The Journal of Clinical Investigation

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J Clin Invest. 2017;127(4):1202-1214. https://doi.org/10.1172/JCI88894.

Review Series

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REVIEW SERIES: NUCLEAR RECEPTORS
Series Editor: Mitchell A. Lazar

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Distinct but complementary contributions of PPAR isotypes to energy homeostasis

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Peroxisome proliferator–activated receptors (PPARs) regulate energy metabolism and hence are therapeutic targets in metabolic diseases such as type 2 diabetes and non-alcoholic fatty liver disease. While they share anti-inflammatory activities, the PPAR isotypes distinguish themselves by differential actions on lipid and glucose homeostasis. In this Review we discuss the complementary and distinct metabolic effects of the PPAR isotypes together with the underlying cellular and molecular mechanisms, as well as the synthetic PPAR ligands that are used in the clinic or under development. We highlight the potential of new PPAR ligands with improved efficacy and safety profiles in the treatment of complex metabolic disorders.

Introduction

Metabolic syndrome (MetS) is a pathophysiologic condition characterized by increased visceral adiposity, dyslipidemia, prediabetes, and hypertension. This cluster of risk factors predisposes to type 2 diabetes (T2D) and nonalcoholic fatty liver disease (NAFLD) and increases the risk of microvascular complications and cardiovascular (CV) events. With the global increase in obesity, the prevalence of MetS has reached epidemic proportions. The pathophysiology of MetS and its comorbidities is complex and includes alterations in lipid and glucose metabolism accompanied by multi-organ inflammation; because of this complexity, current treatments address the individual components (1).

Over the last decades, the PPARs, which are members of the nuclear receptor superfamily of transcription factors (TFs), have been targeted to fight MetS and its complications. Three PPAR isotypes with different tissue distribution, ligand specificity, and metabolic regulatory activities exist in mammals: PPARα (NR1C1), PPARβ/δ (NR1C2), and PPARγ (NR1C3). PPARs regulate many metabolic pathways upon activation by endogenous ligands, such as fatty acids (FAs) and derivatives, or synthetic agonists, which bind to the ligand-binding domain of the receptor, triggering a conformational change. Subsequent recruitment of coactivators to the PPAR/retinoid X receptor heterodimer assembled at specific DNA response elements called PPAR response elements (PPREs) results in transactivation of target genes. In addition, PPAR activation attenuates the expression of pro-inflammatory genes, mostly through transrepressive mechanisms (2). This Review focuses on the metabolic effects of PPAR isotypes as well as synthetic PPAR ligands that are currently used in the clinic or are under development.

Endogenous PPAR ligands

PPARs are activated by FAs and their derivatives, and the level of physiologic receptor activation depends on the balance between ligand production and inactivation. Endogenous PPAR ligands originate from three main sources: diet, de novo lipogenesis (DNL), and lipolysis, all of which are processes that integrate changes in nutritional status and circadian rhythms (3). PPARs control these metabolic processes to maintain metabolic flexibility, a prerequisite for the preservation of health.

Dietary lipids regulate PPAR activity, as evidenced by the increased target gene expression of PPARα in liver (4) and PPARβ/δ in skeletal muscle (SKM) (5) upon high-fat diet (HFD) feeding in mice. Tissue-specific deficiency of FA synthase — a key enzyme in DNL — impairs PPARα activity and identifies DNL as another source of PPAR ligands (6, 7). PPARα ligands originating from DNL are not only simple FAs but include more complex molecules such as phosphatidylcholines (8). Lipolysis is a third source of endogenous PPAR activators. Angiopoietin-like (ANGPTL) proteins are secreted glycoproteins that inhibit lipoprotein lipase (LPL), thereby controlling the plasma lipid pool according to lipid availability and cellular fuel demand. ANGPTL4 expression is induced in several tissues including adipose tissue, liver, and SKM by circulating FAs via PPARs, leading to inhibition of LPL and decreased plasma triglyceride-derived FA uptake, thus forming a negative feedback loop (9). Intracellular lipolysis also provides PPAR ligands. Deficiency of adipose triglyceride lipase, which lipolyzes lipid droplet triglycerides, decreases PPAR target gene expression in various tissues (10–13). Ligand availability is also modulated by FA degradation in peroxisomes, which are regulated by PPARs (14). Thus, PPAR activity relies on a careful balance between ligand production and degradation to meet fluctuating energy demands.

Contrasting metabolic effects of ligand-activated PPARα and PPARγ

Although they share similarities in function and mechanism of action, PPAR isotypes display important physiologic and pharmacologic differences. This section discusses the clinical and genetic evidence of contrasting PPARα and PPARγ effects, and sheds light on the cellular and molecular mechanisms underlying these differences.

Clinical effects of PPARα and PPARγ activation. Fibrates are synthetic PPARα ligands used to treat dyslipidemia. Except for

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Conflict of interest: B. Staels is an advisor for Genfit SA.

Reference information: *J Clin Invest.* 2017;127(4):1202–1214. https://doi.org/10.1172/JCI88894.

the weak pan-agonist bezafibrate, all clinically used fibrates are specific activators of PPARα. Fibrate outcome trials such as the Helsinki Heart Study (HHS) (15), Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) (16), Bezafibrate Infarction Prevention (BIP) (17), Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) (18), and Action to Control Cardiovascular Risk in Diabetes (ACCORD) (19) consistently show beneficial effects on plasma lipids, particularly in normalizing the typical MetS dyslipidemia characterized by an "atherogenic lipid triad" (high LDL cholesterol [LDL-C] and triglycerides, low HDL cholesterol [HDL-C]). Fibrate therapy significantly decreases triglycerides and increases HDL-C, whereas LDL-C decreases except in patients with severe hypertriglyceridemia and low baseline LDL-C. Fibrate therapy, however, does not change circulating FA concentrations (20). Although both the FIELD and ACCORD trials showed a trend towards decreased CV risk (primary endpoint) in T2D, post-hoc and meta-analysis revealed that dyslipidemic patients (high triglyceride and low HDL-C levels) show the highest CV reduction (21, 22). Fibrates do not improve glucose homeostasis in people with T2D (18, 19, 23). However, PPARα activation improves glucose homeostasis in prediabetic patients (24) and may prevent conversion of prediabetes to overt T2D. Fibrates exert few adverse effects. Most compounds induce mild hypercreatininemia and hyperhomocysteinemia, but these effects are pharmacodynamic markers of PPARα activation rather than indicators of renal dysfunction (25). Hepatic carcinogenesis has been observed in rodents treated with fibrates but not in humans or non-human primates, likely due to lower peroxisome and peroxisomal β-oxidation levels in human liver (26).

