

Nuclear Receptors (Non-Steroids)

Key References

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Overview

The receptors for several classes of non-steroidal compounds, including retinoids, thyroid hormones and vitamin D, also act as ligand-dependent transcription factors. In addition, a large number of receptors without known ligands have been discovered based on sequence homology, particularly in the DNA binding domain, with known intracellular receptors. Ligands for some of these receptors have been identified, although many remain "orphan" receptors. Ligand-bound receptor complexes, which generally heterodimerize with a retinoid X receptor (RXR), act as transcription factors by binding to specific hormone response elements.

Three isoforms of retinoic acid receptors (RARs) and three isoforms of RXRs have been identified. All-trans retinoic acid was found to be a potent enhancer of RAR-dependent gene expression. Although it does not bind to RXRs, it is able to weakly activate RXR-dependent gene expression. A metabolite of all-trans-retinoic acid, the geometric isomer 9-cis retinoic acid, was subsequently found to bind to and activate the RXRs as well as the RARs. Based upon this work, isoform-specific agonists and antagonists have been identified. These studies have helped determine that RARs and RXRs have unique roles and different pharmacological effects.

The peroxisome proliferator-activated receptors (PPARs) heterodimerize with RXR isoforms to regulate gene expression by binding to peroxisome proliferator response elements. Ligands of PPAR α , such as gemfibrozil and clofibrate, are clinically effective at lowering triglycerides and low density lipoproteins (LDLs) and raising high density lipoproteins (HDLs). Recent studies have shown that PPAR γ activation with

thiazolidinediones, such as rosiglitazone or pioglitazone, is clinically useful to sensitize patients to insulin and is extremely useful in the treatment Type II diabetes. Interestingly, treatment of the RXR-PPAR heterodimer with RXR-selective ligands also yields insulin sensitization in animal models.

Triiodothyronine is the principle biologically active endogenous thyroid hormone. These hormones act upon all thyroid hormone receptor isoforms. Thyroid hormones are involved in early growth and development and have a well recognized calorogenic effect. The calorogenic response causes increased oxygen consumption in many tissues including heart, skeletal muscle, kidney and liver. Thyroid hormones have many other effects upon the cardiovascular system and also stimulate cholesterol metabolism. Lack of thyroid hormone decreases energy levels, activity and temperature control. Recent work has demonstrated that despite the great similarity of the binding sites of TR α and TR β , selective compounds can be synthesized. This could be valuable since TR α appears to mediate some of the negative effects of thyroid hormone.

Vitamin D is rapidly converted to an active metabolite 1,25-dihydroxyvitamin D which binds directly to Vitamin D receptor. This hormone plays a central role in the maintenance of plasma calcium and phosphate homeostasis. Vitamin D facilitates calcium and phosphate absorption from the small intestine and enhances calcium and phosphate mobilization from bone as well as decreasing calcium and phosphate excretion from the kidneys. Vitamin D also has immune system functions.

Recently, the ligands for several orphan intracellular receptors found in the liver

have been discovered. Two of these, the liver X-receptor (LXR) and farnesoid X-receptor (FXR), are involved in lipid metabolism and cholesterol homeostasis. LXR activation by oxysterols induces transcription of the rate limiting enzyme in bile acid synthesis, CYP7A1, while FXR activation by bile acids leads to down-regulation of CYP7A1 as well as several proteins involved in bile acid metabolism. These discoveries may prove very useful in future efforts in clinical control of lipids.

The ability to regulate the expression of enzymes of the cytochrome P450 class is exhibited by additional orphan receptors that appear to play a key role in the detoxification of xenobiotics. Thus, a total of five intracellular receptors, including PXR, CAR, LXR, FXR, and PPAR, may primarily serve to regulate cytochrome P450 enzymes in response to both endogenous hormones and xenobiotics.

