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PPARs AS LIPID SENSORS AND MASTER REGULATORS IN INFLAMMATION

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Abstract

The peroxisome proliferator-activated receptors (PPARs) are ligand-dependent transcription factors whose activation affects genes controlling vital processes in body. They emerged as links between lipids, metabolic diseases, and immune system. The human body tissue such as adipose tissue, liver, skeletal muscle, intestines, and blood vessel walls maintains the whole-body metabolic homeostasis, are prone to inflammation when metabolism is disturbed, a complication that promotes type 2 diabetes and cardiovascular disease. This review discusses the protective roles of PPARs in inflammatory conditions and the therapeutic anti-inflammatory potential of PPAR ligands. The production of IL-1 β by kuffer cells leads to lipid accumulation through suppression of PPAR-α dependent FA oxidation, PPAR-β/δ and p65, suggesting inhibition of NF-kB and recently PPAR-γ shows its dual benefit for both hypertriglyceridemia and insulin resistance, represents its broad potential in the treatment of metabolic disease. This review represents the protective roles of PPARs in inflammatory conditions such as skin wound repair and lipid metabolism.

Keywords: Endogenous ligands, healing, inflammation, PPARs, PUFA.

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PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS

Metabolic syndrome such as obesity, dyslipidaemia, glucose intolerance hypertension and low grade inflammation has appeared to be a link between insulin resistance, obesity and type 2 diabetes [1]. In recent years, a number of studies showed that a family of transcription factors, named the peroxisome proliferator-activated receptors (PPARs), improved several of the metabolic abnormalities associated with the metabolic syndrome.

Peroxisome proliferator activated receptors (PPARs) belong to the nuclear receptor super family which are ligand-activated transcription factors [2].Three isoforms of PPARs, encoded by different genes as PPAR-α, PPAR-γ and PPAR-β/δ (simply δ) [3]. Pharmaceutical agonists of PPARs are widely used in the management of metabolic and cardiovascular effects. These agents also show the direct and indirect action on diabetic kidney [4]. The PPARs heterodimerize with 9-cis-retinoic acid receptor (RXR) to form a heterodimer complex which shows the interaction with specific DNA-response elements of the target genes that are involved in the regulation of lipid and carbohydrate metabolism [5]. Activated PPARs play important roles in cell- differentiation, regulation of cellular development and the metabolism of body fuels [6,7].

Their biological effects depend on shape of ligand binding domain or modifying by co-activator or co-repressor polypeptides. PPARs may also bind to several endogenous ligands such as free fatty acids, prostaglandins eicosanoids, and leukotrienes [8,9].

Role of PPARs in Major Tissues

Adipose Tissue

Adipocyte and macrophages produces inflammation cytokines such as TNF-α, IL-6 and express TLRs (Toll-like receptors). Free fatty acid level elevated in obesity and their effects may be mediated by TLRs and it connect the metabolism to innate immunity [10].Crosstalk between TLRs and PPAR-γ is documented by several observations and TLRs and TLR4 gene expression is upregulated in adipose tissue of PPAR-α null mice [11]. In obese animals, macrophages shift to the classically activated macrophages (CAMs), also termed M1 macrophages, produce proinflammatory cytokines and act as effectors of cell killing as adiposity increases. These macrophages produce TNF-α, IL-6, and the inducible isoform of nitric oxide synthase [12, 13].

Eosinophil-derived IL-4 and IL-13 are required to sustain adipose alternatively activated macrophages (AAMS) and maintenance of the lean phenotype promotes oxidative metabolism, which is favored by PPAR-γ and PPAR-β/δ. In adipocytes, PPAR-β/δ inhibits NF-kB activity and reduces the production of the proinflammatory cytokines involved in insulin resistance [14, 15].

Liver

Chronic overfeeding results in liver injury and increase TGs storage in hepatocytes leads to apoptosis and inflammation pathways and development of insulin resistance. Kuffer cells and hepatic stellate cells accumulate at site of injury initiates the tissue repair and fibrosis. Sometimes injury may leads to NAFLD (nonalcoholic fatty liver disease) & NASH (nonalcoholic steatohepatitis) . During NAFLD kuffer cells coexist with dominant hepatic cells and lipid metabolism [16]. The production of IL-1 β by kuffer cells leads to lipid accumulation through suppression of PPAR-α dependent FA oxidation, TNF-α stimulated triglyceride storage which causes steatosis and inhibition of kuffer cells prevents diet induced steatosis and insulin resistance [17]. PPAR-

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β/δ has a role in attenuating chemically-induced liver toxicity and IL-4 triggers the anti-inflammatory M2 phenotype in Kupffer cells via PPAR activation signature genes Arg1, Clec7a, Chi3l3, and Tgfβ1 [18]. PPAR-γ promotes hepatic steatosis and loss of PPAR-γ function in hepatocytes protects from diet-induced fat accumulation in the liver in preclinical model. No beneficial effect on hepatic inflammation was observed after PPAR-γ deletion in both hepatocytes and macrophages, but there were possible confounding factors in this study related to the high-fat diet [19].

