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Review Article

Biology of Peroxisome proliferator-activated receptors in energy homeostasis and future prospective in therapeutics for metabolic disorders: A mini-review

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Abstract

The peroxisome proliferator-activated receptors (PPARs) are an important transcription factor that regulates the expression of genes involved in lipid energy metabolism. PPARs expression and role vary among tissues depending on involvement in metabolism. Availability of substrate for energy modulates the expression and function of PPARs. Dysfunction of PPARs is linked to metabolic syndrome and PPAR ligands are used as therapeutic agents in metabolic disorders. The benefits of PPAR ligands come with some potential side effects which jeopardize the use of these agents in therapy. This mini-review covers general fundamental issues such as structure, mechanism, and tissue expression patterns of PPARs and provides a critical assessment of the present state and future potential for PPAR ligands as therapeutic agents for metabolic disorders such as metabolic syndrome.

Keywords: PPAR, energy metabolism, metabolic disorder, therapeutic agents.

INTRODUCTION:

The peroxisome proliferator-activated receptors (PPARs) were identified as “novel members of the steroid hormone nuclear receptors family”. These nuclear receptors were found to be activated by diverse groups of peroxisome proliferators like clofibrate, herbicides, plasticizers, and leukotrienes inhibitors and are functionally involved in the transcriptional regulation of lipid metabolism and hepatocarcinogenesis [1]. The first member of the PPAR family, named PPAR alpha (PPARα), activates peroxisome proliferation responsive genes and promotes peroxisome Acyl Co an oxidase activity, an enzyme of β oxidation [1]. Other members of the PPAR family are PPAR beta/delta (PPARβ/δ) and PPAR gamma (PPARγ), and these receptors are having close structural and functional similarities with PPARα [2]. These receptors have critical roles in energy metabolism; however, their distribution, expression and physiological activities vary among various tissues [3]. PPARs are ligand-dependent receptors, and in the presence of agonists, they form heterodimers with Retinoid X receptors (RXR) and this association results in a conformational change and transcriptional alteration [4]. Other co-activator proteins also add up with PPAR-RXR heterodimer to form a complex, and this complex attaches to peroxisome proliferator responsive elements (PPRE) in specific genes to activate their expression [4, 5]. Reports also indicate that PPARs are not always dependent on heterodimer partner RXR but also can regulate target gene expression in the absence of a hetero partner [5]. Therapeutic potential of PPAR ligands have been realised and being used in therapy for metabolic disorders. Novel PPAR ligands are under investigation and a promising outcome can be expected. This brief review provides a basic overview of the PPARs and their fundamental biology and describes their role in energy metabolism. Present state of use of PPAR ligands as therapeutic agent and future potential are highlighted.

Structure, expression, and mechanism of PPARs

Three Isoforms of PPAR Differ in Tissue Distribution

The PPARs exist in three isoforms PPARα, PPARβ/δ, and PPARγ. These isoforms show structural homology but varies in tissue distribution and ligand specificity and therefore, different physiological roles [6]. These isoforms target different genes in the specific tissues, and exhibit overlapping of functions during regulation of lipid homeostasis and energy metabolism [6].

PPARα has been cloned in mice, frogs, rats, rabbits, porcine, and humans [1, 2]. PPARα are primarily involved in regulation of lipid metabolism, and hence, they are preferentially expressed in abundance in tissues like liver [3]. Along with liver, other tissues which are actively involved in fat catabolism also show higher expression of PPARα; such as

skeletal muscles, heart, brown fat, kidneys. Additionally, PPARα are also expressed in brain tissues and these receptors are associated with neuroprotective effect and in lungs, these receptors primarily prevent acute lung injury [7, 8].

PPARβ/δ was first identified in humans and subsequently cloned in xenopus, mouse, and other species [2]. This isoform of PPAR is ubiquitous; however, some tissues have higher expression levels. Its abundant expression has been reported in the liver, adipose tissue, skeletal muscle, kidneys, heart, and gastrointestinal tract [6].

