R E V I E W   A R T I C L E

Peroxisome Proliferator – Activated Receptors and The Metabolic Syndrome

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Abstract

BACKGROUND: Obesity is a growing threat to global health by virtue of its association with insulin resistance, inflammation, hypertension, and dyslipidemia, collectively known as the metabolic syndrome (MetS). The nuclear receptors PPARα and PPARγ are therapeutic targets for hypertriglyceridemia and insulin resistance, respectively, and drugs that modulate these receptors are currently in clinical use. More recent work on the PPARδ has uncovered a dual benefit for both hypertriglyceridemia and insulin resistance, highlighting the broad potential of PPARs in the treatment of metabolic disease.

CONTENT: We have learned much about PPARs, the metabolic fat sensors, and the molecular pathways they regulate. Through their distinct tissue distribution and specific target gene activation, the three PPARs together control diverse aspects of fatty acid metabolism, energy balance, insulin sensitivity glucose homeostasis, inflammation, hypertension and atherosclerosis. These studies have advanced our understanding of the etiology for the MetS. Mechanisms revealed by these studies highlight the importance of emerging concepts, such as the endocrine function of adipose tissue, tissue-tissue cross-talk and lipotoxicity, in the pathogenesis of type 2 diabetes mellitus and CVD.

SUMMARY: The elucidation of key regulators of energy balance and insulin signaling have revolutionized our understanding of fat and sugar metabolism and their intimate link. The three 'lipid-sensing' (PPARα, PPARγ and PPARδ) exemplify this connection, regulating diverse aspects of lipid and glucose homeostasis, and serving as bonafide therapeutic targets.

KEYWORDS: Peroxisome Proliferator, Activated Receptor, Metabolic Syndrome.

Introduction

The metabolic syndrome, is characterized by abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance, inflammation, and prothrombotic states (1).

The major sequelae are cardiovascular disease and type 2 diabetes mellitus, but the syndrome also increases the risk of polycystic ovary syndrome, fatty liver, cholesterol gallstones, asthma, sleep disturbances, and some forms of cancer (2). The pathogenesis of the MetS is thought to involve a complex interaction of multiple factors, which include obesity and abnormal fat distribution; insulin resistance; hepatic, vascular, and immunologic factors; and lifestyle and genetic contributions (3).

Recent advances in our understanding of adipose tissue biology and, in particular, its endocrine function and the dysregulated state associated with obesity characterized by enlarged adipose cells have provided insight into the mechanisms involved (4).

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Increased adipose tissue mass contributes to augmented secretion of proinflammatory adipokines, particularly tumor necrosis factor-α (TNFα), along with diminished secretion of the "protective" adiponectin. TNFα and adiponectin are antagonistic in stimulating nuclear transcription factor-κB (NF-κB) activation. Through this activation, TNFα induces oxidative stress, which exacerbates pathological processes leading to oxidized low-density lipoprotein and dyslipidemia, glucose intolerance, insulin resistance, hypertension, endothelial dysfunction, and atherogenesis. Elevated free fatty acid, glucose, and insulin levels enhance this NF-κB activation and further downstream modulate specific clinical manifestations of metabolic syndrome (5).

Although there has been a debate on the criteria and concept of the metabolic syndrome, the current definition by the National Cholesterol Education Program–Adult Treatment Panel (NCEP-ATP III) and the International Diabetes Federation (IDF) provide adequate screening tools to identify the subjects with high cardiometabolic risk. With these tools in hand the stage is set for attempts to discover the pathophysiology underlying these metabolic abnormalities. The identification of intracellular signaling elements and regulating factors at crossroad steps that direct the metabolic fate of lipids are critical for the understanding of atherogenic dyslipidemia in the MetS. Importantly, several lipid metabolites seem to play a crucial role in the regulation of insulin signaling and action influencing endothelial function and initiating vascular injury. The concept that dysfunctional adipose tissue cannot properly handle the energy surplus derived from excessive calorie consumption combined with sedentary lifestyle sets the stage to identify the main determinants of the MetS in different populations. Resolving these issues is crucial for the optimal management of the MetS and reduction of global CVD risk (6).

Peroxisome proliferator-activated receptor (PPAR)s are a family of 3 (PPARα, β/δ, and γ) nuclear receptor/ligand-activated transcription factors that work in concert as heterodimers with the retinoid X receptors (7). In recent years, there has been great scientific and clinical interest in the actions of PPARα and PPARγ because they are the molecular targets for the clinically used lipid-lowering fibrates and insulin-sensitizing thiazolidinedione classes of drugs, respectively (7,8).

The recent development of highly selective ligands and PPARβ/δ knockout and transgenic mice, however, have now implicated roles for PPARβ/δ in adipose tissue formation, metabolism, wound healing, brain development, placental function, colorectal carcinogenesis, and skeletal muscle function. PPARβ/δ ligands appear highly effective in regulating lipid metabolism, particularly in skeletal muscle, and are currently in phase II clinical trials for treatment of dyslipidemia, aimed particularly at individuals with low HDL levels (9,10,11). All of the PPARs, therefore, appear to be able to target aspects of the MetS (11). Because the MetS represents a major risk factor for cardiovascular diseases, there has been an increasing interest in the roles of PPARs, in particular most recently PPARβ/δ, in vascular biology. Indeed, in addition to the treatment of dyslipidemia, PPARβ/δ ligands may reduce the development in atherosclerosis (11,12).

The discovery cycle involving nuclear receptors has elucidated the molecular and physiological basis for a new class of pharmacophores that show promise for treating the MetS (3).

The Biology of PPARs

PPARs are members of the nuclear receptor superfamily which includes the steroid, retinoid, and thyroid hormone receptors. These receptors are transcription factors that regulate gene expression in response to certain endogenous and exogenous ligands. It is now well established that the PPARs act as central transcriptional mediators in the regulation of several important metabolic processes that influence adipogenesis, insulin sensitivity, glucose homeostasis, lipid metabolism, vascular endothelial function, atherosclerosis progression, and ultimately cardiovascular risk (13).

MOLECULAR BIOLOGY OF PPARS

The three PPARs are ligand-activated transcription factors of the nuclear hormone receptor superfamily. They share a high degree of structural homology with all members of the superfamily, particularly in the DNA-binding domain and ligand- and cofactor-binding domain. Many cellular and systemic roles have been attributed to these receptors, reaching far

beyond the stimulation of peroxisome proliferation in rodents after which they were initially named. PPARs exhibit broad, isotype-specific tissue expression patterns (11).

PPARα(NR1C1)(Nuclear Receptors Nomenclature Committee, 1999) was first described as a receptor that is activated by peroxisome proliferators, hence its name (14). Two additional related isotypes, PPARβ/δ (NR1C2) and PPARγ (NR1C3), were then found and characterized.The PPARβ/γ isotype was called PPARβ when it was first isolated from a Xenopus oocyte library (15). Because the mammalian PPARβ protein sequence was not highly homologous to the Xenopus PPARβ protein sequences, it was named PPARβ when identified in the mouse with the view that there may be four members of this nuclear receptor family (16). PPARβ was also designated FAAR (fatty acid activated receptor) (17) in rats and NUC1 in humans (18). Sequencing of mammalian genomes indicated that there are only three PPAR isotypes. Characterization of PPARs in the chick and comparison with the PPARs of mouse and Xenopus demonstrated that the mammalian PPARβ is the ortholog of the amphibian PPARβ For reasons of clarity, we propose that this receptor be designated herein as PPARβ/δ (16).

PPARα is expressed at high levels in organs that carry out significant catabolism of fatty acids such as the brown adipose tissue, liver, heart, kidney, and intestine (19). Of the three isotypes, PPARβ/δ has the broadest expression pattern, and the levels of expression in certain tissues depend on the extent of cell proliferation and differentiation. Important functions have been assigned to this isotype in the skin, gut, placenta, skeletal muscle, adipose tissue, and brain (10,11,20,21,22). PPARγ is expressed as two isoforms, γ1 and γ2, that differ at their N terminus. PPARγ2 is found at high levels in the different adipose tissues (15,23,24), whereas PPARγ1 has a broader expression pattern that extends to settings such as the gut, brain, vascular cells, and specific kinds of immune and inflammatory cells (25,26).