Thiazolidinediones (TZDs, also referred to as glitazones), synthetic PPARγ ligands, are anti-diabetic drugs with potent insulin-sensitizing effects that confer long-term glycemic control (27). However, their clinical use has been challenged due to side effects such as body weight gain, edema, and bone fractures (2). The increase in body weight upon TZD administration is due to PPARγ-dependent white adipose tissue (WAT) expansion (28) and fluid retention caused by PPARγ activation in the kidney collecting ducts (29). The increased fracture risk in TZD-treated patients results from a PPARγ-driven rebalancing of bone remodeling in favor of net bone loss. Indeed, PPARγ activation in bone marrow stimulates mesenchymal progenitor differentiation into the adipocyte lineage, suppressing osteoblast and hence bone formation through pathways involving protein phosphatase PP5 (30, 31). Moreover, pharmacologic, but not physiologic, PPARγ activation promotes osteoclast formation thereby increasing bone resorption (32, 33). Rosiglitazone and pioglitazone increase plasma levels of the insulin-sensitizing adipokine adiponectin (2). They also increase HDL-C and reduce circulating FA levels (34), but have differential effects on triglyceride and LDL-C levels and CV risk. Pioglitazone, a full PPARγ agonist with modest PPARα-activating properties (35), lowers triglycerides, increases HDL-C, and reduces CV events in people with T2D (36) or who are insulin resistant (37). In contrast, the pure PPARγ agonist rosiglitazone does not decrease CV risk in people with T2D but does increase both HDL-C and LDL-C (38). Hence, the beneficial effects of pioglitazone on triglycerides and CV events are likely due to combined PPARα and PPARγ activation. In summary, activation of PPARα improves the lipid profile, whereas activation of PPARγ improves glycemic control and insulin sensitivity.

Genetic evidence of contrasting PPARα and PPARγ functions. The different phenotypes of patients carrying SNPs and mutations in PPARα or PPARγ coding sequences highlight their contrasting functions. *PPARA* variants are associated with perturbations of lipid metabolism (39) and CV risk (40). *PPARA* SNPs also associate with conversion from impaired glucose tolerance to T2D (41). *PPARA* gene variation also influences the age of onset and progression of T2D (42). In contrast, dominant-negative mutations in the ligand-binding domain of PPARγ result in severe insulin resistance (43). Accordingly, rare variants in *PPARG* with decreased adipogenic properties are associated with increased T2D risk (44). GWAS have also revealed an association between *PPARG* SNPs and T2D, although not all studies concur (45, 46). A recently developed functional assay identified *PPARG* variants with altered PPARγ function (47). SNPs within DNA recognition motifs for PPARγ or cooperating factors that alter PPARγ recruitment to chromatin modulate the response to anti-diabetic drugs (48). Additionally, SNPs in PPARγ DNA-binding sites are highly enriched among SNPs associated with triglyceride and HDL-C levels in GWAS (48). Taken together, these genetic data confirm the functional dichotomy between PPARα and PPARγ in humans, underscoring the effects of PPARα on lipid metabolism and conversion from impaired glucose tolerance to T2D and the role of PPARγ in T2D and the regulation of glucose homeostasis.

Cellular and molecular mechanisms underlying PPARα and PPARγ functions. The function of PPARα (Figure 1) is best characterized in the liver, where it regulates genes involved in lipid and plasma lipoprotein metabolism during the nutritional transition phases (49, 50). During fasting, PPARα increases hepatic uptake and mitochondrial transport of FA originating from adipose tissue lipolysis through transcriptional upregulation of FA transport proteins and carnitine palmitoyltransferases. PPARα induces expression of mitochondrial acyl-CoA dehydrogenases, hence stimulating hepatic FA oxidation (FAO) and increasing acetyl-CoA production. Upon prolonged fasting, acetyl-CoA is preferentially converted into ketone bodies to provide energy for extrahepatic tissues. PPARα also upregulates mitochondrial hydroxymethylglutaryl-CoA synthase (HMGS), a rate-limiting ketogenesis enzyme (51, 52). Glucagon receptor signaling (53) and the IRE1α/XBP1 pathway (54) cooperate with PPARα to control metabolic pathways during fasting. In the fed state, PPARα coordinates DNL to supply FAs, which are stored as hepatic triglycerides and used in periods of starvation. A crucial step in DNL is the citrate-malate shuttle, which controls the efflux of acetyl-CoA from the mitochondria to the cytosol, where it serves as a precursor for FA synthesis. Citrate carrier, an essential component of this shuttle system, is a direct PPARα target gene in hepatocytes (55). Additionally, PPARα increases protein levels of the lipogenic factor SREBP1c by promoting proteolytic cleavage of its precursor (56), hence stimulating transcription of its target genes (57). In these postprandial conditions, mTORC1, activated through the insulin-dependent PI3K pathway, inhibits PPARα-mediated hepatic ketogenesis (58). Thus, PPARα contributes to the maintenance of metabolic flexibility by adapting fuel utilization to fuel availability, and its expression decreases in conditions of metabolic inflexi-

