NUCLEAR RECEPTORS

Liver X and farnesoid X

Overview: Liver X and farnesoid X receptors (LXR and FXR, provisional nomenclature) are members of a steroid analogue-activated nuclear receptor subfamily (ENSF00000000720), which form heterodimers with members of the retinoid X receptor family. Endogenous ligands for LXRs include hydroxycholesterols (OHC), while FXR appears to be activated by bile acids.

Nomenclature	**LXRα**	**LXRβ**	**FXR**
Other names	NR1H3, oxysterols receptor α	NR1H2, oxysterols receptor β, ubiquitously expressed nuclear receptor	NR1H4, bile acid receptor
Ensembl ID	ENSG00000025434	ENSG00000131408	ENSG00000012504
Potency order	20S-OHC, 22R-OHC, 24S-OHC > 25-OHC, 27-OHC (Lehmann *et al*., 1997)	20S-OHC, 22R-OHC, 24S-OHC > 25-OHC, 27-OHC (Lehmann *et al*., 1997)	Chenodeoxycholate > lithocholate, deoxycholate (Makishima *et al*., 1999; Parks *et al*., 1999)
Selective agonists	—	—	ECDCA (Pellicciari *et al*., 2002)
Selective antagonists	—	—	Guggulsterone (Urizar *et al*., 2002)

TO901317 (Repa *et al*., 2000) and GW3965 (Collins *et al*., 2002) are synthetic agonists acting at both LXRα and LXRβ with less than 10-fold selectivity.

Abbreviations: **ECDCA**, 6α-ethyl-chenodeoxycholate, also known as INT747; **guggulsterone**, *trans*-4,17(20)-pregnadiene-3,16-dione; **GW3965**, 3-(3-[*N*-{2-chloro-3-trifluoromethylbenzyl}-{2,2-diphenylethyl}amino]propyloxy)phenylacetic acid hydrochloride; **OHC**, hydroxycholesterol; **TO901317**, *N*-(2,2,2-trifluoroethyl)-*N*-(4-[2,2,2-trifluoro-1-hydroxy-1-{trifluoromethyl}ethyl]phenyl)-benzenesulfonamide

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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-$\Delta^{12,14}$-prostaglandin J_2, prostacyclin, many fatty acids and their oxidation products, lysophosphatidic acid (McIntyre *et al*., 2003), 13-HODE, 15-HETE, Paz-PC, azelaoyl-PAF, and leukotriene B_4. These receptors also bind hypolipidemic drugs (PPARα) and antidiabetic thiazolidinediones (PPARγ). 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	**PPARα**	**PPARβ**	**PPARγ**
Other names	NR1C1	NR1C2, NUC1, FAAR, PPARδ	NR1C3
Ensemble ID	ENSG00000100406	ENSG00000112033	ENSG00000132170
Selective agonists	GW7647, WY14643, clofibrate, fenofibrate, bezafibrate, ciprofibrate, gemfibrozil	L165041, GW501516, GW0742	Rosiglitazone (BRL49653), ciglitazone, troglitazone, pioglitazone, CDDO, GW1929
Selective antagonists	MK886 (Kehrer *et al*., 2001), GW6471 (Xu et al., 2002)	Sulindac (He *et al*., 1999)	CDDO-Me ([Wang *et al*., 2000), GW9662 (Huang *et al*., 1999), diclofenac (6.2, Adamson *et al*., 2002), BADGE (4.0, Wright *et al*., 2000), T0070907 (Lee *et al*., 2002)

As with the estrogen receptor antagonists, many agents show tissue-selective efficacy (e.g. Bishop-Bailey *et al*., 2000; Nakamuta *et al*., 2002; Rocchi *et al*., 2001). Agonists with mixed activity at PPARα and PPARγ have recently been described (e.g. Doebber *et al*., 2004; Guo *et al*., 2004; Xu *et al*., 2004).

Abbreviations: **13-HODE**, 13-hydroxyoctadecadienoic acid; **15-HETE**, 15-hydroxyeicosatetraenoic acid; **Azelaoyl-PAF**, 1-*O*-hexadecyl-2-*O*-(9-carboxyoctanoyl)-sn-glyceryl-3-phosphocholine; **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; **GW1929**, (2*S*)-([2-benzoylphenyl]amino)-3-(4-[2-{methylpyridin-2-ylamino}ethoxy]phenyl)propionic acid; **GW501516**, 2-methyl-4(((4-methyl-2-(4-trifluoromethylphenyl)-1,3-thiazol-5-yl)methyl)sulfanyl)phenoxy)acetic acid; **GW7647**, 2-([4-{2-([{cyclohexylamino}carbonyl][4-cyclohexylbutyl]amino)ethyl}phenyl]thio)-2-methylpropanoic acid; **GW9662**, 2-chloro-5-nitro-*N*-phenylbenzamide; **L165041**, (4-[3-{4-acetyl-3-hydroxy-2-propylphenoxy}propoxyl]phenoxy)acetic acid; **MK886**, 3-(1-[*p*-chlorobenzyl]-5-[isopropyl]-3-tert-butylthioindol-2-yl)-2,2-dimethylpropanoic acid methyl ester; **Paz-PC**, 1-palmitoyl-2-azelaoyl-*sn*-glycero-3-phosphocholine; **T0070907**, 2-chloro-5-nitro-*N*-(4-pyridyl)benzamide; **WY14643**, 2-(4-chloro-6-[{2,3-dimethylphenyl}amino]pyrimidin-2-yl)sulphanylacetic acid, also known as pirinixic acid