PPARs requires heterodimerization with the retinoid X receptor (RXR; NR2B), which belongs to the same receptor superfamily (27,28). This PPAR/RXR heterodimer can form in the absence of a ligand. When activated by a ligand, it modulates transcription via binding to a specific DNA sequence element frequently called a peroxisome proliferator response element (PPRE) (15,27,29,30). This response element, generally of the direct repeat 1 (DR-1) type, is composed of two half-sites that occur as a direct repetition of the consensus sequence AGGTCA with a single nucleotide spacing between the two repeats. The PPRE is usually present in one or multiple copies in the promoter region of target genes but may also be located in the proximal transcribed region of certain PPAR-responsive genes (31). PPAR and RXR bind to the 5' and 3' half-sites of this element, respectively, and the 5'-flanking region mediates the selectivity of binding between different PPAR isotypes (32,33,34). Transcriptional control by PPAR/RXR heterodimers requires interaction with coregulator complexes— either a coactivator for stimulation or a corepressor for inhibition of target gene expression (35,36,37,38).

Thus, selective action of PPARs in vivo results from the interplay at a given time point between expression levels of each of the three PPAR and RXR isotypes, affinity for a specific promoter PPRE, and ligand and cofactor availabilities (11).

A wide variety of natural or synthetic compounds was identified as PPAR ligands. Among the synthetic ligands, the lipid – lowering drugs, fibrates, and the insulin sensitizers, thiazolidinediones, are PPARα and PPARγ agonists, respectively, which underscores the important role of PPARs as therapeutic targets (11).

The prevalent point of view today is that PPARs act as lipid sensors that translate changes in lipid/fatty acid levels from the diet or from food deprivation into metabolic activity, leading to either fatty acid catabolism or lipid storage. The endogenous ligands or mediators of these changes have not been characterized but are probably generated by fatty acid metabolism. Their activities are likely to be influenced by their binding specificities toward the different PPARs and by cell-, tissue-, or organ- specific effects (39,40,41).

The possible pathways that generate lipid mediators from fatty acids, which also serve as PPAR ligands, are recapitulated in Fig. 1. In addition, specific lipolytic pathways, for example the action of lipoprotein lipase and endothelial lipase, can hydrolyze certain circulating lipoproteins to generate PPAR ligands and PPAR activation (43,44,45). Given the variety and distribution pattern in the body of fatty acids and fatty acid derivatives with a wide range of affinity to PPARs, it has been difficult thus far to thoroughly evaluate the contribution of each of these endogenous ligands to the biology of PPARs. However, it is not surprising, based on the characteristics of these endogenous ligands with their broad spectrum of activation efficiency, that PPARs are involved in functions as diverse as lipid and carbohydrate metabolism, immune/inflammatory responses, vascular biology, tissue repair, and cell

differentiation and p roliferation. The d istribution and abundance of t he ligands a lso depend o n a variety o f pathophysiological situations a ssociated with hyperlipidemia, hypertension, d iabetes, chronic inflammation, c ancer, and a therosclerosis. I t is important to note that some of these endogenous lipid mediators also signal through the classic cell surface G-protein-linked r eceptors and t herefore have m any PPAR-independent effects (11).

PPARγ is expressed in adipocytes, macrophages, and m uscle, where it r egulates development, lipid homeostasis, and g lucose m etabolism. Endogenous PPARγ agonists i nclude f atty a cids and e icosanoids (47,48,49). The PPARγ genetic program includes target genes involved in the uptake of glucose in muscle (c-Cbl associated protein and glucose transporter 4), lipid metabolism (scavenger receptor, adipocyte-fatty-acid–binding protein, lipoprotein lipase, fatty-acid–binding
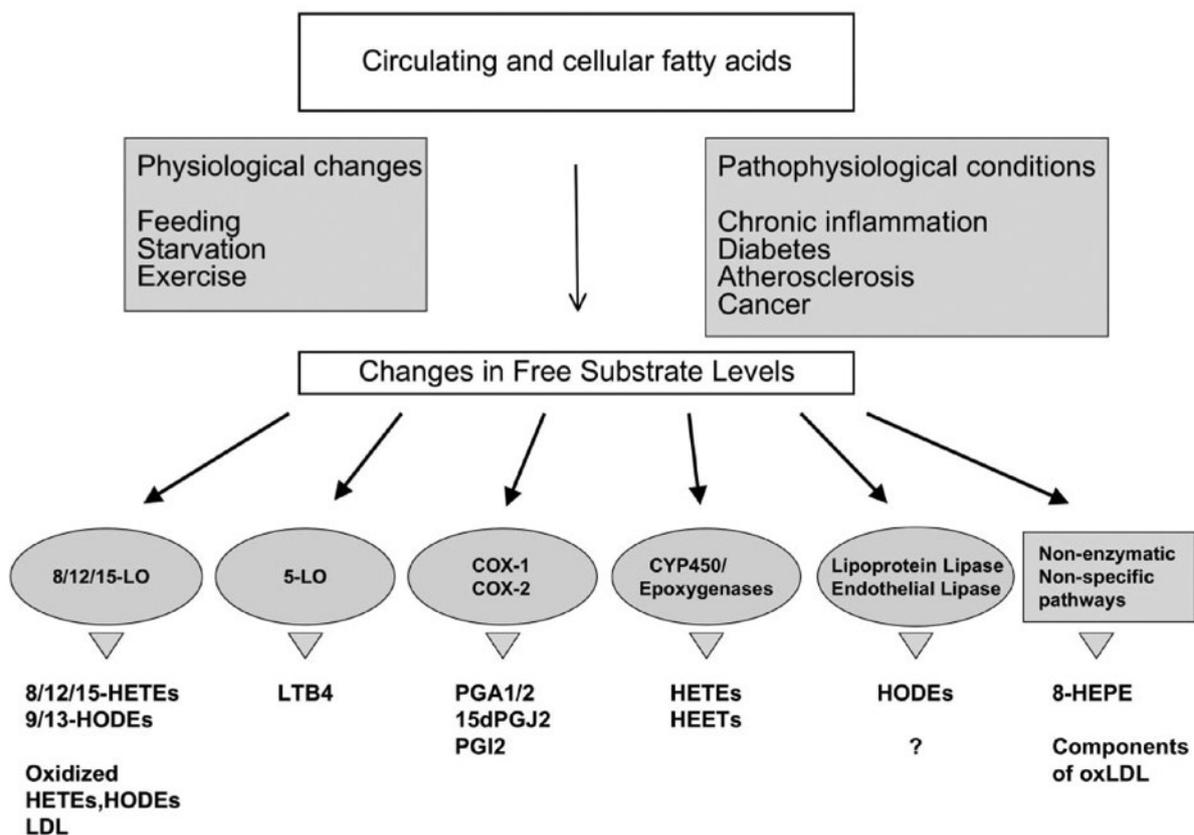

Fig. 1. Endogenous pathways for PPAR ligand production (Adapted from Michalik L, et al. 2006).

Among synthetic ligands, compounds of the fibrate family (clofibrate, f enofibrate, and bezafibrate) and their derivatives have been widely used to characterize PPARα functions (43). Taken together, mouse models suggest that PPARα functions to increase fatty-acid use in the f asting state and that in the pathophysiologic context of a high-fat diet, PPARα-induced f atty-acid catabolism m ight p revent hypertriglyceridemia. Consistent with this prediction, an activated variant of PPAR α (Leu162Val) is associated with low serum TG levels and reduced adiposity (46).

protein, a cyl-CoA s ynthetase, and CYP4B1), and energy expenditure (glycerol k inase and uncoupling proteins 2 and 3) (50,51,52,63,54,55,56,57,58).

In addition to r egulating glucose and lipid metabolism, PPARγ i s a potential modifier o f atherogenesis. Signaling through PPARγ, components of oxidized l ow-density lipoprotein (LDL) i ncrease expression of the scavenger receptor CD36, resulting in lipid a ccumulation in m acrophages (59,60). PPARγ also a ctivates t he m acrophage L XR-ABCA1 cholesterol efflux pathway (61), which m ay explain

the finding that PPARγ ligands inhibit the formation of a therosclerotic lesions in LDL-receptor–deficient mice (62).

The landmark finding that the thiazolidinedione class of insulin sensitizers, including rosiglitazone and pioglitazone, function as high-affinity PPARγ agonists has validated the efficacy of PPARγ modulation in treating the MetS (63).