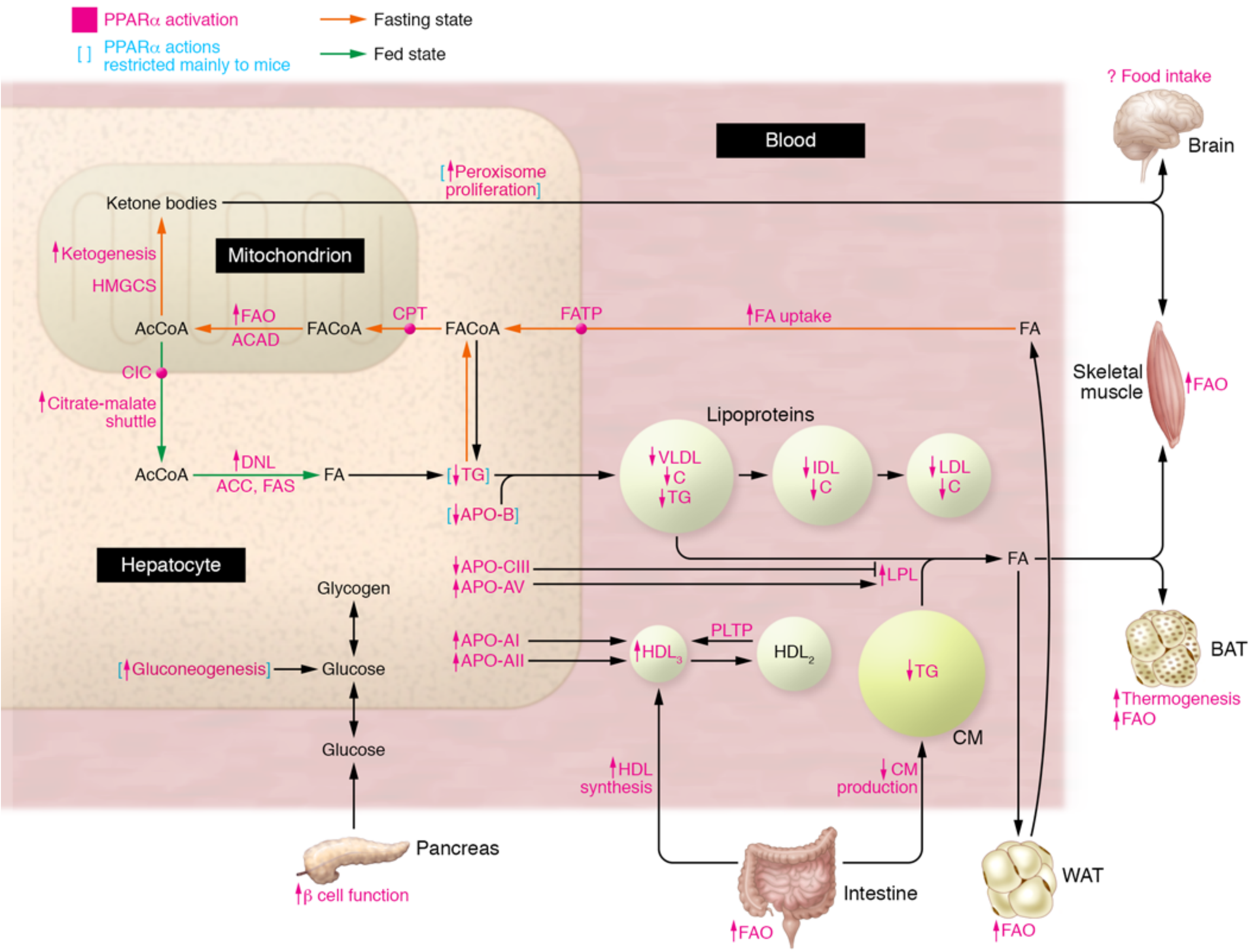

Figure 1. PPARα activation stimulates FA and triglyceride metabolism. During fasting (yellow), FAs released from WAT are taken up by the liver and transported to mitochondria, where FAO takes place, to produce acetyl-CoA (AcCoA), which can be further converted to ketone bodies and serve as fuel for peripheral tissues. In the fed state (green), acetyl-CoA is shuttled to the cytosol, where DNL takes place. The effects of PPARα activation and PPARα target genes are indicated in pink. FAO is also stimulated by PPARα in WAT and SKM. By regulating hepatic apolipoprotein synthesis, PPARα activation decreases plasma levels of triglycerides (TG) and LDL-C and increases HDL-C. PPARα also acts on BAT, gut, and pancreas, but its central effects are unclear. Blue brackets indicate PPARα actions that are mainly restricted to mice and do not occur (e.g., peroxisome proliferation, reduced liver fat content) or occur to a lesser extent (e.g., reduced APO-B production) in humans. ACAD, acyl-CoA dehydrogenase; ACC, acetyl-CoA carboxylase; CM, chylomicron; CPT, carnitine palmitoyltransferase; FACoA, fatty acyl-CoA; FAS, fatty acid synthase; FATP, fatty acid transport protein.

bility such as NAFLD (59). PPARα activity is also dysregulated by microRNA-10b (60), microRNA-21 (61), and JNK (62), all of which are upregulated in NAFLD.

PPARα activation reduces plasma triglyceride-rich lipoproteins by enhancing FA uptake and FAO and increasing the activity of LPL, which hydrolyzes lipoprotein triglycerides. PPARα stimulation of LPL enzyme activity is both direct, through PPRE-dependent activation of *LPL* (63), as well as indirect, through decreasing the expression of the LPL inhibitor and pro-atherogenic APO-CIII (64, 65) and increasing the expression of the LPL activator APO-AV (66). Reduced VLDL production contributes to the triglyceride-lowering effects of PPARα activation mainly in rodents and, likely to a lesser extent, in humans. Interestingly, a SNP in the *TM6SF7* gene reduces VLDL production and lowers circulating triglyceride levels while promoting hepatic steatosis (67), an effect not observed in PPARα agonist–treated patients (68). In line with this, administration of fenofibrate to people with MetS increases the fractional catabolic rate of VLDL-APOB, intermediate-density lipoprotein–APOB (IDL-APOB), and LDL-APOB without affecting VLDL-APOB production (69). The rise in plasma HDL-C upon PPARα activation is linked to increased synthesis of major HDL-C constituents, apolipoproteins APO-AI and APO-AII (70), and induction of phospholipid transfer protein (PLTP) (71). Of note, differences between rodents and humans with respect to apolipoprotein regulation exist, as APO-AI and APO-AV are direct positive PPARα target genes in human but not murine liver (49). Through FAO, PPARα activation leads to energy dissipation not only in the liver but also in SKM (72) and WAT (73). In brown adipose tissue (BAT) PPARα stimulates lipid oxidation as well as thermogenesis in synergy with PPARγ coactiva-