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CURRENTLY ACCEPTED NAME	Retinoic acid receptor ^a	Retinoid X receptor ^b	Thyroid hormone receptor ^c	Vitamin D receptor	Peroxisome proliferator-activated receptor ^d
ALTERNATE NAME	RARs	RXRs	TR	VDR	PPARs
STRUCTURAL INFORMATION	448-462 aa (human)	462-533 aa (human)	490 aa (human)	427 aa (human)	468-505 aa (human)
RECEPTOR SELECTIVE AGONISTS	All-trans-retinoic acid (R2625) 9-cis-Retinoic acid (R4643) TTNPB (T3757)	9-cis-Retinoic acid (R4643) LGD 1069	L-Triiodothyronine (T2877 , T2752) Thyroxine (T2376 , T2501) Triac	Dihydroxyvitamin D ₃ (D1530)	Wy 14,643 (PPAR α) (C7081) L-765,041 (PPAR δ) Prostaglandin J2 (PPAR γ) (P9807) Thiazolidinediones (PPAR γ) (C3974)
RECEPTOR SELECTIVE ANTAGONISTS	SR 11335 Ro 41-5253	LG 100754	Not known	Not known	LG100641 (PPAR γ antagonist)
SIGNAL TRANSDUCTION MECHANISMS	Modulation of gene expression by ligand-dependent transcription factors				
RADIOLIGANDS OF CHOICE	[³ H]-Retinoic acid [³ H]-9-cis-Retinoic acid	[³ H]-9-cis-Retinoic acid	[¹²⁵ I]-Triiodothyronine [¹²⁵ I]-Thyroxine	[³ H]-Dihydroxyvitamin D ₃ [³ H]-Hydroxyvitamin D ₃ [³ H]-8(S)HETE (PPAR α)	[³ H]-Rosiglitazone (PPAR γ) [³ H]-L-783,483 (PPAR δ)
TISSUE EXPRESSION	Ubiquitous	Ubiquitous	Ubiquitous (TR α 2 primarily in pituitary and CNS)	Ubiquitous	α : liver, heart, muscle and vascular wall γ : adipose tissue, pancreas, vascular endothelium and macrophages δ/β : ubiquitous with highest expression in skin, brain and adipose tissue
PHYSIOLOGICAL FUNCTION	Embryonic patterning and organogenesis, cell proliferation, differentiation, apoptosis, and homeostatic control	Embryonic patterning and organogenesis, cell proliferation and differentiation. Function as heterodimers with members of the nuclear receptor superfamily	Growth, development and regulation of homeostasis	Calcium absorption and skeletal metabolism	Lipid and glucose metabolism
DISEASE RELEVANCE	Skin diseases, cancer	Cancer, metabolic disease	Obesity	Bone disease, cancer	Atherosclerosis, hypertriglyceridemia, insulin resistance, diabetes, lipid disorders, inflammatory diseases

Abbreviations

L-765,041: [4-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]phenoxy]acetic acid

L-783,483: [4-(3-(7-Propyl-3-trifluoromethylbenzisoxazol-6-yloxy)-propylthio)-3-chlorophenyl]acetic acid

LG 100754: (2E,4E,6Z)-7-[3-(n-Propoxy)-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl]-3-methylocta-2,4,6-trienoic acid

LGD 1069: 4-[1-(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)propenyl]benzoic acid

Ro 41-5253: RARa226-414

SR 11335: 4-[5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-4-(2,2,2-trifluoro-1-methoxyethyl)-2-anthracenyl]benzoic acid

TTNPB: (E)-4-[2-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-1-propenyl]benzoic acid

Wy 14,643: [4-Chloro-6-(2,3-xylylidino)-2-pyrimidinylthio]acetic acid

FOOTNOTES

a Three isoforms (α,β,γ) that differ in DNA sequence, but no clear evidence for pharmacological differences.

b Three isoforms (α,β,γ) that differ in DNA sequence, but no clear evidence for pharmacological differences.

c Two isoforms (α,β) that differ in DNA sequence, with increasing evidence for pharmacological differences.

d Three isoforms ($\alpha,\gamma,\delta/\beta$) that differ in both sequence and pharmacological activity.