PPARδ is expressed ubiquitously and is activated by fatty acids and components of very-low-density lipoprotein (VLDL) (43,47). PPARδ target genes control β-oxidation in murine brown fat (long-chain and very-long-chain acyl-CoA synthetase, longchain and very-long-chain acyl-CoA dehydrogenase, and acyl-CoA oxidase), energy expenditure (uncoupling proteins 1 and 3), and lipid storage (macrophage adipose differentiation–related protein) (64,65). In the pathophysiological context of a high-fat diet, PPARδ could function to increase adipose fatty-acid catabolism and may play a role in VLDL–induced

lipid accumulation in therosclerotic foam cells. A high-affinity synthetic PPARδ agonist has been shown to increase HDL and decrease LDL, TG, and fasting insulin in obese rhesus monkeys. These studies suggest that therapeutic activation of PPARδ has the potential to decrease diet-induced obesity without activating the PPARγ dependent adipogenic program (66).

PPARs AND CONTROL OF METABOLISM

Lipids are essential for energy homeostasis, reproductive and organ physiology, and numerous aspects of cellular biology. They are also linked to many pathological processes, such as obesity, diabetes, heart disease, and inflammation. To meet the different demands from a variety of tissues, the human body has evolved a sophisticated lipoprotein transport system to deliver cholesterol and fatty acids to the periphery (Fig. 2) (67).
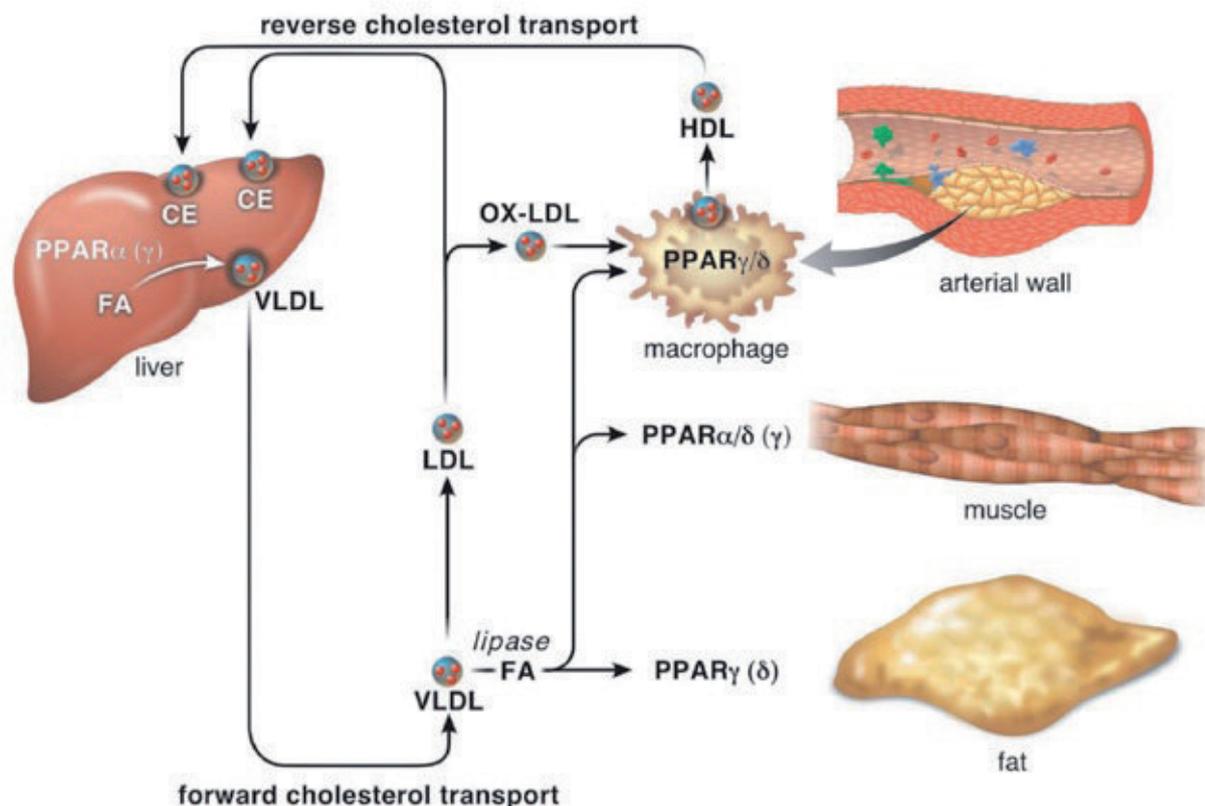

Fig. 2 Circulating lipoproteins deliver both energy substrates and endogenous activators for PPARs (Adapted from Lee CH, et al, 2003).

Disturbances in this system are integral components of lifethreatening diseases, best exemplified by the metabolic syndrome, which refers to patients who are insulin-resistant (hyperinsulinemic), dyslipidemic (elevated TG and decreased HDLC levels) (68).

Lipids and their derivatives have a role in the genetic control of their own systemic transport, cellular uptake, storage, mobilization, and use. Fine tuning of these metabolic processes is a hallmark of healthy organisms. Lipid homeostasis depends on factors that are able to transduce metabolic parameters into regulatory events representing the fundamental components of the general control system (69).

The identification of fatty acids as endogenous ligands for PPARs has provided a unique approach to study lipid homeostasis at the molecular level (68).

Liver is the key site of metabolic integration where fatty acids are mobilized and, depending on the body's needs, either stored or used as an energy source. In the fasting state, the fuel sources of the body shift from carbohydrates and fats to mostly fats, and fatty acids that were stored during feeding are released from the adipocyte and taken up by liver. There they are either reesterified to TGs and assembled into VLDL or broken down through β-oxidation and used to generate ketone bodies. Earlier studies have demonstrated that in the liver, PPARα directly regulates genes involved in fatty acid uptake [fatty acid binding protein (FABP)], β-oxidation (acyl-CoA oxidase) and ω-oxidation (cytochrome P450). Gene targeting studies confirmed that PPARα is essential for the up-regulation of these genes caused by fasting or by pharmacological stimulation with synthetic ligands such as the fibrates (70,71,72).

Fasting also results in severe hypoglycemia, hypoketonemia, and elevated plasma levels of nonesterified fatty acid, indicating a defect in fatty acid uptake and oxidation caused by dysregulation of these genes (73,74). In line with these observations, the fibrate class of drugs including fenofibrate and gemfibrozil, which are synthetic ligands for PPARα, lower serum TGs and slightly increase HDL cholesterol levels in patients with hyperlipidemia (75), most likely due to induction of fatty acid oxidation through activation of PPARα. PPARα has also been shown to down-regulate apolipoprotein C-III, a protein which inhibits TG hydrolysis by LPL. This activity of PPARα ligands further contributes to the lipid-lowering effect (68).

Apolipoprotein A-V (apoA-V) is now recognized as a key regulator of serum TG levels. Administration of the PPARα agonist caused a 50% decrease in TG that reversed at washout. Serum apoA-V concentrations increased 2-fold, correlated inversely with TG, and were reversible at washout. The apoA-V/apoC-III ratio increased 2-fold, with this increase also reversible at washout. These data demonstrate for the first time that a PPARα agonist increases circulating apoA-V protein levels and the apoA-V/apoC-III ratio (76).

Unlike its function in the adaptive response to fasting, the role of PPARα in cardiovascular pathogenesis appears to be detrimental. Cardiac-specific PPARα overexpression increases fatty acid oxidation and concomitantly decreases glucose transport and use, a phenotype similar to that of the diabetic heart, indicate that PPARα senses fatty acids and induces their use, and thus plays a causative role in cardiomyopathy. The net effect, however, of fibrate intervention in cardiovascular disease is likely beneficial because systemic TG reduction should result in less fat accumulation in the heart and at the vessel wall (68).

Adipocytes are the main site for lipid storage and modulate the levels of lipids in the blood stream in response to hormonal signals. PPARγ has high expression in this tissue and has been shown to potentiate adipocyte differentiation from fibroblasts (54). The PPARγ2 isoform prevents lipotoxicity by (a) promoting adipose tissue expansion, (b) increasing the lipid-buffering capacity of peripheral organs, and (c) facilitating the adaptive proliferative response of β-cells to insulin resistance (77).