PPARγ is a critical regulator of lipid metabolism and adipocyte differentiation, and therefore, these receptors show higher expression in adipose tissues [9]. Other tissues such as the liver, intestine, bone marrow, and immune cells have also reported to express PPARγ [10]. PPARγ is the most studied member of the PPAR family, and its four sub-isoforms of PPARγ have been identified: PPARγ 1,2,3 and 4. These sub-isoforms vary slightly in structure and distribution of expression [3].

Structure of PPARs resembles other nuclear receptors

All the isotypes of PPARs belong to the nuclear receptor family and share the common structural features with other nuclear receptors. These nuclear receptor family members contain a highly conserved DNA binding domain (DBD) and a ligand binding domain (LBD). A hinge region holds DBD and LBD together [11]. Along with DBD and LBD, variable N-terminal (NTD) and C-terminal domains are also present [11]. DBD contains two highly conserved zinc finger motifs, which help to anchor to the chromatin. LBD is situated in the C-terminal half of the receptors and forms a ligand-binding site by folding into three layers of α helix. The C-terminal region also contains ligand-dependent transactivation function domain (AF-2) adjacent to LBD [11, 12].

The crystal structure reveals that LBD contains 13 α-helices and 4-stranded β sheets. Unlike other nuclear receptors, PPARs have one extra helix in LBD between Helix H3 and the β strand [4]. The crystal structure shows a large y-shaped ligand-binding pocket in PPARs contrary to other nuclear receptors. These ligand-binding pockets have an entrance and two pockets (Arm 1 and Arm 2) that help in interaction with many structurally different ligands [4]. Arm 1 promotes co-activator binding by holding activation domain (AF-2) helix in active conformation, and hydrophobic Arm 2 helps in binding of ligand via Vander Waals interaction [13].

Ligand specificity of PPARs depend on structure and activity relationship

Fatty acids are natural ligands for all three PPARs, additionally synthetic ligands specific to the subtype of PPARs are also being used in research and therapeutics. The size of the ligand-binding pocket at LBD of three PPARs is almost similar. However about 20% differences in 34 amino acid residues of the binding cavity is one of the reasons for the ligand specificity [13]. Variances in the detailed topology of binding pockets cause the difference in ligand specificity. PPARβ structure shows a narrow region adjoining to the AF-2 helix, which hinders the binding of PPARγ agonists like, farglitazar and GW409544. This hindrance in agonists binding could be a potential reason for farglitazar and GW409544 to fail in clinical trials for hepatic fibrosis, type 2 diabetes, and hyperlipidemia [14]. Another example, Fibrate molecules are weak ligand for PPARδ, but a Met453Val mutation reduces the steric hindrance for ligand, and binding affinity of fibrate to PPARδ increases significantly [15].

Transcriptional regulation by PPAR-RXR heterodimer

PPAR forms a heterodimer with RXR and in the presence of co-activators, a complex is formed, which binds to peroxisome proliferator responsive elements (PPRE) at the promoter site of the target gene and then causes the effect [4, 5]. PPAR-RXR complex is a permissive complex which requires a ligand only on one of the receptors of heterodimer for transcriptional activity [16]. Modulation of transcriptional activity is dependent on the binding of a ligand, as this is one of the factors which decide affinity between PPAR and RXR.

There are two major models of PPAR transcriptional regulation namely, PPRE-dependent and PPRE-independent. PPRE-dependent model explains PPAR dependent transactivation. Ligand-activated PPAR-RXR heterodimer forms a complex with co-activator proteins such as members of the SCR (steroid receptor co-activator) family and CBP (CREB binding protein) family [17]. Other co-activators PBP/MED1, HAT and PIC (transcriptional preinitiation complex) are recruited to complete an activated complex at PPRE [17]. LBD and AF-2 domain plays a critical role in recruiting co-activators and forming the complex [18]. PPRE-dependent repression of transcription has also been identified. Upon activation of PPRE bound PPARα, heterodimer complex interacts with p65 and inhibit binding with complement C3 promoter [18]. This inhibits transcriptional activity of NFκB (nuclear factor kappa B). Co-repressors such as SMRT and NCoR attach with PPAR and prevent binding of PPAR-RXR complex to DNA [19]. When a ligand binds, the co-repressor separates from heterodimer, and this facilitates binding with PPREs.