Skeletal muscle and heart

Fatty Acids (FAs) overload and saturated FAs such as palmitate leads to skeletal muscle lipotoxicity which is characterized by inflammation, insulin resistance, and cell death [20].When activated by the monounsaturated FA oleate, PPAR-α and PPAR-β/δ channel palmitate toward triglyceride accumulation and mitochondrial β-oxidation rather than toward the production of deleterious diacylglycerols and ceramides [21]. The treatment of human skeletal muscle cells with the synthetic PPAR-β/δ agonist GW501516 increases FA oxidation via PPAR-β/δ and AMP kinase and activation of PPAR-β/δ by GW501516 prevents palmitate-induced NF-kB activity and insulin resistance in mouse skeletal muscle cells [22,23]. If palmitate is converted to diacylglycerols, the serine kinase protein kinase C u (PKCu), which is abundant in skeletal muscle, is activated leading to impairment of insulin sensitivity and signaling. PKCu activates IKKb, which in turn phosphorylates IkB, thereby promoting NF-kB inflammatory pathways (e.g., TLR-2 and COX-2) and various proinflammatory mediators (e.g., IL-6 and TNF-a) [24]. Interestingly, COX-2 upregulation also promotes the production of PGE2, which limits the expression of these two proinflammatory cytokines. Proinflammatory factors produced under the control of NF-kB, such as TNF-α, MCP-1, and IL-6, which are secreted by cardiac cells under various pathophysiological stimuli, may participate in myocardial inflammation [25]. PPAR-β/δ d may serve as a therapeutic target to prevent cardiac hypertrophy and heart failure in metabolic disorders [26]. PPAR-α, in association with the NAD-dependent deacetylase sirtuin 1 (Sirt1), reduces inflammation and cardiac hypertrophy, and increases FA oxidation [27].

Activated PPAR-β/δ dampens LPS-induced TNF-α inflammation signaling in cultured cardiomyocytes, and blocks palmitate-induced inflammatory pathways in mouse heart and human cardiac cells through protein– protein interaction between PPAR-β/δ and p65, suggesting inhibition of NF-kB [28]. PPARγ attenuates progressive cardiac fibrosis in cardiomyocyte and macrophage-specific PPAR-γ-null mice infused with angiotensin II to trigger cardiac fibrosis, and then treated with pioglitazone, it is the macrophage and not myocyte PPAR-γ that attenuates fibrosis [29].

Vascular walls

PPAR-α expression in hepatic cells represses the production of secreted inflammatory proteins, which modulate systemic inflammation and its associated vascular response [30] and recently oscillatory shear stress stimulates the expression of microRNA-21, which inhibits the vascular anti-inflammatory action of PPAR-α by directly reducing PPAR-α expression in ECs, thus contributing to the proinflammatory response [31].

GW0742 and GW501516 reduce atherosclerosis in low-density lipoprotein receptor (LDLR) null mice, possibly by decreasing monocyte chemotactic protein-1 (MCP-1), intercellular adhesion molecule- 1,

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and TNF-α expression. Deletion of PPAR-β/δ from foam cells increases the availability of Bcl-6, and inhibition of proatherogenic and proinflammatory pathways by two key regulators of GPCR signaling, RGS4 and RGS5 which in turn reduces the atherosclerotic lesion area [32,33]. In mouse models, the disruption of PPAR-γ in smooth muscle cells and macrophages increases atherosclerosis and hypercholesterolemia respectively [34,35]. Inactivation of PPAR-γ in the ECs causes endothelial dysfunctions under high-cholesterol diet, and this demonstrates that endothelial PPAR-γ prevents the initiation of atherosclerosis [36]. Together, above findings highlight the anti-inflammatory role of PPAR-γ in cell types that is crucial to the progression of cardiovascular diseases.