PPARγ also promotes cholesterol efflux through the induction of a transcriptional cascade involving the nuclear sterol receptor LXRα and its downstream target ABCA1, a membrane transporter that is important for HDL-mediated reverse cholesterol transport (61,78,79,80). In this view, one would predict that in the absence of proportionately increased ox-LDL, pharmacological activation of PPARγ should shift the balance from lipid loading to lipid efflux and improve the status of the atherosclerotic lesion (68).

PPARδ has recently been shown to mediate VLDL signaling in the macrophage (43). VLDL treatment in cultured macrophages results in lipid accumulation and up-regulation of adipose differentiation-related protein, a lipid droplet-coating protein that has been implicated in lipid storage (81). Adipose differentiation-related protein was subsequently identified as a direct PPARδ target gene, and components of VLDL released by LPL serve as ligands for the receptor (68).

Exercise increases fatty acid oxidation (FAO), improves serum HDLC and TG, and upregulates skeletal muscle PPARδ expression. In parallel, PPARδ agonist-upregulated FAO would induce fatty-acid uptake (via peripheral lipolysis), and influence HDLC and TG-rich lipoprotein particle metabolism, as suggested in preclinical models (82). In their report, Oliver et al demonstrate that a selective PPARδ agonist increases ABCA1 expression and cholesterol efflux from cells and increases HDLC in primates. PPARδ agonists may provide a new approach to the treatment of cardiovascular disease by promoting reverse cholesterol transport (66).

Molecular and functional analyses suggest that PPARδ activation reduces hepatic glucose output by increasing glycolysis and the pentose phosphate shunt and promoting fatty acid synthesis in the liver. This uncovered hepatic activity thus constitutes the earliest component of the regulatory mechanism by which PPARδ regulates insulin sensitivity, in addition to its known function in fatty acid β-oxidation (83).

Coupling increased hepatic carbohydrate catabolism with its ability to promote β-oxidation in muscle allows PPARδ to regulate metabolic homeostasis and enhance insulin action by complementary effects in distinct tissues. The combined hepatic and peripheral actions of PPARδ suggest new therapeutic approaches to treat type II diabetes (83).

It is now evident that PPARs, which are activated by various lipid molecules, function in distinct target tissues and coordinately regulate different metabolic pathways. PPARα and PPARδ potentiate fatty acid use in liver and muscle, respectively, whereas PPARγ promotes lipid storage in adipocytes. In this dynamic system, lipids are shuttled between these tissues according to the needs of the body by lipoproteins. In this view, lipoproteins not only deliver energy substrates but also carry endogenous activators for these receptors (68).

PPARs AND OBESITY

The cluster of medical sequelae, collectively referred to as the MetS, poses one of the most serious threats to public health that our society faces. Why does obesity carry with it a stereotyped collection of medical problems? That is, why is adipose tissue unable to store excess calories in a safe way? The answer to this question is not clear, but it may reflect the reality that fat is not simply a storage depot, but rather a dynamic tissue that constantly communicates with other key tissues in the body, including liver, muscle and the appetite centers in the brain. In the past decade, tremendous advances in understanding this system of signals and sensors have been made, and the emergence of PPARs as key regulators of obesity and metabolism shedding light on how problems begin and how they may be therapeutically approached (41).

The initial suggestion that PPARγ stimulated adipogenesis was based on the observation that overexpression of PPARγ in cells was by itself sufficient to induce adipocyte differentiation (54). Consistent with this, PPARγ increases the expression of genes that promote fatty acid storage, whereas it represses genes that induces lipolysis in adipocytes (84).

PPAR-γ is a master regulator in the formation of fat cells and their ability to function normally in the adult (85). PPARγ is induced during adipocyte differentiation, and forced expression of PPARγ in nonadipogenic cells effectively converts them into mature adipocytes (54). In addition, PPARγ knockout mice fail to develop adipose tissue (86,87,88). Consistent with these findings, humans with dominant-negative mutations in a single allele PPARG (the gene encoding PPARγ) have partial lipodystrophy and insulin resistance (89,90,91). In vitro studies suggest that PPARγ is the ultimate effector of adipogenesis in a transcriptional cascade that also involves members of the C/EBP transcription factor family (92,93).

Fat cells develop from a fibroblast-like preadipocyte to a mature, lipid-enriched adipocyte. The underlying transcriptional regulatory network that controls the maturation of adipocytes has been the focus of intense research and is reviewed elsewhere (94).

The highest levels of PPARγ are expressed in adipose tissue (23,24). In 1994, Spiegelman and colleagues discovered that expression and activation of PPARγ was sufficient to induce adipogenesis (54). The essential role of PPARγ in adipogenesis has been clearly demonstrated in functional and genetic knockdown experiments (86,87).

In addition to its importance in adipogenesis, PPARγ plays an important role in regulating lipid metabolism in mature adipocytes. Much of what is known about this role of PPARγ, and indeed many other aspects of its biology, followed the discovery that thiazolidinedione (TZD) antidiabetic drugs are highaffinity agonist ligands for PPARγ (63). TZDs appear to coordinately activate gene expression leading to an increase in net lipid partitioning into adipocytes. Target genes directly regulated by PPARγ that are involved in this pathway include lipoprotein lipase

(55), fatty-acid transport protein (95), and oxidized LDL receptor 1 (96), which all favor adipocyte uptake of circulating fatty acids; phosphoenolpyruvate carboxykinase (97,98), glycerol kinase (58), and the glycerol transporter aquaporin 7 (99), which promote recycling rather than export of intracellular fatty acids. Together, these pathways lead to the net flux of fatty acids from the circulation and other tissues into adipocytes. Although increased fat storage would be expected to boost the size of adipocytes, TZD treatment actually leads to smaller adipocytes (100). This is partly due to increased adipocyte differentiation, leading to new smaller cells. In addition, TZDs induce the coactivator PPARγ-coactivator 1a (PGC-1α), which promotes mitochondrial biogenesis (101), leading to an increase in fatty-acid oxidation that further protects against adipocyte hypertrophy (102).

At a molecular level, how does activation of PPARγ, a protein that is mainly present in adipose cells, lead to systemic insulin sensitization? Two plausible mechanisms should be considered. First, pharmacologic activation of PPARγ in adipose tissue improves its ability to store lipids, thereby reducing lipotoxicity in muscle and liver. This model involves activation of genes encoding molecules that promote a combination of lipid storage and lipogenesis, such as aP2 (fatty-acid binding protein), CD36 (receptor for lipoproteins), lipoprotein lipase (hydrolysis of lipoproteins), FATP-1 (fatty acid transporter), glycerol kinase, and SREBP-1 and SCD-1 (regulators of sterol and fatty acid synthesis, respectively). Activation of this metabolic pathway causes body-wide lipid repartitioning by increasing the TG content of adipose tissue and lowering free fatty acids and TG in the circulation, liver and muscle, thereby improving insulin sensitivity (58, 103). Second, PPARγ-specific drugs alter the release of signaling molecules from fat, including leptin, TNFα, resistin and adiponectin, which by virtue of serum transport have far-reaching metabolic effects in other tissues. For example, PPARγ agonists inhibit the expression of TNFα and resistin, which both promote insulin resistance (58,104,11105,106). On the other hand, PPARγ agonists stimulate the production of adiponectin, which promotes fatty acid oxidation and insulin sensitivity in muscle and liver. As a result, hepatic glucose production is reduced and muscle glucose use is increased (107,108,109). This pathway is mediated by adiponectin receptors and downstream AMP-activated protein kinase (110,111), making the intracellular AMP-activated kinase pathway another potential pharmacologic target for type 2 diabetes mellitus. Besides the aforementioned mechanisms, it is possible that PPARγ directly modulates the insulin signal transduction pathway in adipose tissue by increasing the expression of intracellular proteins such as c-Cbl-associated protein (CAP), which stimulates glucose transport (51).

