

Peroxisome Proliferator-Activated Receptors (PPARs)

Key References

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Overview

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily of ligand-activated transcription factors that are related to retinoid, steroid and thyroid hormone receptors. PPARs play an important role in many cellular functions including lipid metabolism, cell proliferation, differentiation, adipogenesis and inflammatory signaling. PPARs have been found to interact with a number of endogenous lipids and drugs for the treatment of human metabolic diseases.

There are three distinct PPAR subtypes that are the products of different genes and are commonly designated PPAR α [NR1C1], PPAR β (also known as PPAR δ) [NR1C2] and PPAR γ [NR1C3]. Each receptor shows a differential pattern of tissue expression and is activated by structurally diverse compounds. PPARs possess a highly conserved DNA binding domain (region C) and a diverse ligand-independent activation domain (region A/B), which can confer constitutive activity on the receptor. Phosphorylation within the A/B region modulates receptor activity. In the case of PPAR α , insulin enhances transcriptional stimulation by phosphorylating the MAP kinase sites Ser 12 and Ser 21, whereas MAP kinase-mediated phosphorylation of Ser 112 of mouse PPAR γ 2 lowers transcriptional activity. The C-terminal ligand binding domain (region E/F) is the site of ligand docking and has the most diversity between the pharmacologically distinct subtypes. X-ray crystallography of both human PPAR β and PPAR γ has revealed important residues responsible for ligand binding, heterodimerization and co-factor interactions.

PPAR α is expressed in tissues exhibiting high rates of β -oxidation such as liver, kidney, heart and muscle. In liver, PPAR α regulates lipid metabolism and in rodents, but not in man, PPAR α activation induces hepatomegaly and proliferation of liver peroxisomes. PPAR β is ubiquitously expressed in tissues and has been implicated in membrane lipid synthesis and turnover. PPAR β is abundant in many tissues during development, especially in the adult rat digestive tract where a high rate of cell renewal and differentiation is required. PPAR γ is highly expressed in adipose tissue and is a key transcription factor involved in the terminal differentiation of white and brown adipose tissue. There is evidence that both PPAR α and PPAR γ could interfere with atherosclerosis, in part by exerting an anti-inflammatory response.

PPARs regulate gene expression by complexing with a heterodimeric partner RXR (retinoid X receptors) and subsequent binding to specific response elements (PPREs) in the promoter regions of target genes. Structurally distinct PPREs are recognized by PPAR α , β and γ . PPAR-RXR heterodimers can also be activated by ligand binding to either receptor partner independently.

Over the last decade, a greater understanding of the mechanism of transcriptional regulation by nuclear receptors has emerged. Complex formation with additional proteins is required and these accessory proteins bind to the nuclear receptors in a ligand-dependent manner. The nuclear receptor corepressor (N-CoR) and silencing mediator of retinoid and thyroid receptors (SMRT) proteins, bind and mediate repression of transcription by

the unliganded receptors. Coactivator proteins such as SRC1 and CBP/p300 are recruited by agonist bound receptors and promote initiation of transcription by remodeling the chromatin structure while coactivators such as the PPAR binding protein (PBP) interact directly with the transcriptional machinery. The binding of ligand triggers a series of events which results in conformational changes that lead to recruitment of coactivators and dissociation of corepressors. The tissue specific expression of these cofactors may be responsible for the transcriptional regulation and response differences observed in different cell types *in vivo*.

PPAR α agonists (such as the fibrates) have shown therapeutic utility as lipid lowering agents whereas PPAR γ agonists, such as the glitazones (thiazolidinediones) are marketed as antidiabetic agents. With the involvement of PPARs in many diverse metabolic pathways, there is great clinical interest in the potential utility of PPAR ligands for the treatment of cancer, inflammation, psoriasis, atherosclerosis, dyslipidaemia, neurological disorders, obesity and diabetes.

Peroxisome Proliferator-Activated Receptors (PPARs)

CURRENTLY ACCEPTED NAME	PPAR α	PPAR β	PPAR γ
OTHER NAMES	NR1C1	NR1C2 PPAR δ NUC1 FAAR	NR1C3
STRUCTURAL INFORMATION	468 aa (human)	440 aa (mouse) 441 aa (human)	475 aa (mouse) 475 aa (human γ 1) 506 aa (human γ 2)
SUBTYPE SELECTIVE AGONISTS ^a	8(S)-HETE (H 4019) LTB ₄ (L 0517) TTA (T 1698) Wy-14,643 (C 7081) Clofibrate (C 6643) Fenofibrate (F 6020) GW 9578	Prostaglandin A ₂ (P 4547) L-165,041 ^b L-631,033	15-Deoxy- $\Delta^{12,14}$ Prostaglandin J ₂ Ciglitazone (C 3974) Troglitazone (CS-045) Pioglitazone (AD-4833) Rosiglitazone (BRL 49653) JTT-501 (malonic amide active metabolite) AD-5075 MCC-555 GI 262570 GW 1929 GW 7845 CDDO FMOC-leucine (F 0259)
NON-SELECTIVE LIGANDS	L-796,449 Bezafibrate (B 7273) ^c	L-796,449 Bezafibrate (B 7273) ^c	L-796,449 Bezafibrate (B 7273) ^c
PPAR α/γ SELECTIVE LIGANDS	SB-213068 SB-219994 KRP 297 9-HODE 13-HODE (H 9146) GW 2331	—	SB-213068 SB-219994 KRP 297 9-HODE 13-HODE (H 9146) GW 2331
PPAR α/β SELECTIVE LIGAND	GW 2433	GW 2433	—
PARTIAL AGONISTS AND ANTAGONISTS	—	Sulindac (S 8139) ^d	GW 0072 ^e BADGE (D 3415) ^f L-764,406 ^g GW 9662 (M 6191) ^h
COACTIVATORS	PGC-1 CBP	—	PGC-1 PGC-2 SRC-1 (NCoA-1) PBP/DRIP205/TRAP220
COREPRESSORS	—	—	SMRT/TRAC-2

FOOTNOTES

- a** Selectivity > 5-fold unless otherwise indicated.
b L-165,041 has 2.6-fold selectivity for murine PPAR β /PPAR γ , but is 18-fold selective for human PPAR β /PPAR γ .
c Human PPAR β /PPAR α 2.5-fold selectivity and murine PPAR β /PPAR γ selectivity 2-fold.
d Antagonist activity of compound under review.