PPARs and their expression patterns

PPARs control expression of genes that function in lipid and carbohydrate metabolism, vascular biology, tissue repair, cell proliferation and differentiation, and sexual dimorphism. PPAR-α, PPAR-β/δ, and PPAR-γ exhibit isotype-specific but partially overlapping expression patterns. Tissues that perform significant catabolism of FAs, such as brown adipose tissue, liver, heart, kidney, and intestine, express high levels of PPAR-α. PPAR-β/δ which plays an important role in the skin, gut, placenta, skeletal and heart muscles, adipose tissue, and brain. PPAR-γ is found in two isoforms, γ1 and γ2, that differ at their N termini and PPAR-γ1 has a relatively broad expression pattern including the gut, brain, vascular cells, and immune and inflammatory cells, whereas PPAR-γ2 is found at high levels mainly in adipose tissues [37]. Ligand-dependent transrepression is mediated via interference with nuclear receptors such as activator protein-1 (AP-1) and nuclear factor-κB (NF-κB) [38]. Moreover, there is evidence that not all PPAR ligands stimulate transactivation and transrepression pathways to a similar extent and their relative importance may be different in different tissues [39].

Endogenous ligands of PPARs

Different types of natural compounds, including n-3 and n-6 FAs, eicosanoids, and a few endocannabinoids and phospholipids, have been identified as PPAR ligands[40].

Unsaturated FAs, saturated FAs (weaker), leukotriene B4, 8(S)-hydroxyeicosatetraenoic acids, 8,9-epoxyeicosatrienoic acids, 11,12-epoxyeicosatrienoic acids, oleoylethanolamide (OEA), palmitoylethanolamide (PEA), and 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine are PPAR-α ligands. Unsaturated FAs, saturated FAs (much weaker), prostacyclin, 4-hydroxy-2-nonenal (4-HNE), 4-hydroxydodeca-(2E, 6Z)-dienal (4-HDDE) and very low-density lipoprotein components are PPAR-β/δ ligands. Unsaturated FAs, oxidized and nitrated FAs, 15-HETE, 9/13- HODEs, 13-oxo-ODE, 15-deoxy-D12,14-prostaglandin J2, phospholipid cyclic phosphatidic acid (CPA), and oxLDL components are PPAR-γ ligands [41,42,43].

Addition to these natural ligands, a wide range of synthetic ligands have been developed, which are used to treat dyslipidemia (fibrates) and diabetes (thiazolidine-2, 4-diones or TZDs) and their activity depends on their presence in cells or tissues enriched in PPARs, their binding specificity toward the different PPARs and the availability of coregulators that can act either as coactivators or corepressors of transcription [44,45].

Given the variety and anatomic distribution of endogenous PPAR ligands, and the combinations in which they occur depending on physiological (e.g., abundance and

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composition of food, physical activity) and pathophysiological conditions (e.g., hyperlipidemia, hypertension, diabetes, chronic inflammation, cancer, and atherosclerosis), it is difficult to evaluate thoroughly the roles of each PPAR ligands in a given cell at a fixed time-point, and this remains a major challenge in the field. It is tempting to speculate that the diversity of PPAR functions has been acquired in association with the rich variety of ligands.

Polyunsaturated fatty acids and their derivatives (PUFA) and inflammation

Eicosanoids belongs to the families of prostaglandins, prostacyclins, thromboxanes or leukotrienes that control inflammatory and immune processes and might have effects on cardiovascular disease, blood pressure, and arthritis. Eicosanoids are produced from the oxidation of either omega-6 (n-6) or omega-3 (n-3) 20-carbon essential fatty acids (FAs) that are not synthesized in human body and must obtain from the diet[46].

In several pathological conditions inflammation acts as a driving force for diseases such as obesity, nonalcoholic steatohepatitis (NASH), atherosclerosis, acute cardiovascular events, and Crohn's disease. Normally, inflammatory responses are controlled to avoid excessive damage to the host. If inflammatory responses are not properly controlled, promotes the acute or chronic diseases characterized by excessive production of arachidonic acid derived eicosanoids, inflammatory cytokines, and adhesion molecules.

Diets rich in fish-derived n-3 eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) increase the incorporation of these FAs into the phospholipids of immune cell membranes, and give rise to eicosanoids such as prostaglandin E3 and the anti-inflammatory derivatives of DHA and EPA, the resolvins . Thus, FA type determines the pro- or anti-inflammatory properties of the lipid derived mediators produced, impacts upon receptor signaling, and influences cytokine production [47].