There may be an appropriate level of PPARγ/RXR activity for insulin sensitivity. This raise the possibility that there may be a hitherto unrecognized U-shaped relationship between PPARγ/RXR activity and insulin resistance within physiologically "normal" limits (Figure 3) (112).
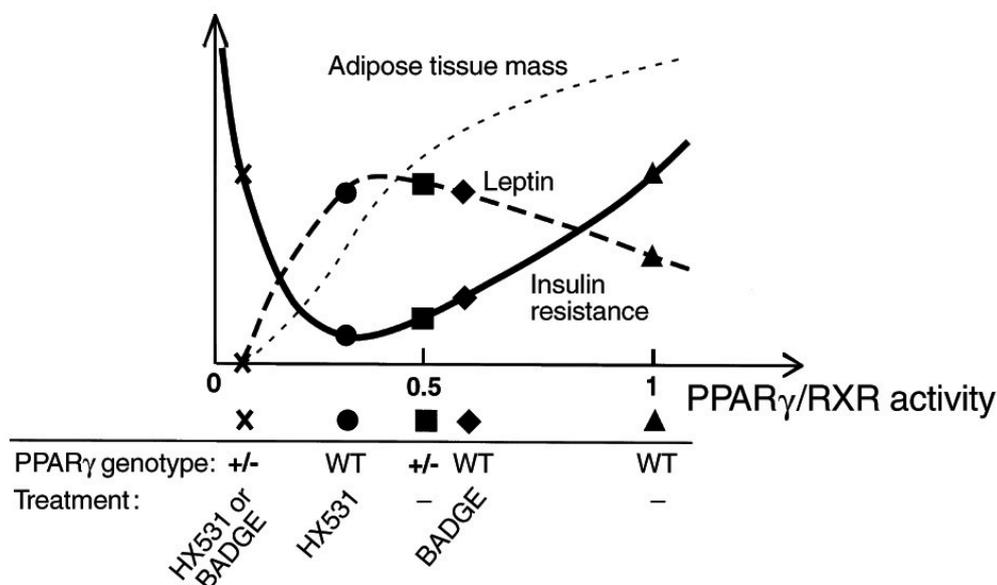

Fig. 3. One possible model for the relatioship between PPARγ/RXR activity and insulin sensitivity on the HF diet
(Adapted from Yamauchi T et al, 2001).

Yamauchi et al have shown herein that PPARγ/RXR promotes fat storage in the body by a combination of direct induction of molecules involved in TG accumulation and suppression of leptin gene expression as well as inactivation of PPARα−signaling pathways. In times of fasting, this PPARγ/leptin/PPARα network maximizes energy storage, which is quite advantageous for survival. In times of feast, which are the norm in industrialized nations nowadays, however, this network causes excessive adiposity, insulin resistance, and obesity related diseases such as diabetes. Thus appropriate antagonism of PPARγ/RXR, which simultaneously leads to appropriate agonism of leptin and PPARα, may be a logical approach to protection against obesity and related diseases such as type 2 diabetes (112).

PPARγ, function as an important adipocyte determination factor. In contrast, TNFα inhibits adipogenesis, cause dedifferentiation of mature adipocytes, and reduces the expression of several adipocyte – specific genes. Reduced PPARγ gene expression is likely to represent an important component of the mechanism by which TNFα exerts its antiadipogenic effects (113).

Insulin receptor substrate (IRS)-1 and IRS-2 have dominant roles in the action of insulin (114), but other substrates of the insulin receptor kinase, such as Gab1, c-Cbl, SH2-B and APS, are also of physiological relevance (115,116,117,118). Although the protein downstream of tyrosine kinases-1 (Dok1) is known to function as a multisite adapter molecule in insulin signaling (119,120,121), its role in energy homeostasis has remained unclear. Hosooka et al show that Dok1 regulates adiposity. Dok1 promotes adipocyte hypertrophy by counteracting the inhibitory effect of ERK on PPARγ and may thus confer predisposition to diet-induced obesity. (122).

The nuclear receptor corepressors NCoR and SMRT repress gene transcription by recruiting a histone deacetylase complex.Their roles in PPARγ action have been controversial. Recent evidence, however, suggests that NCoR and SMRT repress PPARγ-mediated transcriptional activity on specific promoters in the adipocyte. In addition, by repressing PPARγ action, these corepressors inhibit the ability of adipocyte differentiation to proceed (123).

PPARδ initially received much less attention than the other PPARs because of its ubiquitous expression and the unavailability of selective ligands. However, genetic studies and recently developed synthetic PPARδ agonists have helped reveal its role as a powerful regulator of fatty acid catabolism and energy homeostasis (9,22). The PPARδ agonist GW501516 was shown to lower plasma TG levels in obese monkeys while raising high-density lipoprotein levels, prompting the initiation of clinical trials to assess its efficacy in hyperlipidemic patients (66). Studies in adipose tissue and muscle have begun to uncover the metabolic functions of PPARδ. Transgenic expression of an activated form of PPARδ in adipose tissue produces lean mice that are resistant to obesity, hyperlipidemia and tissue steatosis induced genetically or by a highfat diet. The activated receptor induces genes required for fatty acid catabolism and adaptive thermogenesis. Interestingly, the transcription of PPARγ target genes for lipid storage and lipogenesis remain unchanged. In parallel, PPARδ-deficient mice challenged with a high-fat diet show reduced energy uncoupling and are prone to obesity. Together, these data identify PPARδ as a key regulator of fat-burning, a role that opposes the fat-storing function of PPARγ (64). Thus, despite their close evolutionary and structural kinship, PPAR-γ and PPARδ regulate distinct genetic networks. The thermogenic function of PPARδ is markedly similar to that of the nuclear cofactor PGC-1α (124,125). Indeed, PPAR strongly associates with PGC-1α both in cultured cells and in tissue, so it is possible that many metabolic effects of PGC-1α may be mediated through PPARδ(41).

Upon agonist stimulation of PPARδ, KLF5 was deSUMOylated, and became associated with transcriptional activation complexes containing both the liganded PPARδ and CREB binding protein (CBP). This activation complex increased the expression of Cpt1b, Ucp2 and Ucp3. Thus, SUMOylation seems to be a molecular switch affecting function of KLF5 and the transcriptional regulatory programs governing lipid metabolism (126).

Activation of PPARδ with the specific agonist GW501516, however, coordinately upregulates expression of genes involved in fatty acid oxidation and energy uncoupling, which markedly diminishes weight gain while increasing O2 consumption in mice fed a high-fat diet (64, 127,128). Likewise, skeletal muscle–specific overexpression of an activated form of PPARδ protects mice from diet-induced obesity. As a result, PPARδ is now considered to be an attractive target for treatment of metabolic syndrome (126). PPARδ as a nuclear receptor, represents a bonafide target. In particular, its ability to induce adaptive thermogenesis and protection against both dietary and genetic obesity (24).

PPARs AND CONTROL OF INFLAMMATORY RESPONSES

In addition to the regulation of lipid metabolism, PPARs and LXRs play roles in influencing inflammatory and immune responses. PPARs can be activated by eicosanoids, which are produced by metabolism of arachidonic acids and other long-chain PUFAs during inflammatory responses (36,48,49,59,129). For example, ligands for PPARα are leukotriene LTB4 and 8(S)-hydroxyeicosatetraenoic acid (HETE), whereas 15deoxy-prostaglandin J2 (15d-PGJ2), 15- HETE, and 13-hydroxyoctadecadienoic acid (HODE) act as ligands for PPARγ. Interestingly, the expression of PPARs is differentially regulated by factors that control the development of immune responses. PPARγ expression is dramatically upregulated in macrophages and T cells during the inflammatory response and can be induced in vitro by interleukin (IL)-4 and other immunoregulatory molecules (130,131) In contrast, IFNγ and lipopolysaccharide (LPS) repress the expression of PPARγ (132). PPARγ is highly expressed in elicited peritoneal macrophages, while low levels of PPARα are present (133). The opposite pattern is observed in primary human monocytes (134). PPARα and PPARγ have been shown to inhibit the expression of proinflammatory genes, suggesting that they might inhibit inflammatory responses in vivo. Activation of PPARα resulted in the induction of genes involved in fatty acid oxidation with the subsequent degradation of fatty acids and fatty acid derivatives like LTB4. In addition, the response to LTB4 and arachidonic acid was prolonged in mice lacking the PPARα gene as compared with wild-type mice (135). However, some in vivo studies show proinflammatory effects for PPARα ligands, such as an increase in the plasma levels of TNFα during endotoxemia (136) and in the production of monocyte chemoattractant protein (MCP-1) by endothelial cells (137). Thus, PPARs and LXRs negatively regulate transcriptional programs involved in the development of inflammatory responses (138).