PPRE-independent transcriptional regulation by PPARα describes repression of gene activity. PPRE-independent transcriptional repression sometimes does not require a PPAR-RXR heterodimer partner [5]. PPARα

represses vascular inflammatory genes by interaction with transcription factors p65 and cJun. This inhibits AP-1 and NFκB signaling pathways [20]. This PPRE-independent mechanism modulates transcriptional activities of non-PPRE containing genes [5].

PPARs in energy homeostasis

PPARs are energy metabolism regulator

PPARs, in specific, PPARα and PPARγ are critical regulators of cellular and systemic energy metabolism and play a vital role in glucose homeostasis, lipid and cholesterol metabolism [21]. The expression level of PPARα and PPARγ is higher in metabolically active tissues such as the liver (major site of energy homeostasis), skeletal muscles, and adipose tissues [21]. Generally, PPARα and γ promote fatty acid oxidation and fatty acid uptake in the liver and skeletal muscles. These receptors upregulate the expression of apolipoproteins (ApoA-I and ApoA-II) and increase HDL's plasma level [22]. PPARα exhibits a lipo-protectant role by upregulating mitochondrial and peroxisomal oxidation; whereas, PPARγ is a key regulator of differentiation and maturation of adipocytes, promotes lipid synthesis and storage [18, 23]. PPARs are also involved in insulin sensitivity and serve as a successful therapeutic target to treat type-2 diabetes. Table-1 presents the physiological roles of different PPARs.

Table-1: Major physiological roles of different PPARs
***Tissues in bold have high expression**

	Gene Target	Tissue expression*	Physiological Role
PPARα	β-oxidation pathway (Acyl Co-A oxidase, Thiolase), Fatty Acid transport protein, Fatty Acid translocase (FAT/CD36), Sterol 12-hydroxylase (Cyp8B1), Lipoprotein Lipase, Apolipoprtein A-I and A-II	**Liver**, skeleton muscle, Heart, brown adipose tissues, Kidney, Brain, Lungs	• Lipid catabolism and homeostasis, • regulation of inflammatory process and vascular integrity, • mediate hypolipidemic action of fibrate, • promote FA oxidation, FA uptake, Apolipoprtein A-I and A-II in Liver • Increase triglycerides, HDL and reduce FFA, VLDL, cytokines, NF-kB in vessels
PPARβ/δ	Lipid uptake, metabolism and efflux regulating genes	Liver, adipose tissue, skeleton muscle, kidney, Heart, and gastrointestinal tract (Ubiquitous expression)	• Mediate insulin sensitivity, • Regulate glucose homeostasis and vascular integrity, • Promote glucose uptake and glycogen synthesis in skeleton muscle • Decrease cytokine, FFA, Resistin and NF-kB
PPARγ	Fatty Acid binding protein(aP2), Fatty acid Transport Protein, Fatty acid translocase (FAT/CD36)	γ1-**adipose tissue**, heart, colon, skeleton muscle, spleen, and pancreas	• Glucose homeostasis, lipid storage • Adipocyte differentiation and maturation • Promote FA oxidation • Reduce TG
		γ2-**brown and white adipose tissues**	
		γ3-**Immune cells** (macrophages, lymphocytes, monocytes), white adipose tissue, large intestine	
		γ4-endothelial cells	

PPARs senses nutritional changes in the body

Dietary nutrition constituents are determining factors for the induction of PPARs, which promote anabolism and storage of energy in the postprandial state [6]. This activation of PPARs is due to the availability of natural ligands [24]. In a fasting state, PPARs promote gene activities that are involved in free fatty acid uptake by tissues and stimulate gluconeogenesis, glycogenolysis, and ketogenesis [24]. Insulin is a master hormonal regulator of whole-body energy metabolism and acutely regulates the expression of PPARγ in adipose tissue. A complex cross-talk happens between PPARs and insulin, and eventually, insulin sensitivity gets modulated [25]. Upregulation of PPARα and PPARβ/δ is observed in liver and skeletal muscle during fasting state [9]. In basal conditions, when adequate nutrition is available, PPARγ plays a crucial role in energy metabolism involving adipose tissue. In contrast, PPARα in the liver is vital in the fasting scenario [23].