Signaling through cell-surface receptors

Lipid mediators such as PUFA and their derivatives are ligands for the PPARs, as well as for cell-surface G protein-coupled receptors (GPCRs) and Toll-like receptors (TLRs) [48,49] whose dysfunctions can cause inflammatory and immune disorders [50]. FAs can bind to and activate GPCRs: long-chain FAs activate GPR119, medium- and long-chain FAs activate GPR43, GPR120, and GPR40, and short-chain FAs activate GPR41. The inflammatory mediator leukotriene B4 (LTB4) acts via the leukotriene B4 receptor (BLT2), another member of this seven transmembrane domain receptor superfamily. TLRs recognize structurally conserved molecules derived from pathogens, trigger innate immune responses and prime antigen-specific adaptive immunity and also associated with inflammatory and autoimmune diseases.

In macrophages, saturated FAs leads to inflammatory responses via TLR2/TLR4 and long-chain n-3 FAs inhibit TLR2/TLR4 expression, activity, and downstream signaling, by at least two mechanisms: inhibition of TLR2/TLR4 expression, and PPAR activation [51].

The examples given in Tables 1 show that some lipid mediators bind either to cell-surface (GPCR, TLR) or nuclear receptors (PPARs), whereas others simultaneously activate both types of receptors, resulting in serve to fine-tune for many homeostatic pathways, but are also associated with metabolic disturbances and inflammation [52].

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Table 1 Cell-surface receptors binding of ligands

Ligands	Receptor/s	Model	Mechanism studied and outcomes	Ref.
LTB4	PPAR-α, BLT2 and PPAR-α	Cell lines, human peripheral blood PMNs, mice	LTB4 is a physiologically relevant PPAR-α agonist. PPAR-α decreases secretion of LTB4 and stimulates its breakdown. LTB4 plays a central role in the regulation of inflammation through its ability to exert both proinflammatory effects via BLT2 and anti-inflammatory effects via PPAR-α.	[53]
LTE4	MK571-sensitive GPCR (CysLT3R?)	LAD2 cell line isolated from the bone marrow of a patient with MC leukemia. Primary human mast cells (hMCs)	LTE4 activates hMCs by a pathway involving cooperation between an MK571-sensitive GPCR thereby linking extracellular LTE4, PPAR-γ-dependent ERK activation, inducible expression of COX2, and generation of PGD2. The indirect mechanism of PPARγ activation remains to be elucidated.	[54]
Farnesyl phosphate and diphosphate	PPARs and LPA GPCRs	RH7777 cells stably transfected with either LPA1, LPA2, or LPA3 and PC3 prostate cancer cells endogenously expressing all three EDG-family LPA GPCRs	Farnesyl phosphates are endogenous ligands of lysophosphatidic acid receptors (LPAx) and PPARs. Inhibition of LPA GPCRs and activation of PPARs. Both farnesyl phosphate and farnesyl diphosphate potently and specifically antagonize LPA-elicited intracellular Ca2+-mobilization mediated through the LPA3 receptor and activate PPARγ-mediated gene transcription.	[55]
Acetate and propionate	GPCR43 and PPAR-γ	C57BL/6J mice Primary adipocytes and stromal-vascular cells from adipose tissues 3T3-L1 cells and differentiation into adipocytes	Acetate and propionate stimulate the expression of GPCR43 and PPAR-γ in differentiated adipocytes, with stimulation of fat accumulation. GPCR43 and its ligands function as regulators of adipogenesis in adipocyte development and differentiation.	[56]
Lysophosphatidic acid (LPA)	PPARgand LPA GPCRs	RAW264.7 monocytic cells	LPA activates PPARγ and LPAx receptors. LPA can couple activated tumor cells or platelets to PPARγ stimulation and gene regulation in neighboring as well as distal target cells	[57]
GW1929 (synthetic)	PPARγ	Spontaneously hypertensive rats (SHR rats)	PPARγ modulates the expression/activity of GPCRs. PPARγ-mediated improvement in hypertension may involve transcriptional regulation of GPCR kinase-2 (GRK-2) activity	[58]