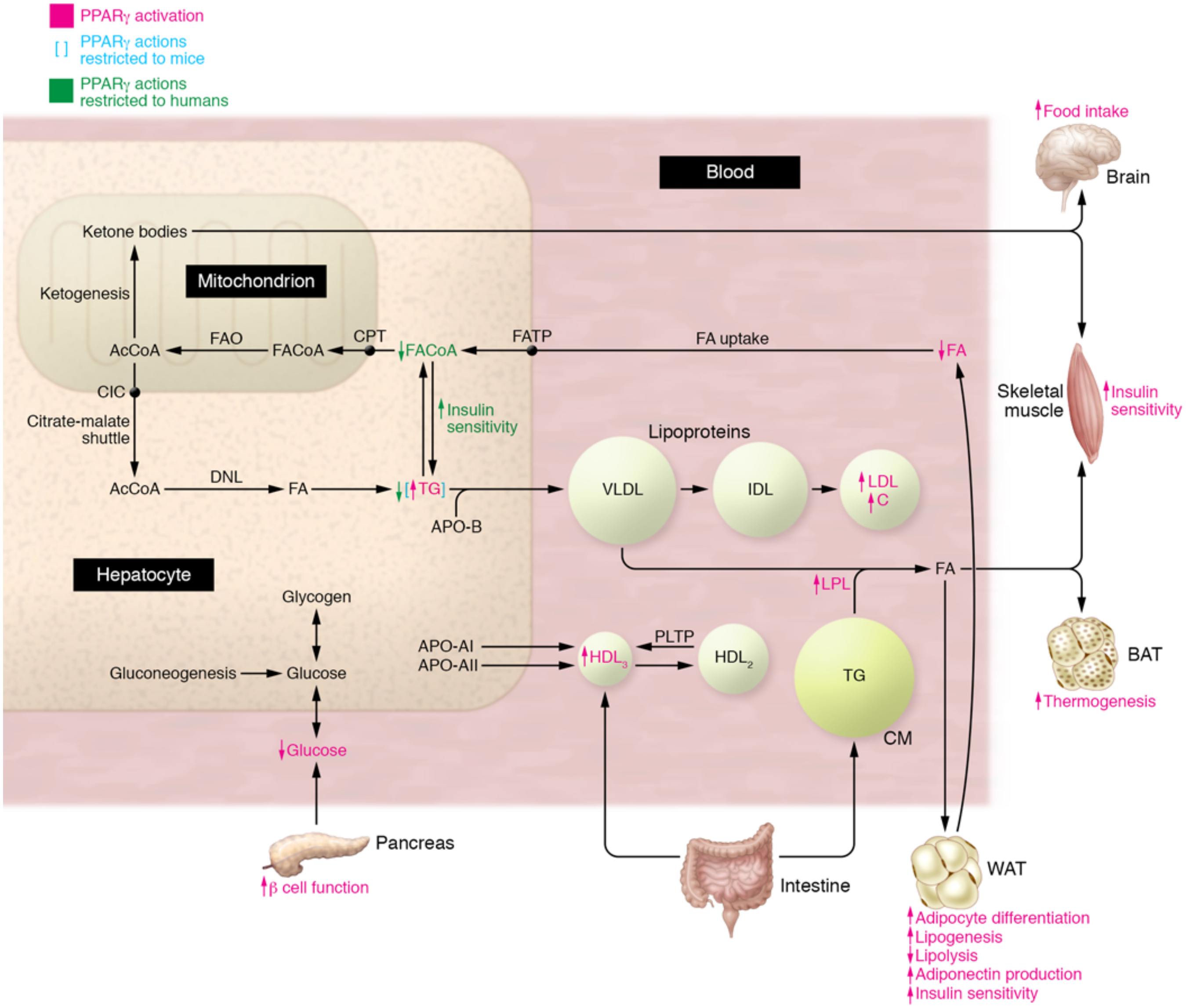

Figure 2. PPARγ activation increases whole-body insulin sensitivity. In WAT, PPARγ activation (effects are indicated in pink) enhances FA uptake and storage, lipogenesis, and adipogenesis (lipid steal action). PPARγ activation lowers circulating FA levels, alleviating lipotoxicity and increasing insulin sensitivity. PPARγ agonism induces adiponectin production by WAT, further enhancing insulin sensitivity and lowering blood glucose. PPARγ also exerts metabolic effects on BAT, brain, and pancreas. Increased hepatic steatosis upon PPARγ activation occurs in mice but not in humans (blue brackets), who display increased hepatic insulin sensitivity due to reduced FA flux from WAT.

tor-1α (PGC1A) (74). While PPARα activation reduces weight gain in rodents (73), there is no evidence of PPARα effects on body mass in humans (18, 19).

The inability of fibrates to improve glucose homeostasis in people with T2D (18, 19) may result from several mechanisms. Glucose handling in liver and peripheral tissues is reduced as a consequence of increased FAO (75). PPARα activation also reduces pyruvate kinase (PK) and induces PDK4 expression in the liver, decreases glycolysis, and enhances gluconeogenesis in mice (76). As discussed above, clinical and genetic data have revealed a role for PPARα in preventing conversion from impaired glucose tolerance to overt T2D. This effect of PPARα might stem from pancreatic β cell protection from lipotoxicity (77) and decreases in insulin clearance mediated by the biliary glycoprotein CEACAM1 (78).

PPARγ is highly expressed in WAT, where it controls FA uptake and lipogenesis. Target genes contributing to this activity include FA binding protein-4 and the FA translocase CD36 (79). Additionally, PPARγ is a master regulator of white adipocyte differentiation. Multiple TFs including the glucocorticoid receptor (GR) and STAT5A cooperatively induce PPARγ during adipogenesis (28), while other TFs such as C/EBPα cooperate with PPARγ to stimulate genomic binding and transcription of target genes (80), thereby regulating both housekeeping and adipocyte-specific functions (81). These PPARγ-mediated changes in gene expression are preceded by chromatin remodeling involving both adipocyte-specific TFs such as C/EBPβ (82) as well as ubiquitous TFs such as CCCTC-binding factor (CTCF) (83). Interestingly, promotion of adipogenesis by the mTORC1 complex occurs through stimulation of PPARγ translation (84) and transcriptional activity (85), which contrasts with the inhibitory effect of mTORC1 on PPARα (discussed above) (58).

In contrast to WAT, PPARγ target genes in BAT encode thermogenic proteins and inducers of mitochondrial biogenesis such as PGC1A and uncoupling protein-1 (UCP1, also known as thermogenin). PPARγ promotes brown adipocyte differentiation, but additional TFs including PPARα are required to switch on their thermogenic program (74).