PPARα in liver and response to fasting

Hepatic metabolism is highly adaptive that needs precise transcriptional regulation. In the feeding state, an anabolic approach leads to the synthesis of glycogen and fatty acids, whereas the fasting state exhibits fatty acid catabolism along with ketogenesis [9, 26]. The fasted catabolic pathway is mediated by PPARα in hepatocytes and feeding anabolic pathway signals through insulin receptors [9]. PPARs, mainly PPARα, and insulin are key regulators in hepatic metabolism [26].

Polyunsaturated fatty acids (PUFAs) are natural endogenous ligands for PPARα and on activation; they target genes that transcribe rate-limiting enzymes of fatty acid β-oxidation such as acyl-CoA oxidase 1 and acyl-coenzyme A (CoA) dehydrogenase [27]. A high-fat diet lacking PUFAs induces fatty liver, and serum shows a high level of fatty acids. This induced fatty liver can be reversed by PPARα activation by PUFA rich diet promoting FA β-oxidation [21]. PPARα also controls the biosynthesis of sphingolipid through activation of key enzymes serine palmitoyltransferase and long-chain acyl-CoA synthetase genes expression [28]. Fenofibrate, a synthetic ligand of PPARα, upregulates the synthesis of sulfatide in the liver and increases sulfatide level in serum [29]. Sulfatide prevents thrombosis and improves cardiovascular health [29]. PPARα regulates the level of hepatocyte fibroblast growth factor 21 (FGF-21), which binds with its receptors in target tissues and indirectly enhances glucose transport in extrahepatic tissues by GLUT1 [30]. PPARα has been found to be involved in non-alcoholic fatty liver and steatohepatitis induced liver cirrhosis and hepatocellular carcinoma [31]. The severity of fibrosis is dependent on the expression of PPARα [31].

In an adaptive response to fasting, the liver is the primary source of ketone bodies. PPARα controls ketogenesis in the liver through regulation of expression of a rate-limiting enzyme, hydroxymethylglutaryl-CoA synthase 2 [32]. *Pparα* gene knockout mice show fatty liver in normal fed conditions, but fasting worsens the severity of pathology [33]. Loss of fatty acid oxidation causes increased plasma FFAs, and this is accompanied by hypoglycemia, hypoketonemia and hypothermia [34]. In response to fasting, PPARα dependent FGF-21 induction tries to rescue the liver from fatty liver and hypoketonemia [34]. FGF-21 via lipase regulates the release of FAs in white adipose tissue (WAT), and then these FFA are picked up by the liver for oxidation [34]. PPARα mediated regulation of hepatic metabolism involves PGC1α. The liver phenotype of PGC1α null mice is similar to the PPARα null mice. This reflects hepatic metabolism regulation by PGC1α mediated action of PPARα [35]. Fasting induces PGC1α that regulates fatty acid oxidation and gluconeogenesis [35].

PPARγ in Adipose tissues and nutritional response

Excess energy is stored in white adipose tissue and fulfills the energy requirement later in the condition of starvation and simultaneously, it has endocrinal importance [36]. PPARγ is a chief regulator of energy metabolism in adipose tissue and helps in maintaining whole-body energy homeostasis [36]. PPARγ is activated in adipocyte differentiation and the non-adipogenic cell is differentiated into adipocyte when PPARγ is expressed ectopically [12]. Deletion of PPARγ in mice develops lipodystrophy in the differentiated adipocyte. This reveals that PPARγ is not only important for differentiation of adipocyte but survival too [37]. PPARγ mediated adipocyte differentiation involves CCAAT/enhancer-binding protein (C/EBP) transcription factors [38].