- e** Partial agonist in transactivation assays, but inhibitor of adipocyte differentiation. Displays reduced ability to recruit coactivators to transcription complex.
f Antagonist inhibiting adipocyte differentiation, but binds to PPAR γ in a binding assay.
g Irreversible PPAR γ ligand.
h Interaction only demonstrated *in vitro*.

Peroxisome Proliferator-Activated Receptors (PPARs) (continued)

INTERACTING PROTEINS ^h	RIP140 TRAP220 TRAP100	—	TRAP100 DRIP
RADIOLIGANDS OF CHOICE	[³ H]-GW 2331 [¹²⁵ I]-SB-236636	[³ H]-GW 2433 [³ H]-L-783,483	[³ H]-BRL 49653 (Rosiglitazone) [¹²⁵ I]-SB-236636 [³ H]-AD-5075 [³ H]-GW 2331

ABBREVIATIONS

AD-5075: 5-[4-[2-Hydroxy-2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]benzyl]-thiazolidine-2,4-dione
BADGE: Bisphenyl A diglycidyl ether
CBP: CRE binding protein
CDDO: 2-Cyano-3,12-dioxooleana-1,9-dien-28-oic acid
DRIP: Vitamin D receptor-interacting proteins
FARR: Fatty acid-activated receptor
GI 262570: (S)-2-(2-Benzoylphenylamino)-3-[4-[2-(5-methyl-2-phenyl-2-oxazol-4-yl)ethoxy]phenyl]propionic acid
GW 0072: (±)-(2S,5S)-4-[4-[5-[(Dibenzylcarbamoyl)methyl]-2-heptyl-4-oxothiazolidin-3-yl]butyl]benzoic acid
GW 1929: (S)-3-[4-[2-(Methyl-pyridin-2-ylamino)ethoxy]phenyl]-2-[2-benzoylphenylamino]propanoic acid
GW 2331: 2-[4-[2-[3-(2,4-Difluorophenyl)-1-heptyl-ureido]ethyl]phenoxy]-2-methylbutyric acid
GW 2433: 2-(4-[3-[1-[2-(2-Chloro-6-fluoro-phenyl)-ethyl]-3-(2,3-dichloro-phenyl)-ureido]propyl]-phenoxy)-2-methyl-propionic acid
GW 7845: 2-((S)-1-Carboxy-2-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-ethylamino)-benzoic acid methyl ester
GW 9578: 2-[4-[2-[3-(2,4-Difluorophenyl)-1-heptylureido]ethyl]-phenylsulfanyl]-2-methylpropionic acid
GW 9662: 2-Chloro-5-nitro-N-phenyl-benzamide
8(S)-HETE: 8(S)-(5Z,9E,11Z,14Z)-8-Hydroxyeicosa-5,9,11,14-tetraenoic acid
9-HODE: (10E,12Z)-9-Hydroxyoctadeca-10,12-dienoic acid
13-HODE: (9Z,11E)-13-Hydroxyoctadeca-9,11-dienoic acid
JTT-501: 4-[4-[2-(5-Methyl-2-phenyl-oxazol-4-yl)ethoxy]benzyl]isoxazolidine-3,5-dione
KRP-297: 5-(2,4-Dioxothiazolidin-5-ylmethyl)-2-methoxy-N-[4-(trifluoromethyl)benzyl]benzamide
L-165,041: [4-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propoxy]phenoxy]-acetic acid
L-631,033: (E)-3-[4-(2-Acetyl-6-hydroxy-undecyl)phenyl]propanoic acid
L-764,406: 2-Benzenesulphonylmethyl-3-chloroquinoxaline
L-783,483: [3-Chloro-4-[3-[7-propyl-3-(trifluoromethyl)benzo[d]isoxazol-6-yloxy]propylsulfanyl]phenyl]-acetic acid
L-796,449: [3-Chloro-4-[3-(3-phenyl-7-propyl-3-benzofuran-6-yloxy)propylsulfanyl]phenyl]-acetic acid
MCC-555: 5-[6-(2-Fluorobenzoyloxy)naphthalen-2-ylmethyl]thiazolidine-2,4-dione
NCoA-1: Nuclear receptor coactivator
N-CoR: Nuclear receptor corepressor
PBP: PPAR binding protein
PGC: Peroxisome proliferator-activated receptor gamma coactivator
RIP: Retinoid X receptor interacting protein
SB-213068: 3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-ethoxypropanoic acid
SB-219994: S-(−)-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoic acid
SB-236636: (αS)-4-[2-(2-Benzoxazolylmethylamino)ethoxy]-α-ethoxy-3-iodo-benzenepropanoic acid
SMRT: Silencing mediator of retinoid and thyroid receptors
SRC-1: Steroid receptor coactivator-1
TRAC: Thyroid hormone receptor-associating factor
TRAP: Thyroid receptor-associated proteins
TTA: Tetradecylthioacetic acid
Wy-14,643: [4-Chloro-6-(2,3-dimethylphenylamino)pyrimidin-2-ylsulfanyl]acetic acid