PPARγ enhances whole body insulin sensitivity through multiple mechanisms (Figure 2). By augmenting WAT expandability, PPARγ shifts lipids from liver and SKM to WAT, thereby indirectly increasing glucose utilization in liver and peripheral tissues. As a result of this "lipid stealing," lipotoxicity, which impairs insulin signaling, is alleviated. PPARγ also regulates the expression of adipocyte hormones that modulate liver and SKM insulin sensitivity such as adiponectin and leptin (86, 87). Results of a Mendelian randomization study refuted a causal role for adiponectin in CV disease (88), which may explain why pure PPARγ agonists, such as rosiglitazone, are not cardioprotective. Finally, PPARγ activation improves pancreatic β cell function and survival by preventing FA-induced impairment of insulin secretion (77) and enhancing the unfolded protein response (89). Thus, whereas PPARα activation leads to energy dissipation, activation of PPARγ stimulates energy storage in WAT, thereby sensitizing liver and peripheral tissues to insulin.

The contrasting mechanisms of action of PPARα and PPARγ are also illustrated by their opposite function on hepatic lipid metabolism. Reduced hepatic steatosis due to increased FAO in hepatocytes occurs upon PPARα activation in rodent models of NAFLD (90, 91), while PPARγ activation in rodents (but not humans) increases liver fat accumulation by enhancing hepatic expression of PPARγ-dependent genes involved in lipogenesis (79, 92). Interestingly, hepatic PPARγ expression levels determine liver steatosis: mice with low hepatic PPARγ expression are resistant to diet-induced development of fatty liver when treated with rosiglitazone, whereas liver steatosis is exacerbated in obese mice expressing high hepatic levels of PPARγ (93). In mice, PPARγ expression in liver is regulated by the dimeric AP-1 protein complex, thereby controlling hepatic steatosis (94). However, in humans with NAFLD, PPARγ expression is unaltered (59) and TZD treatment decreases hepatic steatosis, likely due to decreased FA flux from WAT to liver (95, 96).

Energy homeostasis is also regulated by inter-organ communications involving the brain and the gut. Neuronal PPARγ deletion in mice diminishes food intake and energy expenditure, thus reducing weight gain upon HFD feeding, suggesting that brain PPARγ exerts hyperphagic effects and promotes obesity (97). Similarly, central PPARα activation may also increase food intake (6), although not all studies concur (98). In the intestine, PPARα activation suppresses postprandial hyperlipidemia by enhancing intestinal epithelial cell FAO (99). Furthermore, intestinal PPARα activation reduces cholesterol esterification, suppresses chylomicron production, and increases HDL synthesis by enterocytes (100).

Molecular basis for differential activities of PPARα and PPARγ. The exact mechanisms through which the different PPAR isotypes — which share similar DNA-binding motifs — bind and regulate different genes remain to be established. Several explanations and hypotheses have been put forward. First, PPARα is predominantly expressed in the liver, whereas PPARγ expression is highest in WAT (2). The different PPARs emerged during evolution from gene duplications, but subsequent sequence variations of their promoters and 3′-UTRs have contributed to acquisition of differential expression patterns and functions (101). Tissue-specific chromatin and TF environments also play a role by restricting PPAR recruitment to selective enhancers and therefore specifying PPAR target genes (28). This is illustrated by the tissue-specific PPARγ cistromes in white adipocytes and macrophages, both of which express high PPARγ levels. The macrophage-specific PPARγ cistrome is defined by the pioneer TF PU.1 (102), which induces nucleosome remodeling and histone modifications, promoting the recruitment of additional TFs (103). In white adipocytes, however, these macrophage-specific binding regions are marked with repressive histone modifications, thus disabling PPARγ binding (104). Furthermore, PPARγ cistromes differ between white adipocyte depots (epididymal vs. inguinal) in association with depot-specific gene expression patterns (105).

Nutritional status also contributes to differential PPAR regulation. PPARα is a metabolic sensor, switching its activity from coordination of lipogenesis in the fed state to promotion of FA uptake and FAO during a fasting state (49). PPARα activation during fasting involves PGC1α coactivator induction by the fasting-induced TF EB (106). In addition to PPARα itself (107), circadian transcription of genes encoding acyl-CoA thioesterases coordinates cyclic intracellular production of FA ligands (108). The TF CREBH, a circadian regulator of hepatic lipid metabolism, rhythmically interacts with PPARα and regulates its activity (109). Adjustment of PPARα transcriptional activity to nutritional status is also controlled by kinases phosphorylating PPARα or its coregulators. In the fed state, PPARα activity is enhanced through insulin-activated MAPK and glucose-activated PKC, while glucagon-activated PKA and AMPK increase PPARα signaling in fasting (49). Moreover, the fasting response is co-controlled by PPARα and GRα, which show extensive chromatin colocalization and interact to induce lipid metabolism genes upon prolonged fasting through genomic AMPK recruitment (110). Conversely, GRβ antagonizes glucocorticoid signaling during fasting via inhibition of GRα and PPARα, thus increasing inflammation and hepatic lipid accumulation (111).

PPARγ activity is higher in the fed state, in line with its role in lipid synthesis and storage. PPARγ activity in WAT is repressed during fasting via mechanisms involving SIRT1 (112) or AMPK (113). In mice, the amplitude of hepatic circadian clock gene expression is reduced by HFD feeding (114), whereas circadian rhythmicity of PPARγ and genes containing the PPARγ binding site is induced (115). Thus, the HFD-induced transcriptional reprogramming relies at least in part on changes in expression, oscillation pattern, and chromatin recruitment of PPARγ. Gut microbiota, which also exhibit circadian activity (116), are drivers of HFD-induced hepatic transcriptional reprogramming by PPARγ in mice (117). Nutritional status also links PPARs to FGF21 signaling, as fasting increases PPARα-dependent FGF21 expression in liver, further enhancing FAO and ketogenesis (118). In WAT, PPARγ induces FGF21 expression (119), where it acts as an autocrine factor in the fed state, regulating PPARγ activity through a feedforward mechanism (120). In the pancreas, PPARγ agonism reverses high glucose–induced islet dysfunction by enhancing FGF21 signaling (121). FGF1 is also induced by PPARγ in WAT, and the PPARγ/FGF1 axis is critical for maintaining metabolic homeostasis and insulin sensitization (122).

Combating inflammation: a shared function of PPARα and PPARγ

MetS is accompanied by a low-grade inflammatory state in different metabolic tissues — termed meta-inflammation — characterized by increased secretion of pro-inflammatory chemokines and cytokines, many of which (including TNF-α, IL-1, and IL-6) influence lipid metabolism and insulin resistance (123). Besides differentially regulating lipid and glucose metabolism, PPARα and PPARγ also counter inflammation. However, the anti-inflammatory effects of PPARα and PPARγ activation are likely distinct due to differences in tissue and cell type expression.