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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, and the RAR-selective synthetic agonist TTNPB. Retinoid X receptors are NR2B family members and are activated by 9-*cis*-retinoic acid and the RXR-selective agonists LGD1069 and LG100268. These receptors form RXR–RAR heterodimers and RXR–RXR homodimers (Mangelsdorf and Evans, 1995; Chambon, 1996). Cytoplasmic cellular retinoid binding proteins I (ENSG00000114115), II (ENSG00000114113), III (ENSG00000139194) and IV (ENSG00000162444) are thought to control the levels of intracellular retinoids available for interaction with their receptors (Li, 1999). [^{3}H]-ATRA and [^{3}H]-9-*cis*-retinoic acid have been used to label RARs and RXRs, respectively.

Nomenclature	**RARα**	**RARβ**	**RARγ**
Other names	NR1B1	NR1B2, HBV-activated protein	NR1B3
Ensembl ID	ENSG00000131759	ENSG00000077092	ENSG00000172819
Selective agonists	Ro406055 (Delescluse *et al*., 1991)	—	—
Selective antagonists	Ro415253 (Apfel *et al*., 1992)	—	—

LE135 is an antagonist with selectivity for RARα and RARβ compared to RARγ (Li *et al*., 1999)

Nomenclature	**RXRα**	**RXRβ**	**RXRγ**
Other names	NR2B1	NR2B2	NR2B3
Ensembl ID	ENSG00000078380	ENSG00000112472	ENSG00000143171

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

Abbreviations: **ATRA**, all-*trans*-retinoic acid; **LE135**, 4-(7,8,9,10-tetrahydro-5,7,7,10,10-pentamethyl-5*H*-benzo[*e*]naphtho[2,3-*b*][1,4]diazepin-13-yl)benzoic acid; **LG100268**, 6-(1-[3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl]cyclopropyl) nicotinic acid; **LGD1069**, 4-(1-[3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl]ethenyl) benzoic acid; **Ro406055**, 4-([5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl]carboxamido)benzoic acid (also known as AM580); **Ro415253**, 4-[2-(7-heptoxy-4,4-dimethyl-1,1-dioxo-2,3-dihydrothiochromen-6-yl)prop-1-enyl]benzoic acid, also known as LG629; **TTNPB**, (*E*)-4-(2-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl]-1-propenyl)benzoic acid

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Steroid hormone

Overview: Steroid hormone receptors 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. The activated receptors then bind 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 (AP-1) and nuclear factor κB (NF-κB). Splice variants of each of these receptors can form functional or nonfunctional 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).

7TM receptors responsive to estrogen and progestins have recently been described in man (Filardo and Thomas, 2005; Zhu *et al*., 2003a, b), although their physiological significance has yet to be elucidated.

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 *et al*., 1993)	Cortisol, corticosterone ≫aldosterone, deoxycortisone (Rupprecht *et al*., 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
Probes	[^{3}H]-Aldosterone	[^{3}H]-Dexamethasone	[^{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	**Estrogen α**	**Estrogen β**
Preferred abbreviation	ERα	ERβ
Other names	Estradiol	Estradiol
Ensembl ID	ENSG00000091831	ENSG00000140009

Estrogen receptors may be blocked nonselectively by tamoxifen and raloxifene, and labelled by [^{3}H]-estradiol and [^{3}H]-tamoxifen. Many agents thought initially 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 & Smith, 2000). Additional 'orphan' estrogen-receptor-related proteins have been described (ERRα ENSG00000173153; ERRβ ENSG00000119715; ERRγ ENSG00000057103).

Abbreviations: **ORG2058**, 16-α-ethyl-21-hydroxy-19-norpregn-4-ene-3,20-dione; **R1881**, 17β-hydroxy-17α-methyl-estra-4,9,11-triene-3-one, also known as methyltrienolone; **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; **ZK112993**, 11β-(4-acetylphenyl)-17β-hydroxyl-17α-(1-propinyl)-4,8-estradiene-3-one

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Thyroid hormone

Overview: Thyroid hormone receptors (TRs, provisional nomenclature) are nuclear hormone receptors of the NR1A family, with diverse roles regulating macronutrient metabolism, cognition and cardiovascular homeostasis. TRs are activated by thyroxine (T4) and thyroid hormone (T3). Once activated by a ligand, the receptor acts as a transcription factor either as a monomer, homodimer or heterodimer with members of the retinoid X receptor family.

Nomenclature	**TRα**	**TRβ**
Other names	NR1A1, THRA, erbAα, erbA1, EAR7	NR1A2, THRB, erbAβ, erbA2
Ensemble ID	ENSG00000126351	ENSG00000151090
Rank order of potency	T3 > T4	T3 > T4
Selective agonists	—	GC1 (Chiellini *et al*., 1998)

One splice variant, TRα_2, lacks a functional DNA-binding domain and appears to act as a transcription suppressor. Although radioligand binding assays have been described for these receptors, the radioligands are not commercially available.

Abbreviations: **GC1**, (3,5-dimethyl-4-[4-hydroxy-3-isopropylbenzyl]phenyloxy)acetate

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