PPARα activators reduced cytokine-induced expression of VCAM-1 and ICAM-1 in human carotid artery endothelial cells in culture. Pasceri et al (139) reported that fibrates reduced C-reactive protein (CRP)–induced expression of monocyte chemoattractant protein (MCP)-1 in human umbilical vein endothelial cells. With regard to clinical studies, Marchesi et al observed that 3-month therapy with fenofibrate in hyperTGmic patients decreased VCAM-1 and ICAM-1 levels in the fasting state.

A molecular rationale for suppression of IL-1–induced CRP transcription is provided by the fact that fenofibrate upregulates I-κB protein expression. This reduces nuclear translocation of p50–NF-κB, resulting in decreased amounts of nuclear p50–NF-κB and CCAAT/enhancer binding protein-β complexes, the major determinants of CRP transcription. These results provide strong evidence for a direct suppressive effect of fenofibrate on CRP expression, independent of cholesterol lowering and atherogenesis (140,141).

Endothelial dysfunction associated with the metabolic syndrome and other insulin-resistant states is characterized by impaired insulin-stimulated nitric oxide production from the endothelium and decreased blood flow to skeletal muscle. Thus, improvement in insulin sensitivity leads to improved endothelial function (142).

Teissier et al extend our insight into the connections between PPARs, LDL metabolism, and oxidative stress (143). The oxidized form of LDL (ox-LDL) promotes inflammation in part via ox-LDL uptake by scavenger receptors and subsequent nuclear factor κB activation. They find that synthetic PPAR agonists induce the production of reactive oxygen species (ROS) in a PPARα–dependent manner by inducing NADPH oxidase, a key enzyme in oxidative stress (144). Moreover, these investigators offer the intriguing notion that ROS interact with LDL to activate PPARα and subsequently limit inflammation, as indicated by PPAR-dependent repression of inducible nitric oxide synthase (iNOS) gene transcription (145).

The PPARα–induced increase in ROS was attributable to the induction of NADPH oxidase, because (1) preincubation with the NADPH oxidase inhibitor diphenyleneiodinium prevented the increase in ROS production (2) PPARα agonists increased O_2-production measured by superoxide dismutase–inhibitable cytochrome c reduction (3) PPARα agonists induced mRNA levels of the NADPH oxidase subunits p47^{phox}, p67^{phox}, and gp91^{phox} and membrane p47^{phox} protein levels and (4) induction of ROS production was abolished in p47$^{phox-/-}$ and gp91$^{phox-/-}$ macrophages. Finally, induction of NADPH oxidase by PPARα agonists resulted in the formation of oxidized LDL metabolites that exert PPARα–independent proinflammatory and PPARα–dependent decrease of lipopolysaccharide-induced inducible nitric oxide synthase expression in macrophages. These data identify a novel mechanism of autogeneration of endogenous PPARα ligands via stimulation of NADPH oxidase activity (143).

Several reports (146,147,148) have indicated that PPARγ agonists reduce macrophage inflammatory responses, such as the elaboration of cytokines, nitric oxide, and matrix metalloproteinases (MMPs). In contrast, other reports have indicated that PPARγ agonists stimulate the expression of proinflammatory receptors and cytokines (59,60,149,150,151). Finally, there are even reports that PPARγ agonists have no impact at all on macrophage inflammatory cytokine production (150,152).

PPARγ generally inhibits inflammatory response genes by negatively interfering with the NF-κB, STAT, and AP-1 signaling pathways in a DNA-binding independent manner (153). Indeed, PPARγ modulates chemokine gene expression by inhibiting expression of MCP-1 and its receptor CCR2 in monocyte/macrophages (154,155). PPARγ also plays a role in the regulation of CXC chemokine pathway. CXCR2 upregulation by PPARγ leads to the acquisition of IL-8/Groβ responsiveness, as measured by enhanced reactive oxygen species (ROS) formation (156).

PPARγ expression in human ECs has been demonstrated by reverse transcription polymerase chain reaction (157) and more definitively using Western blotting and immunohistochemistry (158). Subsequent data suggested that PPARγ activation can influence target genes and processes that are of central relevance to endothelial biology. One such example is the role of chemokines (chemoattractant cytokines), signals for inflammatory cell recruitment (158).

Recently, Huang et al demonstrated that the PPARγ ligands, either 15-deoxy-Δ prostaglandin J2 (15d-PGJ2) or ciglitazone, increased endothelial nitric oxide (•NO) release without altering endothelial nitric oxide synthase (eNOS) expression. However, the precise molecular mechanisms of PPARγ-stimulated endothelial •NO release remain to be defined. Superoxide anion radical (O2•-) combines with •NO to decrease •NO bioavailability. NADPH oxidase, which produces O2•-, and Cu/Zn-superoxide dismutase (Cu/Zn-SOD), which degrades O2•-, thereby contribute to regulation of endothelial cell •NO metabolism. These findings further elucidate the molecular mechanisms by which PPARγ ligands directly alter vascular endothelial function (159).

CCAAT/enhancer-binding proteins (C/EBPs) upregulate transcription of various inflammatory cytokines and acute phase proteins, such as interleukin (IL)-1β, IL-6, TNFα, and cyclooxygenase-2. Recent studies have demonstrated that PPARγ is present in atherosclerotic lesions, and negatively regulates expression of these genes. Interestingly, PPARγ gene promoter has tandem repeats of C/EBP-binding motif, and C/EBP-δ plays a pivotal role in transactivation of PPARγ gene. Recent findings strongly suggest that C/EBP-δ is negatively autoregulated via transactivation of PPARγ. This feedback mechanism probably downregulates transcription of inflammatory cytokines and acute phase proteins, and modulates inflammatory responses in the early process of atherosclerosis (160).

PPARδ controls the inflammatory status of the macrophage. Deletion of PPARδ from foam cells increased the availability of inflammatory suppressors, which in turn reduced atherosclerotic lesion area by more than 50%. Lee et al propose an unconventional ligand-dependent transcriptional pathway in which PPARδ controls an inflammatory switch through its association and disassociation with transcriptional repressors. PPARδ and its ligands may thus serve as therapeutic targets to attenuate inflammation and slow the progression of atherosclerosis (161).

PPARδ, but not PPARγ, is the major nuclear VLDL sensor in the macrophage, which is a crucial component of the atherosclerotic lesion. In addition to β-oxidation and energy dissipation, activation of PPARβ by VLDL particles induces key genes involved in carnitine biosynthesis and lipid mobilization mediated by a recently identified TG lipase, transport secretion protein 2 (also named desnutrin, iPLA2ζ, and adipose TG lipase), resulting in increased fatty acid catabolism. Unexpectedly, deletion of PPARδ results in derepression of target gene expression, a phenotype similar to that of ligand activation, suggesting that unliganded PPARδ suppresses fatty acid utilization through active repression, which is reversed upon ligand binding. This unique transcriptional mechanism assures a tight control of the homeostasis of VLDL-derived fatty acid and provides a therapeutic target for other lipid-related disorders, including dyslipidemia and diabetes, in addition to coronary artery disease (162).

Ligand activation of PPARδ in ECs has a potent antiinflammatory effect, probably via a binary mechanism involving the induction of antioxidative genes and the release of nuclear corepressors. PPARδ agonists may have a potential for treating inflammatory diseases such as atherosclerosis and diabetes (163).

Administration of GW501516 to mice upregulated TGF-β1, whereas the expression of proinflammatory genes including MCP-1 was significantly attenuated in the thoracic aorta. Taken together, these results demonstrate the presence of a novel TGF-β1⬚

mediated pathway in the antiinflammatory activities of PPARδ (164).

PPARs AND HYPERTENSION

The quest for better understanding for the pathophysiological basis of hypertension and atherosclerosis is ongoing. The complexity of hypertension and atherosclerosis and of the underlying mechanisms is becoming increasingly apparent (165).

Tordjman et al (166) explore the role of the candidate gene, PPARα, in the regulation of blood pressure and atherogenesis. PPARα is believed to impart direct protection in the vessel wall by intervening at essentially every level of the atherogenic process: inflammation, monocyte recruitment and adhesion, cholesterol transport, plaque formation, and thrombosis, mostly through downregulation of NF-κB and AP-1 (167,168,169). In contrast to the plethora of data regarding the atherogenic process, the role of PPARα in the regulation of vascular tone and blood pressure is still unclear. Several studies conducted in different rat models of hypertension yielded inconsistent results (170,171).