In WAT, fenofibrate and rosiglitazone reduce the expression of several pro-inflammatory mediators, including IL-6 and the chemokines CXCL10 and MCP1 (124). PPARγ also inhibits pro-inflammatory cytokine production by WAT-resident macrophages and modulates macrophage polarization (125). Although innate immune cells such as macrophages were initially thought to be the main drivers of WAT inflammation and metabolic dysregulation, important roles of the adaptive immune system, including WAT Tregs, have recently emerged (126). PPARγ acts as a molecular orchestrator of WAT Treg accumulation, phenotype, and function (127, 128). Indeed, the WAT Treg transcriptome alterations in obese mice depend on PPARγ phosphorylation by cyclin-dependent kinase 5 (CDK5) (127). In addition, PPARγ expression in WAT Tregs is necessary for complete restoration of insulin sensitivity in obese mice upon pioglitazone treatment (128). On the other hand, activation of $CD4^+$ T cells is accompanied by mTORC1-dependent PPARγ induction and enhanced expression of FA uptake genes, enabling rapid T cell proliferation and optimal immune responses (129). PPARα and PPARγ also modulate the inflammatory response in liver and vascular wall (130, 131).

Inhibition of pro-inflammatory gene expression is the main process underlying the anti-inflammatory properties of PPARα and PPARγ. Several mechanisms have been proposed for transcriptional repression by PPARs that are not mutually exclusive. These include direct physical interaction of PPARα or PPARγ with several pro-inflammatory TFs including AP-1 and NF-κB (132, 133). Repression of inflammation independently of direct PPARα DNA binding results in anti-inflammatory and anti-fibrotic effects in a mouse model of non-alcoholic steatohepatitis (NASH) (134). In addition to this PPRE-independent transrepression mechanism, interaction between NF-κB and PPRE-bound PPARα also occurs, leading to repression of TNF-α–mediated upregulation of complement C3 gene expression and protein secretion during acute inflammation (135). Moreover, simultaneous activation of PPARα and GRα increases the repression of NF-κB–driven genes, thereby decreasing cytokine production (136). Transcriptional repression of pro-inflammatory genes by PPARγ may include ligand-activated PPARγ sumoylation, which targets the receptor to corepressor complexes assembled at inflammatory gene promoters. This prevents promoter recruitment of the proteasome machinery that normally mediates the inflammatory signal–dependent removal of corepressor complexes required for gene activation. As a result, these complexes are not cleared from the promoters and inflammatory genes are maintained in a repressed state (137). In addition to downregulating the expression of pro-inflammatory genes, PPARα (138) and PPARγ (139) also suppress inflammation by upregulating genes with anti-inflammatory properties, such as IL-1Ra, suggesting a possible cooperation between PPAR-dependent transactivation and transrepression to counter inflammation.

The anti-inflammatory properties of PPARα likely contribute to the improved lobular inflammation and hepatocellular ballooning observed in NAFLD patients treated with pioglitazone (140) or elafibranor (141), a dual PPARα/β(δ) agonist. Pioglitazone reduces hepatic steatosis in NAFLD patients (140), likely due to PPARγ activation. The pure PPARγ agonist rosiglitazone also lowers liver fat in humans (96), whereas the pure PPARα agonist fenofibrate does not (68). Administration of fenofibrate to people with dyslipidemia lowers plasma levels of atypical deoxysphingolipids (142), which increase upon the transition from simple steatosis to NASH (143). Thus, activation of both PPARα and PPARγ appears to be beneficial in human NAFLD, although the underlying mechanisms clearly differ. Whereas the effects of PPARα agonism on inflammation and ballooning are due to direct PPARα activation in the liver, the effects of PPARγ on hepatic steatosis are likely mediated by indirect mechanisms such as suppression of FA flux to the liver; this is in line with the low expression and absence of PPARγ induction in human fatty liver (59).

PPARβ/δ, the clinically enigmatic third PPAR

Selective synthetic PPARβ/δ agonists are not yet clinically available; however, beneficial effects of PPARβ/δ activation on various MetS components have been reported and include both differences and similarities to PPARα and PPARγ, such as reduced inflammation (144–146).

PPARD variants are associated with cholesterol metabolism (147), insulin sensitivity (148), T2D risk (149), and CV risk (40). In obese men, administration of the synthetic PPARβ/δ agonist GW501516 lowers liver fat content and plasma levels of insulin, FAs, triglycerides, and LDL-C (150). These beneficial effects on plasma lipids are also observed in overweight patients treated with seladelpar (MBX-8025), a novel PPARβ/δ agonist (151). Thus, PPARβ/δ agonism combines the metabolic effects of PPARα and PPARγ activation on lipid metabolism and glucose homeostasis, respectively. Preclinical studies support this conclusion, as the administration of GW501516 to overweight monkeys (152) or obese rats (153) lowered serum LDL-C and raised HDL-C while improving insulin sensitivity.

PPARβ/δ activation protects from diet-induced or genetically induced obesity in mice by increasing energy expenditure (154). In BAT, activation of PPARβ/δ induces the expression of thermogenic genes, including UCP1, and FAO genes (154). PPARβ/δ agonism also promotes FAO in SKM (155), WAT (156), and liver (157). PPARβ/δ in brain controls energy expenditure, as neuron-specific PPARβ/δ deletion increases susceptibility to diet-induced obesity (158). Thus, similar to PPARα, PPARβ/δ activation induces energy dissipation. Interestingly, both isotypes crosstalk in liver, where PPARβ/δ stimulates the production of the PPARα