In a postprandial state, when excess nutrients are present, fatty acid uptake by CD36 and FATP1in the adipocyte is induced by PPARγ [39], and an increase in plasma triglycerides is diminished. Lipogenesis and lipid storage associated genes such as FABP4, glycerol kinase, SREBP-1, stearoyl-CoA desaturase 1 (SCD-1) and perilipin are induced by PPARγ [40]. PCK2 isoform of phosphoenolpyruvate carboxykinase (PEPCK), an enzyme in glucose metabolism in adipocytes, is induced by PPARγ [41]. PEPCK is required for the glycerol-3-phosphate enzyme in triglyceride storage [41]. C/EBP additionally involves in PPARγ controlled insulin sensitivity in adipose tissue [42]. Another type of adipose tissue is brown adipose tissue (BAT), which involves in energy expenditure. Similar to WAT, BAT expresses a high level of PPARγ. PPARγ is critical in mitochondrial biogenesis, a characteristic of BAT. This also involves C/EBPβ along with PRDM16, PGC1-α and β, transcriptional co-activators [43]. PPARγ regulates BAT-specific genes, but UCP1 (a hallmark of BAT) involve in energy expenditure is independent of PPARγ [43].

During the period of fasting, expression of PPARγ goes down in adipose tissue and uptake of FFA from circulation is reduced [44]. Food deficient state induces Sirt1 (sirtuin 1) that silences the PPARγ activity by utilizing its cofactors SMRT and NCoR. This mechanism facilitates the mobilization of fatty acids from WAT in the fasted state [45]. Other studies also reiterate that PPARγ level is decreased in fasting state and this activates AMP-activated protein kinase (AMPK) in adipose tissue and lipoprotein lipase level is increased [46]. The glucose homeostatic role of PPARγ involves the improvement of insulin sensitivity in skeletal muscle and insulin secretion by beta cells of the islets of Langerhans in the pancreas [47].

PPAR ligands as a therapeutic agent

Metabolic syndrome comprises multiple abnormalities such as obesity, diabetes, and dyslipidemia. Evidence provided earlier proves that PPARs are critically involved in regulation of metabolism and energy homeostasis, thus targeting PPARs can revolutionize therapeutics for metabolic disorders.

Past and Present

PPAR ligands are being used to treat metabolic disorders before we knew these were PPAR ligands. Fibrates are the first synthetic PPAR ligands synthesized in the early 1950s and later they showed the hypocholesterolemic effect. Fibrate such as clofibrate was used clinically to reduce lipid level, VLDL and LDL in hypercholesterolemia. Meanwhile, other fibrates such as gemfibrozil and fenofibrate were synthesized. These new syntheses were found to be safer with minimal side effects. An understanding of the mechanism of action of these fibrates in the 1990s gave a boost to clinical trials for metabolic disorder treatment. Fibrates are potent agonists of PPARα; therefore, they function to regulate fatty acid and lipid metabolism primarily in the liver, along with skeletal muscle, cardiac muscle and kidney [48]. Fenofibrate is used to treat dyslipidemia and hypercholesteremia and this was also found to improve cardiovascular symptoms and diabetic retinopathy [49]. It increases good lipid, HDL and reduces triglycerides in the blood [49].

Thiazolidinedione (TZD) is a major class of the PPARγ agonist. Its antidiabetic property was explored in the 1980s, and then troglitazone (a TZD) was approved to treat type 2 diabetes in 1997. Troglitazone was later discontinued due to hepatotoxic side-effect-related casualties. Subsequently, in later years, pioglitazone and rosiglitazone were approved for diabetes treatment, and often, its therapeutic regimen included metformin, an antihyperglycemic agent. Side effects of rosiglitazone are very much debated, and a study in 2007 reasoned rosiglitazone as a risk for myocardial infarction and cardiac-associated deaths [50]. Many countries including India have withdrawn rosiglitazone from the market, but FDA continued with some restrictions after reviewing results from the 2009 population-based cohort study [51]. Pioglitazone was found comparatively safer but banned in India due to its link with heart failure. Apart from the antidiabetic effect, pioglitazone has shown promising results to enhance left-ventricular diastolic function in hypertensive patients [52]. Balaglitazone is a partial PPARγ agonist that completed phase 3 of the clinical trial for type-2 diabetes [53].

Another synthetic compound, GW501516 is a PPARβ/δ agonist. Since PPARβ/δ regulates muscle energy metabolism, GW501516 is often used to enhance physical performance by promoting muscle fiber metabolism [54].