Evidence that PPARα regulates the expression of the RAS starting with its rate-limiting step, renin. Based on the findings of the current study and on some published data, we suggest that, in the setting of an activated RAS and high endogenous levels of Ang II, PPARα activation could be detrimental. In this context, PPARα activation is likely to promote even higher levels of Ang II, increase oxidative stress, raise blood pressure, and ultimately hasten atherosclerosis. Further investigations aimed at delineating the relationships between the transcription factor PPARα and the components of the RAS and their respective molecular effectors are needed (166).

Evidence demonstrate that short-term clofibrate treatment modulates vasomotor tone, producing effects that are consistent with antagonism of AT1-mediated but promotion of AT2-mediated renal and systemic hemodynamic effects of angiotensin II. These effects appear to involve nitric oxide production and are accompanied by concomitant changes in the expression of AT receptors – increased expression of AT2 receptors but diminished expression of AT1 receptors. PPARα ligands also protect against pathological damage especially resulting from angiotensin II hypertension (172).

Endothelin-1 (ET-1) is a vasoactive peptide that causes vasoconstriction and vasodilation by binding to ETA receptors on vascular smooth muscle cells and ETB receptors on endothelial cells, respectively (173,174,175).

The role of cytochrome P450 (CYP450) hydroxylase metabolites in the maintenance of arterial pressure is complex because of their contrasting hypertensive and antihypertensive properties (176). Clofibrate, a PPARα agonist, has been shown to reduce arterial pressure in Dahl salt-sensitive rats on high salt diet by inducing the genes that code for CYP4504A (CYP4A) enzymes in the renal cortex (177,178). CYP4A is the enzyme responsible for the synthesis of 20-HETE. Interestingly, 20-HETE has actions to reduce sodium transport and, like ETB receptor activation, has been implicated in salt-dependent hypertension (179,180,181,182,183). Therefore, chronic PPARα agonist treatment reduces salt-dependent hypertension produced by ETB receptor blockade in male and female Sprague–Dawley rats. This suggests a possible relationship between ETB receptor activation and the maintenance of CYP4A protein expression in the kidney of rats fed a high-salt diet (184).

Docosahexaenoic acid (DHA), PPARα activator, reduces blood pressure in some hypertensive models by unclear mechanisms. PPARα activator DHA attenuated the development of hypertension, corrected structural abnormalities, and improved endothelial dysfunction induced by Ang II. These effects are associated with decreased oxidative stress and inflammation in the vascular wall (180).

In the absence of dexamethasone, fenofibrate lowered fasting TG and cholesterol but unexpectedly increased systolic blood pressure by ambulatory monitoring. These data suggest that PPARα activation in humans does not correct insulin resistance induced by glucocorticoids and may adversely affect blood pressure (185).

The current study by Tordjman et al is of prime importance, because the investigators have successfully focused our attention on a controversy that involves PPARα. This central molecule which action had been considered until now beneficial and a prime therapeutic target, may in fact turn out to be a candidate gene for hypertension and for atherosclerosis and, thus, a foe to human health. More in-depth research is required to establish if, when, and how PPARα might indeed be involved in the generation of high blood pressure and atherosclerosis in humans, issues that remain, at present, unresolved (165).

PPARγ is an attractive molecule given its role as a fatty acid sensor and the increased incidence of hypertension in obese patients. It remains possible that

PPARγ may represent a link among obesity, metabolic dysfunction, and activity of either the circulating or tissue renin-angiotensin system in hypertension. There is no doubt that the mechanisms regulating the renin-angiotensin system by PPARγ will prove to be quite complex given the positive stimulation on renin transcription reported in this issue, along with the negative impact on the AT1 receptor reported previously. That TZDs are generally thought to modestly lower blood pressure suggests that a delicate balance must exist between the effects of PPARγ on the renin-angiotensin system (renin versus AT1 receptor) and other vasoconstrictors, such as ET-1 (186).

Among the transcription factor binding sites in the enhancer is the hormone response element (HRE). Several members of the nuclear hormone receptor superfamily, including retinoic acid receptor and RXR, have been shown to bind to the HRE and to regulate renin gene expression (187). In addition, vitamin D has been reported to negatively modulate renin gene expression through a vitamin D receptor– dependent mechanism, which may involve the HRE (187,188). Because the HRE is homologous to a PPRE, and PPARγ, retinoic acid receptor-α, RXRα, and vitamin D receptor are all members of the same subfamily of ligand-activated transcription factors, it should not be surprising that PPARγ may have to be included among those transcription factors thought to regulate renin expression.

PPARγ activation by TZDs causes a down-regulation of AT1 receptor gene expression via a PPARγ-dependent mechanism in vascular smooth muscle cells. Therefore, PPARγ may play a role in the regulation of Ang II action (189).

PPARs AND THE METABOLIC SYNDROME

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities, which is characterized by abdominal obesity, insulin resistance, dyslipidemia, elevated blood pressure, and a proinflammatory and prothrombotic milieu (200,201).

MetS appears to affect a significant proportion of the population. While up to 80% of the almost 200 million adults worldwide with diabetes will die of CVD, people with MetS are also at increased risk, being twice as likely to die from and three times as likely to have a heart attack or stroke compared to people without the syndrome (192). Subjects with MetS have a five – fold greater risk of developing T2D if not already present (193).

Whether or not it is accepted that MetS is a specific disease entity or just a constellation of symptoms, the prevalence of this condition is increasing worldwide and patients need to tackle these risk factor through either lifestyle or pharmacological approaches, in order to reduce the odds of developing diabetes and cardiovascular disease (CVD) (194).

PPARs are intimately involved in nutrient sensing and the regulation of carbohydrate and lipid metabolism. PPARα and PPARδ appear primarily to stimulate oxidative lipid metabolism, while PPARγ is principally involved in the cellular assimilation of lipids via anabolic pathways. These may nevertheless have much greater significance for the public health burden in the abnormal lipid and carbohydrate metabolism of the MetS (195).

One of the hallmarks of MetS is depressed levels of HDLC, which occurs in 37% of patients with MetS (194). Whereas HDLC is not the primary target of lipid-modulating therapy, it is recognized as an important secondary target of therapy, and, thus, treatments that raise HDLC may be important in reducing CVD risk (197).

The identification of PPARs as molecular targets for drugs to treat hypertriglyceridemia and type 2 diabetes mellitus has fueled interest in their biology and potential as targets to treat the metabolic syndrome (198). In keeping with their roles as lipid sensors, ligand-activated PPARs turn on feed-forward metabolic cascades to regulate lipid homeostasis via the transcription of genes involved in lipid metabolism, storage, and transport. Additionally, PPARs may suppress inflammation through mechanisms involving the release of antiinflammatory factors or the stabilization of repressive complexes at inflammatory gene promoters (161,199).

The pathophysiology underlying the MetS is incompletely understood, but insulin resistance appears to be an important component (199,200). Insulin resistance is marked by hyperinsulinemia, enhanced hepatic gluconeogenesis, and impaired insulin-stimulated glucose uptake into skeletal muscle and fat. Elevated levels of circulating FFAs, associated with obesity and insulin resistance, increase fat accumulation in insulin target tissues and contribute to defective insulin action. Obese adipose tissue–derived inflammation and altered adipokine secretion may also inhibit insulin signals and affect systemic metabolism (201). The resulting hyperglycemia, dyslipidemia, hypertension, and inflammation of the MetS cause endothelial dysfunction and hasten atherogenesis (198).

Hypertriglyceridemia and abdominal obesity are key components of the MetS. They may result from an inability of adipose tissue to sequester fatty acids appropriately for storage (202). Instead, fatty acids are deposited as ectopic fat in skeletal muscle (203), liver (204), and other organs (205). It is thought that such fat accumulation is linked to impaired metabolic function of the tissue (206,207). Obesity-related insulin resistance involves the release of mediators, such as FFAs, TNFα, or resistin from adipocytes and decreased production of adiponectin, all of which impair insulin action in skeletal muscle (207).