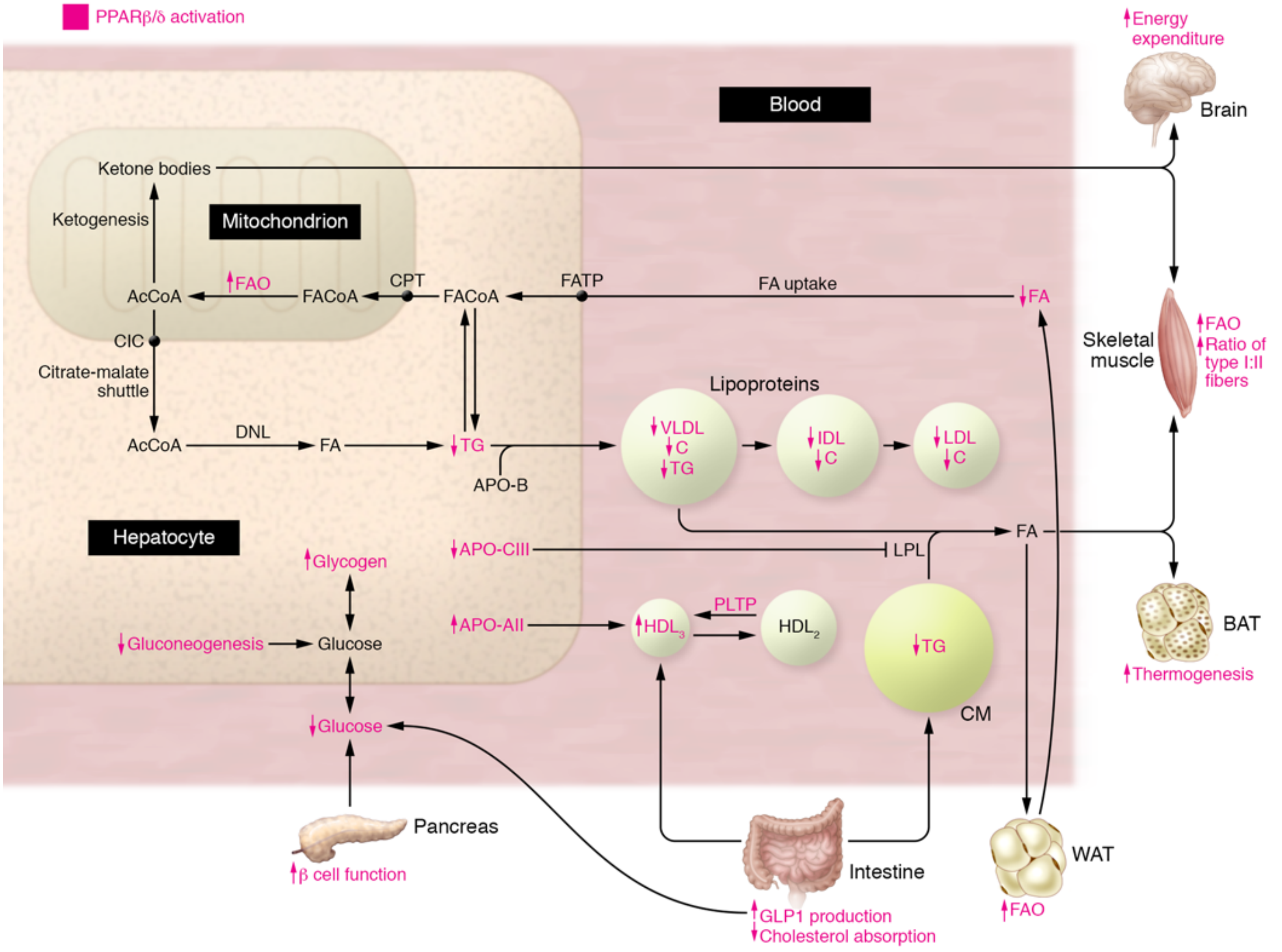

Figure 3. PPARβ/δ activation enhances glucose and lipid homeostasis. In SKM, PPARβ/δ activation (effects are indicated in pink) favors fiber type switching toward type I oxidative fibers, which have a higher glucose-handling capacity compared with type II fibers. PPARβ/δ also augments FAO in SKM, liver, and WAT and enhances hepatic glucose metabolism and pancreatic β cell function. PPARβ/δ activation decreases FAs, triglycerides, and LDL-C and increases HDL-C levels in blood. Metabolic effects of PPARβ/δ agonism also take place in brain and gut.

ligand 16:0/18:0-phosphatidylcholine as well as PPARα expression and DNA-binding activity, thereby increasing hepatic FAO (159). Enhanced FAO upon PPARβ/δ activation contributes to its plasma lipid-lowering effects, together with decreased cholesterol absorption (160) and increased trans-intestinal cholesterol efflux (161). PPARβ/δ also raises HDL-C by increasing hepatic APO-AII (162) and PLTP (163) expression.

PPARβ/δ agonism improves insulin sensitivity through several mechanisms (Figure 3). In SKM, PPARβ/δ activation favors fiber type switching, from type II fast-twitch glycolytic to type I slow-twitch oxidative fibers (164), via mechanisms involving PGC1α (165) and an estrogen-related receptor γ/microRNA regulatory circuit (166), thereby improving glucose handling (167). The type I fiber fraction is reduced in people with T2D (168), which may contribute to altered glucose homeostasis. Mice with myocyte-selective PPARβ/δ deficiency exhibit decreased type I fiber count, which precedes the development of a diabetic phenotype (165). PPARβ/δ also improves glucose handling and insulin sensitivity in the liver. GW501516 treatment suppresses hepatic glucose output and enhances glucose disposal by increasing glucose flux through the pentose phosphate pathway (169). Liver-restricted PPARβ/δ overexpression reduces fasting glucose levels and stimulates hepatic glycogen production via upregulation of glucose utilization pathways (170). Additionally, stress-induced JNK signaling is reduced, contributing to improved hepatic insulin sensitivity (170). PPARβ/δ agonism promotes pancreatic β cell mitochondrial function and ATP production, thereby improving glucose-stimulated insulin secretion (171). Furthermore, PPARβ/δ increases intestinal production of the incretin glucagon-like peptide 1 (GLP1) (172).

In summary, the mechanisms underlying the metabolic effects of PPARβ/δ resemble those of PPARα, which promotes energy dissipation, as opposed to PPARγ, which promotes energy storage. PPARβ/δ normalizes plasma lipids through enhanced FAO in several tissues, coupled to actions on hepatic apolipoprotein metabolism and intestinal cholesterol homeostasis. In contrast to PPARα and similar to PPARγ, activation of PPARβ/δ enhances insulin sensitivity. The mechanisms underlying PPARβ/δ-mediated improvement in glucose handling are not similar to PPARγ, but

Table 1. Selective PPAR modulators

Compound	Reported effects	Status
PPARα agonists		
Pemafibrate (K-877)	Improved lipid profile in patients with dyslipidemia (175)	Phase 3 CV outcome trial ongoing for treatment of dyslipidemia
LY518674	Increased cholesterol efflux in patients with MetS (191)	Discontinued
PPARγ agonists		
INT131	Improved glucose tolerance in people with T2D (176)	Phase 2 trial ongoing for treatment of T2D
PPARβ/δ agonists		
GW501516	Improved lipid profile and insulin sensitivity in overweight monkeys (152) and obese rats (153)	Discontinued
Seladelpar (MBX-8025)	Improved lipid profile and insulin sensitivity in overweight patients with dyslipidemia (151, 181)	Phase 2 trial ongoing for treatment of hyperlipidemia

instead involve PPARβ/δ-specific actions on SKM fiber type distribution, hepatic glucose metabolism, and pancreatic islet function.