Different PPARα/γ dual agonists such as aleglitazar, farglitazar, muraglitazar, ragaglitazar, saroglitazar, and tesaglitazar are under investigation. The clinical trials of aleglitazar for type 2 diabetes (ClinicalTrials.gov Identifier NCT01871428, NCT01042769, NCT01398267), for chronic kidney diseases associated with T2D (NCT01893242, NCT01043029) and for T2D related cardiovascular disorders (NCT01715818, NCT01042769) are currently running in different phases. Similarly, clinical trials for other PPARα/γ dual agonists are in continuation; muraglitazar and tesaglitazar are being tested for type 2 diabetes and dyslipidemia (NCT00094991, NCT00245388, NCT00229710), saroglitazar is under trial for liver-related pathologies (NCT03863574). Though these trials give hope for potential therapies for metabolic disorders in the future, some undesired outcomes have slowed the pace of development. For example, the clinical trial of farglitazar was suspended after phase 2 when it failed to show efficacy in liver cirrhosis [14]. Table-2 presents the clinical status of different PPAR ligands.

Table-2: Examples of PPAR ligands and their therapeutic clinical status.
**** Ligands in bolds are natural ligands**

	Ligands**	**Clinical status**
PPARα	**Unsaturated fatty acids, Leukotrienes B4, 8-hydroxy-iecosatetraenoic acid,**	
	Fenofibrate, Gemfibrozil, Bezafibrate, Pemafibrate, Ciprofibrate	Approved
	K111, ZYH7, Macuneos, LY518674	Phase II
	Clofibrate, DRF10945, GFT14, Clinofibrate, Ronifibrate, Gw590735, KRP101, MP136, NS220	Discontinued
PPARβ/δ	**Unsaturated fatty acids, Carbaprostacyclin, component of VLDL**,	
	Seladelpar, Fonadelpar	Phase III
	MA0211, CER002, SAR351034, KD3010	Phase I

	GW0742, L165041	Pre-clinical
	GW501516, HPP593	Discontinued
PPARγ	**Unsaturated fatty acids, 15-hydroxy-iecosatetraenoic acid, 9-hydroxy-octadecadienoic acid, prostaglandin PGJ2**	
	Rosiglitazone, Pioglitazone,	Approved
	Efatutazone, CHS131, OMS 405, GED-0507-34-levo-2	Phase 2
	Troglitazone, Ciglitazone, Balaglitazone, CLX0921, FK614, MK0533, Neteglitazone, DS6930, S26948, INT131	Discontinued

Dual Agonists	
PPARα/γ	Oxeglitazar, Saroglitazar, Farglitazar, Muraglitazar, Naveglitazar, Tesaglitazar, Aleglitazar, Ragaglitazar, Peliglitazar, DSP8658, LY510929, ONO5129
PPARα/δ	Elafibranor
PPARγ/δ	T3D595
Pan-PPAR agonist	Lanifibranor
	Chiglitazar
	GSK625019, Sodelglitazar, DRL11605

Risk Assessment

Undoubtedly, PPAR agonists are potent pharmacological agents because of their involvement in physiological regulation. Several studies reported adverse effects mediated by PPAR ligands. TZDs, the most used PPAR ligand, cause edema, hepatotoxicity, and heart failure [51]. Troglitazone was discontinued due to its severe hepatotoxicity. Gemfibrozil is reported to inhance obesity, congestive heart failure, liver hypertrophy, muscle weakness, and cancer [55]. Rosiglitazone and pioglitazone have been proven as a risk for cardiovascular health [51]. Other agents like fibrates also have been showing hepatotoxic side effects. PPAR modulators are potential agents for cancer therapy, but the tumourigenic property of PPAR agonists have been also reported [56]. The role of PPAR ligands in gastrointestinal toxicity, immunological side effects, and developmental toxicity are being explored [57]. All together, clinically approved PPAR agonist shows side effects at various levels ranging from headache and cold to hepatotoxicity and cardiotoxicity-related deaths [57]. Therefore, this poses the question, “are PPAR ligands a safe alternative as a drug for metabolic syndrome and associated comorbidities and should we use PPAR ligands as therapeutics?”

