulbar muscular atrophy (Kennedy's disease).

Nomenclature	Estrogen α	Estrogen β
Preferred abbreviation	ER α	ER β
Other names	Estradiol	Estradiol
Ensembl ID	ENSG00000091831	ENSG00000140009

Estrogen receptors may be blocked nonselectively by tamoxifen and raloxifene, and labelled by [³H]-estradiol and [³H]-tamoxifen. Many agents considered to be antagonists at estrogen receptors appear to have tissue-specific efficacy (e.g. tamoxifen is an antagonist at estrogen receptors in the breast but is an agonist at estrogen receptors in the uterus), hence the descriptor SERM (selective estrogen receptor modulator) (see Dutertre and Smith, 2000). Additional 'orphan' estrogen-receptor-related proteins have been described (ERR α ENSG00000173153; ERR β ENSG00000119715; ERR γ ENSG00000057103).

Abbreviations: **ORG2058**, 16 α -ethyl-21-hydroxy-19-norpregn-4-ene-3,20-dione; **R1881**, 17 β -hydroxy-17 α -methyl-estra-4,9,11-triene-3-one (also known as methyltrienolone); **RU26988**, 11 β ,17 β -dihydroxy-21-methyl-17 α -pregna-1,4,6-trien-20-yl-3-one; **RU28318**, 3-oxo-7-propyl-17-hydroxy-androstan-4-en-17-yl; **RU28362**, 11 β ,17 β -dihydroxy-6-methyl-17-(1-propionyl)androsta-1,4,6-triene-3-one; **ZK112993**, 11 β -(4-acetylphenyl)-17 β -hydroxyl-17 α -(1-propinyl)-4,8-estradiene-3-one.

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Peroxisome proliferator activated

Overview: Peroxisome proliferator-activated receptors (PPARs, provisional nomenclature) are nuclear hormone receptors of the NR1C family, with diverse roles regulating lipid homeostasis, cellular differentiation, proliferation and the immune response. PPARs have many potential endogenous agonists (see Bishop-Bailey & Wray, 2003), including 15-deoxy- $A^{12,14}$ -prostaglandin J₂, prostacyclin, many fatty acids and their oxidation products, lysophosphatidic acid (McIntyre *et al.*, 2003), 13-hydroxyoctadecadienoic acid (13-HODE), 15-hydroxyeicosatetraenoic acid (15-HETE) and leukotriene B₄. These receptors also bind hypolipidaemic drugs (PPAR α), antidiabetic thiazolidinediones (PPAR γ) and fatty acids. Once activated by a ligand, the receptor forms a heterodimer with members of the retinoid X receptor family and can act as a transcription factor. Although radioligand binding assays have been described for all three receptors, the radioligands are not commercially available.

Nomenclature	PPAR α	PPAR β	PPAR γ
Other names	NR1C1	NR1C2, NUC1, FAAR, PPAR δ	NR1C3
Ensembl ID	ENSG00000100406	ENSG00000112033	ENSG00000132170
Selective agonists	GW7647, WY14643, clofibrate, fenofibrate, bezafibrate, ciprofibrate, gemfibrozil	L165041	Rosiglitazone (BRL49653), ciglitazone, troglitazone, pioglitazone, CDDO
Selective antagonists	MK886 (Kehrer <i>et al.</i> , 2001)	Sulindac (He <i>et al.</i> , 1999)	CDDO-Me (Wang <i>et al.</i> , 2000), GW9662 (Huang <i>et al.</i> , 1999), diclofenac (6.2, Adamson <i>et al.</i> , 2002), BADGE (4.0, Wright <i>et al.</i> , 2000)

As with the estrogen receptor antagonists, many agents show tissue-selective efficacy (e.g. Bishop-Bailey *et al.*, 2000; Rocchi *et al.*, 2001; Nakamuta *et al.*, 2002).

Abbreviations: BADGE, bisphenol A diglycidyl ether; CDDO, 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid; CDDO-Me, 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid methyl ester; GW7647, 2-([4-{2-([cyclohexylamino]carbonyl)[4-cyclohexylbutyl]amino}ethyl]phenyl]thio)-2-methylpropanoic acid; GW9662, 2-chloro-5-nitro-*N*-phenylbenzamide; MK886, 3-(1-[*p*-chlorobenzyl]-5-[isopropyl]-3-tert-butylthioindol-2-yl)-2,2-dimethylpropanoic acid methyl ester; L165041, (4-[3-{4-acetyl-3-hydroxy-2-propylphenoxy}propoxy]phenoxy)acetic acid; WY14643, *N*-(3-[2-quinolinylmethoxy]phenyl)-trifluoromethanesulfonamide

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Retinoic acid and retinoid X

Overview: Retinoic acid receptors (provisional nomenclature) are nuclear hormone receptors of the NR1B family, with the vitamin A-derived agonists all-*trans* retinoic acid (ATRA) and 9-*cis*-retinoic acid. Retinoid X receptors are NR2B family members and are activated by 9-*cis*-retinoic acid. These receptors form RXR–RAR heterodimers and RXR–RXR homodimers (Mangelsdorf and Evans, 1995; Chambon, 1996). Cytoplasmic cellular retinoid binding proteins (CRBP) I (ENSG00000114115), II (ENSG00000114113), III (ENSG00000139194) and IV (ENSG00000162444) are considered to control the levels of intracellular retinoids available for interaction with their receptors (Li, 1999). [³H]-ATRA and [³H]-9-*cis*-retinoic acid have been used to label RARs and RXRs, respectively.

Nomenclature	RAR α	RAR β	RAR γ
Other names	NR1B1	NR1B2, HBV-activated protein	NR1B3
Ensembl ID	ENSG00000131759	ENSG00000077092	ENSG00000172819

Nomenclature	RXR α	RXR β	RXR γ
Other names	NR2B1	NR2B2	NR2B3
Ensembl ID	ENSG00000078380	ENSG00000112472	ENSG00000143171

ATRA has recently been suggested to be a ligand for the orphan nuclear receptor ROR β (Stehlin-Gaon *et al.*, 2003).

Abbreviations: ATRA, all-*trans*-retinoic acid; CRBP, cellular retinoid binding protein.

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