Current state of PPAR-targeted therapies

Currently used PPAR agonists display weak potencies (PPARα) or are associated with important side effects (PPARγ). Optimization of therapeutic efficacy may be achieved through the development of selective PPAR modulators that retain the beneficial effects of PPAR activation while diminishing unwanted side effects (ref. 173 and Table 1). The selective PPARα agonist pemafibrate (K-877) (174) exhibited greater lipid modifying efficacy than fenofibrate in a phase 2 trial, with little or no effect on serum creatinine and homocysteine levels (175). This compound is undergoing a phase 3 CV prevention trial, PROMINENT (Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Diabetic Patients), in patients with high triglyceride and low HDL-C levels. The non-TZD PPARγ modulator INT131, which improves glucose tolerance in people with T2D without adverse effects on body weight or hemodilution (176), is in phase 2 development. Several compounds that are not direct PPARγ agonists but that inhibit CDK5-mediated PPARγ phosphorylation also exert anti-diabetic activities in obese mice (177–180); whether this will eventually translate to clinical efficacy is unclear. The PPARβ/δ agonist seladelpar (MBX-8025) decreases plasma triglycerides, increases HDL-C, and improves insulin sensitivity and liver function in overweight people with dyslipidemia (151, 181).

Dual PPAR agonists (which activate two PPAR isotypes) and pan-PPAR agonists (which activate all three PPARs) have been developed with the goal of combining the beneficial effects of each receptor isotype (Table 2). The pan-agonist chiglitazar (CS038) improves lipid profiles and insulin sensitivity without increasing body weight in animal models of obesity (182). IVA337, a pan-agonist that prevents and reverses skin fibrosis (183), is currently entering phase 2 trials for the treatment of NASH. Many dual PPARα/γ agonists, termed glitazars, showed improved efficacy on glucose and lipid metabolism in clinical trials, although safety concerns often halted further development (184). Two phase 3 trials with saroglitazar showed improved glucose and lipid profiles in patients with diabetic dyslipidemia compared with pioglitazone (185) or placebo (186). In contrast to the other PPARγ-dominant glitazars, saroglitazar predominantly activates PPARα with only moderate PPARγ agonism, which may explain the lack of typical

Table 2. Dual and pan-PPAR agonists

Compound	Reported effects	Status
Pan-PPAR agonists		
Chiglitazar	Improved lipid profile and insulin resistance in obese mice (182)	Phase 3 trial ongoing for treatment of T2D
IVA337	Improved skin fibrosis in rodents (183)	Phase 2 trial ongoing for treatment of NASH
Dual PPARα/γ agonists		
Saroglitazar	Improved glucose and lipid profiles in patients with dyslipidemia (185, 186)	Marketed in India for dyslipidemia; phase 3 trial ongoing for treatment of T2D
DSP-8658	Improved glucose and lipid profiles in obese mice (192)	Discontinued
Dual PPARβ(δ)/γ agonists		
DB959	Improved glucose and lipid profiles in obese mice (193)	Discontinued
Dual PPARα/β(δ) agonists		
Elafibranor (GFT505)	Improved hepatic steatosis, inflammation, and fibrosis in rodent models of NASH (90) and in patients with NASH (141); improved lipid profile and insulin sensitivity in patients with dyslipidemia or prediabetes (187) and in obese individuals (188)	Phase 3 trial ongoing for treatment of NASH

PPARγ side effects. Elafibranor (GFT505), a dual PPARα/β(δ) agonist, demonstrated protective effects against hepatic steatosis, inflammation, and fibrosis in animal models of NAFLD/NASH (90). In phase 2a trials, elafibranor improved lipid and glucose profiles in dyslipidemic and prediabetic patients (187) and obese individuals (188). The GOLDEN-505 phase 2b study in people with NASH showed that elafibranor treatment induces NASH resolution without worsening fibrosis in a higher proportion of patients compared with placebo (141). The drug was well tolerated and improved glucose homeostasis and CV risk profile, and has since entered phase 3 development for NASH (the RESOLVE-IT trial; NCT02704403).

PPARs are still valuable targets for metabolic diseases

Over the last decades, market withdrawals and failed drug development programs have cast doubts on the clinical value of PPAR-activating compounds. However, this issue is not black and white. The pure PPARγ agonist rosiglitazone as well as dual PPAR agonists with predominant PPARγ-activating properties all displayed important adverse effects that led to restricted use or halted development. However, most of these side effects were either drug specific and hence off-target (189) or related to excessive PPARγ activation. Several fibrate trials, including FIELD and ACCORD, failed to meet the primary endpoint of reduced CV risk; however, such negative outcomes are likely linked to inappropriate patient selection, since subgroup analyzes revealed significant CV risk reduction in those patients with marked dyslipidemia upon trial enrolment (21). Furthermore, in several of these fibrate trials, including BIP and FIELD, the proportion of patients who received statin therapy was unbalanced between placebo and treatment groups. Correction for this nonrandomized statin drop-in in the FIELD study estimated that fenofibrate reduces relative CV risk by 19% (190).

It has become increasingly clear that PPARα and PPARγ agonism display contrasting metabolic effects with different mechanisms of action. Whereas PPARβ/δ agonism is more related to PPARα, subtle differences exist (e.g., in regulation of glucose homeostasis). These findings are in line with the enhanced metabolic actions and improved safety profiles of novel compounds such as dual PPARα/β(δ) ligands, which target both lipid (via PPARα and PPARβ/δ) and glucose (via PPARβ/δ) abnormalities in people with MetS without displaying PPARγ-related adverse effects. Altogether, we are convinced that targeting PPARs in metabolic disorders remains a valuable and promising approach with a future ahead.

Acknowledgments

BS is a member of the Institut Universitaire de France. This work was supported by grants from the European Genomic Institute for Diabetes (grant ANR-10-LABX-46), the European Commission (RESOLVE contract FP7-305707), and the Fondation de France and Fondation pour la Recherche Médicale (contract DEQ20150331724).

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