The Future

Novel ligands have potential

To explore the potential benefits of PPARs-based therapeutic drugs, a number of novel PPAR ligands are synthesised and tested. 9-hydroxy-10(E),12(E)-octadecadienoic acid is a novel PPARα ligand isolated from fermented grain products (Patent US10702492B2). It does not alter triglyceride level in PPARα knockout mice, but the wild type shows a lowered level of TG [58]. 3-hydroxy-2,2-dimethylbutyrate, 9-octadecenamide and hexadecanamide (Patent US10617664B2) have been identified in the hippocampus with PPARα agonistic properties [59]. DY121 is a synthetic novel PPARα agonist (Patent US20190077774A1) claimed to be effective in the treatment of liver and metabolic disorders.

A novel synthetic PPARβ/δ agonist patented by vTv Therapeutics LLC claims to treat muscular atrophy (Patent US9487493B2) for its involvement in inducing oxidative metabolism in slow-twitch muscle fibers [60]. The University of Toledo was granted a patent for analogs of PPARδ and analogs of 20-Hydroxy-PGE2 as a PPARδ agonist and antagonist, respectively (Patent US9695137B2). Both agents have shown the potential to treat or prevent metabolic bone disorder [61]. Another PPARδ agonist has been claimed by Mitobridge Inc. to treat mitochondrial-related muscular disorders (Patent US20170304255A1).

5-hydroxy-4-phenylbutenolide is extracted from Chinese vinegar and has PPARγ activating property for which a patent has been filed (Patent US9943501B2). Similarly, phenylacetate and benzoate have been claimed as PPARγ activators to treat autoimmune diseases (Patent US20190000790A1). A new synthetic PPARγ antagonist ‘(E)-2-(5-((4-methoxy-2-(trifluoromethyl)quinolin-6-yl)methoxy)-2-((4-(trifluoromethyl)benzyl)oxy)-benzylidene)-hexanoic acid

(MTTB)' claims to be a competitive antagonist against TZD (Patent US10093628B2) [62]. These all-new discoveries are a great progress in the field of PPAR related therapeutic and can be developed as a potential therapy against metabolic disorder in future.

Optimism

PPARs have a critical involvement in metabolic regulation. There is sufficient evidence proving how PPAR modulators are improving metabolism in metabolic disorders. In current situation, metabolic syndrome associated complications such as dyslipidemia and type 2 diabetes are being managed by PPAR ligands despite having side effects. Several clinical trials are in the pipeline with optimistic outcomes to develop a prospective therapeutic regimen. It is true that despite the effort, only a handful of compounds have reached to bedside.

Nevertheless, there is hope as a number of novel ligands are in the process of discovery and synthesis, which shows the capacity to modulate different PPARs and correct altered physiology. Researchers are now targeting a wide range of disorders that include obesity, cardiovascular-associated metabolic disorders like atherosclerosis, inflammatory diseases, and nervous syndromes [23]. Considering the pace of our scientific investigation in this field, we can be optimistic about getting potentially safe PPAR ligands as therapeutic agents for metabolic disorders. Now the availability of dual agonists such as PPARα/γ dual agonists and PPARα/δ dual agonist raises our hope for a therapeutic outcome.

A new approach to target a combination of nuclear receptors may be a game-changer strategy. PPARs are targeted along with farnesoid X receptor (FXR) and liver x receptors (LXR). FXR is the target for metabolic liver disease, and its combination with PPAR may eliminate adverse side effects [63]. Similarly, the combination of LXR may expand our clinical possibility by correcting metabolic disorders and eliminating unfavorable side effects [64]. Though this combinational approach could lead to more efficacious and safer therapy, we need to understand the pharmacology of drug-drug interaction in the body. Available PPAR agonists are now in consideration for other non-metabolic diseases. Disorders of the nervous system and immune system also adapt PPAR targeting therapies and show promising results in animal models.

So, looking into the present scenario and future potential, we get the answer to the question, "should we use PPAR ligands as therapeutics?" The scientific community is working toward understanding PPAR biology, and eventually, our therapeutics will improve. Till then, we should focus on risk management by restricted and combination therapy.

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Conflicts of interest

The authors declare that they have no conflict of interest.

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