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PPAR and inflammation

PPARs have emerged as targets of drugs used to treat various components of metabolic syndrome, a cluster of risk factors that includes dyslipidemia, insulin resistance, hypertension, inflammation, and coagulation disorders that promote type 2 diabetes (T2DM) and/or cardiovascular events in affected patients. In fact, inflammation is a major determinant of health complications seen in overweight and obesity, which makes the link between nutrition, metabolic organs, and the immune system [59,60,61]. Increased circulating inflammatory cytokines leads to chronic low-grade inflammation and acute-phase proteins, reflects a weak activation of the innate immune system, and this affects the metabolic organs, arteries, heart, and brain and all three PPAR isotypes have demonstrated anti-inflammatory effects in these conditions [62]. PPAR-β/δ mediating anti-inflammatory actions by different mechanism: inhibition of NFkB activation, induction of anti-inflammatory mediators such as TGF-β, and corepressor B-cell lymphoma 6 (BCL-6) proteins, rendering this cofactor available for gene repression [63]. PPARs affect inflammation through direct and indirect mechanisms. LTB4 is a physiological ligand of PPAR-α, whose activation stimulates the expression of genes encoding cytochrome P450 and b-oxidation enzymes responsible for the neutralization and breakdown of LTB4.PPAR-α upregulates the expression of IkB, which blocks the nuclear translocation and activation of the proinflammatory transcription factor NF-kB [64]. It also up regulate soluble interleukin-1 receptor antagonist (IL-1ra), which is stimulated during hepatic inflammation [65].

The best-known mechanism by which PPAR-α inhibits many inflammatory genes is transrepression which is based on the tethering of PPARs to master regulators of inflammation such as NF-kB, activator protein 1 (AP-1), nuclear factor of activated T cells (NFAT), and signal transducers and activators of transcription [66]. In the female liver, sexspecific sumoylation of PPAR-α results in the repression of the cytochrome P450 gene Cyp7b1, which show protective effect of PPAR-α in estrogen- and inflammation-induced cholestasis and toxicity [67].

Recently WY-14643 activated PPAR-α prevents glucocorticoid-induced hyperinsulinemia in mice fed a high-fat diet via the additive effect of PPAR-α and GR-α [68,69]. It also mediate the effect of chylomicron-derived FAs on the expression of angiopoietin-related protein 4 (Angptl4), a protein that is upregulated in macrophages by chylomicron-derived FAs and that protects against the severe proinflammatory effects [70] Another isotype of PPAR as PPAR-γ has several inhibitory effects on inflammation, including reduction of NF-kB transcriptional activities,reduction in the production of proinflammatory molecules in T lymphocytes, and inhibition of genes encoding proinflammatory molecules in macrophages [71]. PPAR-γ was the first reported agonist dependent sumoylation, which promotes binding to nuclear receptor corepressor 1 protein (NCoR) and stabilizes association with promoter-bound NF-kB, thereby leading to the transrepression of inflammatory genes [72].

PPARs are involved in tissue and skin wound repair

The three PPAR isotypes are expressed in rodent and human skin and recently their role has been emerged in skin wound healing except lipid and glucose homeostasis. [73]. The healing process requires the covering of the wound bed with a new protective epidermis, after a skin

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injury. This process comprises several phases: inflammation, re-epithelialisation and remodelling of the scar and inflammatory responses are followed by the proliferation and migration of keratinocytes, comprising the activation and proliferation of fibroblasts and angiogenesis. Importantly, PPAR-α or β/δ are instrumental and playing specific roles in this repair process. A selective decrease of PPAR-α activity in keratinocytes of transgenic mice displays a similar phenotype, which reveals the importance of keratinocytes in orchestrating the inflammatory process [74]. PPAR-β/δ is an important regulator of keratinocyte survival in the wounded epidermis and is involved in cell adhesion and migration [75]. In particular, a novel homeostatic control of keratinocyte proliferation and differentiation was recently found, whereby PPAR-β/δ regulates the signalling of IL-1in dermal fibroblasts [76].

Recently PPAR-β/δ regulates the signalling of IL-1 in dermal fibroblasts and found a homeostatic control of keratinocyte proliferation and differentiation. Whereas PPAR-γ shows minor role in keratinocytes and it's its activity is required for sebaceous gland differentiation. The activation of PPAR-γ with troglitazone and prostaglandin-J2 does not affect epidermal maturation in foetal rat skin where as topical treatments with the PPAR-γ agonists (troglitazone, ciglitazone) increase the expression of differentiation markers and promote epidermal barrier recovery in hairless mice [77].

Therefore, we can conclude that PPAR-α and PPAR-β/δ both play important roles in skin wound repair with isotype-specific timing. Due to their collective diverse functions in skin biology, PPARs represent major research targets for the understanding and treatment of many skin diseases, such as benign epidermal tumours, papillomas, acne vulgaris and psoriasis.

Synthetic anti-inflammatory PPAR ligands: therapeutic perspective

As we study all PPARs drugs are potential targets to treat chronic inflammatory diseases and anti-inflammatory effects of synthetic ligands have been recently reported (Table 2). Fibrates targeting PPAR-α have been fairly successful at treating dyslipidemia; however, the TZDs that are insulin-sensitizer PPAR-γ agonists, despite their efficacy, induce deleterious side effects (e.g., peripheral edema, increased risk of congestive heart failure, increased rate of bone fracture, and weight gain), and this has restrained their clinical use and arrested the clinical development of many promising compounds. Normally fibrates targeting PPAR-α have been used treating dyslipidemia whereas TZDs that are insulin-sensitizer PPAR-γ agonists, except their effectiveness, induce serious side effects (e.g., peripheral edema, increased risk of congestive heart failure, increased rate of bone fracture, and weight gain), arrested their clinical use and clinical development [78].

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Table 2 Pharmaceutical anti-inflammatory PPAR agonist

Compounds	PPAR	Model	Mechanism studied and Outcomes	Ref.
GW501516	PPAR-β/δ	C2C12 and human skeletal muscle cells	Attenuation of fatty acid-induced NF-kB activation and insulin resistance in skeletal muscle cells.	[79]]
MBX 8025	PPAR-β/ δ	Combined dyslipidemic patients	Improvement of multiple metabolic parameters in dyslipidemic overweight patients treated with and without atorvastatin.	[80]
CP900691	PPAR-α	Diabetic cynomolgus monkey	Improvement of plasma lipids, lipoproteins, and glycemic control in diabetic monkeys.	[81]
5-ASA	PPAR-γ	DNBS-induced colitis in mice; organ cultures of human colonic biopsies	Identification of PPARγ as a target of 5-ASA underlying anti-inflammatory effects in the colon.	[82]
Ajulemic acid (AJA)	PPAR-γ /cannabinoid receptor	Cell cultures; zymosan-A-induced murine peritonitis	Identification of PPARγ as target for AJA, providing a potential mechanism for the anti-inflammatory action of AJA, and possibly other cannabinoids. AJA increases formation of the endogenous proresolving and anti-inflammatory eicosanoid, lipoxin A4.	[83]
GED-0507-34-Levo	PPAR-γ	DNBS- and DSS-induced colitis in mice	Compound has strong intestinal anti-inflammatoryand analgesic properties.	[84]
Cevoglitazar	PPAR-α/γ	Obese mice; Zucker rats; diabetic cynomolgus monkey	Reduction of food intake and body weight in obese mice and cynomolgus monkey and improvement of glycemic and metabolic control. In fatty Zucker rats, cevoglitazar functions through PPAR-α agonism resulting in increased β-oxidation. In subcutaneous fat, cevoglitazar induces changes similar to those of fenofibrate suggesting export of fatty acids from this depot.	[85]

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Recently, alternative approaches are being emerged in the development of compounds that simultaneously target more than one receptors. For example, endocannabinoids, as natural activators of PPARs, binds to cannabinoid receptors, to shows analgesic and anti-inflammatory effects [86]. Some of them show their anti-inflammatory effects through PPAR-α or PPAR-γ and further development needed to study such observation. SR1664, a synthetic compound that binds to PPAR-γ uniquely shows its antidiabetic activity without causing serious side effects associated with TDZ [87]. Further studies will reveal that whether a new class of such compounds would specifically target Cdk5-mediated phosphorylation of PPAR-γ, might also promote its anti-inflammatory properties or not. These studies explain that the development of new classes of PPAR-targeted drugs is feasible and may provide novel therapeutic perspectives for inflammatory diseases.

Concluding remarks

PPARs have emerged as crucial moderators of cellular metabolic function, and now become an unavoidable links between lipid signaling and inflammation. The multifaceted roles of PPARs in these processes rely on the diverse control of gene expression in time and space which also integrates signaling through membrane receptors. Currently, considerable evidence suggests that PPAR-α is involved in the pathogenesis of diabetic nephropathy and contributes to the extra metabolic control of renal function. Although the mechanisms of the beneficial effects of fibrates in the kidneys are still under investigation, PPAR-α would be a promising therapeutic target in the management of diabetes and diabetic nephropathy. Developing molecules endocanabinoids and dual agonists simultaneously target more than one component of the integrated cell signaling controlled by PPARs which may provide alternative therapeutic perspectives for novel synthetic anti-inflammatory PPAR ligands.

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