Adipose tissue as an endocrine organ also releases proinflammatory mediators that promote vascular damage and atherosclerosis. TNFα inhibits insulin signaling contributing to insulin resistance and activates multiple mechanisms of inflammation via NF-κB (208). Leptin can alter insulin action and has recently been recognized to be an important mediator of obesity-related hypertension (209). Angiotensinogen, the precursor of angiotenin II, a key mediator of vascular injury, can be produced and secreted by adipose tissue (210). Plasminogen activator inhibitor 1 (PAI-1) is typically increased in the obesity/insulin-resistance state and plays an important role in atherothrombosis (211,212). In contrast, excessive visceral adipose tissue has been shown to be associated with decreased adiponectin levels (111), an important hormone that exerts antidiabetic (109,110) and antiatherogenic functions (213,214). Adiponectin activates AMP-activated protein kinase, which promotes skeletal muscle glucose uptake and suppresses hepatic glucose production (110). Importantly, adiponectin also inhibits NF-κB activation, thus, attenuating inflammation (215). Visfatin, a growth factor with insulin mimetic action, was recently cloned from fat (216). Unlike adiponectin, plasma levels of visfatin increase in parallel with visceral fat in both mice and humans (216), so the role of visfatin in insulin resistance needs additional investigation. Taken together, these observations suggest that the adipocyte is an integral coordinator of the relationship among obesity, diabetes, and CVD (207).

Interestingly, it is possible that the intra – myocellular lipid (IMCL) impact on insulin sensitivity might be modulated by the oxidative disposal of long-chain fatty acyl-CoAs, depending on the efficiency of the regulation of its flux and metabolism within the mitochondrion. These latest findings represent a fascinating and promising novel understanding linking small abnormalities of tissue energy metabolism to a steady tendency toward both weight gain and ectopic fat accumulation – particularly in skeletal muscle – as a common denominator inducing both obesity and insulin resistance (203).

The PPARδ agonist GW501516 attenuated multiple metabolic abnormalities normally associated with the MetS in humans, and this was probably due to an increase in skeletal muscle fatty acid oxidation. Presently, the individual components of the MetS are treated separately; i.e., statins are used for elevated cholesterol, fibrates are used to reduce TG, and metformin and thiazolidinediones are used for hyperglycemia. The wide range of beneficial effects suggested by the response to GW501516 calls for a larger study in patients to evaluate the clinical efficacy of PPARδ agonists for the treatment of hyperlipidemia, liver fat accumulation, obesity, and insulin resistance (217). Thus, PPARδ is pivotal to control the program for fatty acid oxidation in the skeletal muscle, thereby ameliorating obesity and insulin resistance through its activation in obese animals (128).

Accelerated atherosclerosis is a major cause of morbidity and death in insulin-resistant states such as obesity and the MetS, macrophages from obese (ob/ob) mice have increased binding and uptake of oxidized LDL, in part due to a posttranscriptional increase in CD36 protein. Macrophages from ob/ob mice are also insulin resistant, as shown by reduced expression and signaling of insulin receptors. Defective macrophage insulin signaling predisposes to foam cell formation and atherosclerosis in insulin-resistant states and that this is reversed in vivo by treatment with PPARγ activators (218).

Obesity and insulin resistance, the cardinal features of MetS, are closely associated with a state of low-grade inflammation (219,220). In adipose tissue chronic overnutrition leads to macrophage infiltration, resulting in local inflammation that potentiates insulin resistance (220,222).

PPARγ is required for maturation of alternatively activated macrophages. Disruption of PPARγsw in myeloid cells impairs alternative macrophage activation, and predisposes these animals to development of diet-induced obesity, insulin resistance, and glucose intolerance. Furthermore, gene expression profiling revealed that down regulation of oxidative phosphorylation gene expression in skeletal muscle and liver leads to decreased insulin sensitivity in these tissues. These suggest that resident alternatively activated macrophages have a beneficial role in regulating nutrient homeostasis and suggest

that macrophage polarization towards the alternative state might be a useful strategy for treating T2D (223).

PPARs AS THERAPEUTICS TARGETS FOR MetS

Because these nuclear receptors are activated by extracellular signals and control multiple gene targets, PPARs can be seen as nodes that control multiple inputs and outputs involved in energy balance, providing insight into how metabolism and the vasculature may be integrated. The ongoing clinical use of fibrates, which activate PPARα, and thiazolidinediones, which activate PPARγ, establishes these receptors as viable drug targets, whereas considerable in vitro animal model and human surrogate marker studies suggest that PPAR activation may limit inflammation and atherosclerosis. Together, these various observations have stimulated intense interest in PPARs as therapeutic targets and led to large-scale cardiovascular end-point trials with PPAR agonists (224).

The current clinical approach to MetS is to focus on appropriate management of accompanying risk factors. While priority should be given to management of underlying risk factors with therapeutic lifestyle changes, associated major risk factors should be treated according to evidence – based medicine goals and principles, and appropriate clinical attention should be given to the presence of emerging risk factors. Clearly, there are multiple targets for therapy to reduce the high risk of the MetS. While no single treatment for the MetS as a whole yet exist, it is well established that lifestyle changes, for example, changes in diet and increased physical exercise, form the first – line strategy of intervention (194).

In MetS, a condition of impaired fatty acid metabolism in adipose tissue generally results in the increased release of free fatty acids into the circulation. This in turn leads to multiple abnormalities in the circulating lipoprotein profile including low HDL, high TG, and VLDL remnants, with average LDL. The triad of elevated TG, reduced HDL and small dense LDL, along with concomitant increased in TG – rich remnant particles, comprises the atherogenic dyslipidemia of MetS. MetS, with or without progression to T2D, is therefore a major atherogenic factor. CHD risk reduction in MetS requires not only aggressive LDL – C lowering but also management of each aspect of dyslipidemia, including lowering TG levels, increasing HDL – C levels, and increasing the size of the average LDL – C particle. Based on available evidence, LDL – C is the primary target of therapy in MetS (223). In patients with atherogenic dyslipidemia with elevated TG, non – HDL – C represents a secondary target of treatment after the LDL – C goal is achieved. The tertiary goal in these patients is to raise HDL – C when it is reduced after attaining goals for LDL – C and non – HDL – C (194).

PPAR activation can improve metabolic parameters like glucose and lipid levels but also alter directly vascular responses by regulating target genes including those encoding adhesion molecules, The ATP – binding cassette transporter 1 (ABCA 1), lipoprotein lipase, cytokines and chemokines (226). PPAR activation has many anti – atherosclerotic effects with disctinct and overlapping targets. For instance, lipoprotein lipase acts on circulating lipoproteins to activate PPARα and intiates PPARα – dependent positrive feedback loop for TG – rich lipoprotein catabolism (44). Exogenist PPARα agonist such as fenofibrate reduce TNFα – induced activation of NF-ᴋβ (227), a transcription factor integrating inflammation and atherosclerosis. There have been indications that PPARα is involved in the pathogenesis of insulin resistance. In this regard, PPARα knockout mice are protected from diet – induced insulin resistance probably because of of inhibition of PPARα - dependent fatty acid oxidation (227). By contrast, genetic defects in PPARγ can recapitulate all the salient features of MetS in humans (96). Therefore, PPARs are likely to be involved in the development of MetS and, accordingly, can serve as potential therapeutic targets for the prevention and treatment of MetS (228).

Activation of PPARα by fibrates stimulates the oxidation of free fatty acids in the liver (229), diverting them away from TG synthesis and thus reducing the hepatic synthesis of TG-rich lipoproteins (230). The activation of PPARα also induces expression of the gene for lipoprotein lipase (LPL), the enzyme responsible for hydrolyzing TG and phospholipids in TG-rich lipoproteins in plasma (231). Thus, activators of PPARα lower the concentration of plasma TG by reducing its rate of synthesis and increasing its rate of hydrolysis. An additional effect of activating PPARα is the inhibition of synthesis of apolipoprotein (apo) C-III (232). Because apoC-III delays the catabolism of TG-rich lipoproteins, its inhibition provides a further mechanism by which PPARα-activators such as fibrates lower the concentration of plasma TG. Fibrates also impact on the concentration of HDLC in humans, although the precise mechanisms are not known. Fibrates increase expression of the genes for both apo A-I and apo A-II, the 2 main apolipoproteins of HDL

Possible anti-atherogenic mechanisms of fibrates

Direct anti-inflammatory effects in visceral fat

Reduced level of plasma triglyceride

Reduced chylomicron and VLDL remnants

Direct anti-inflammatory effects in artery wall

Increase reversed cholesterol transport
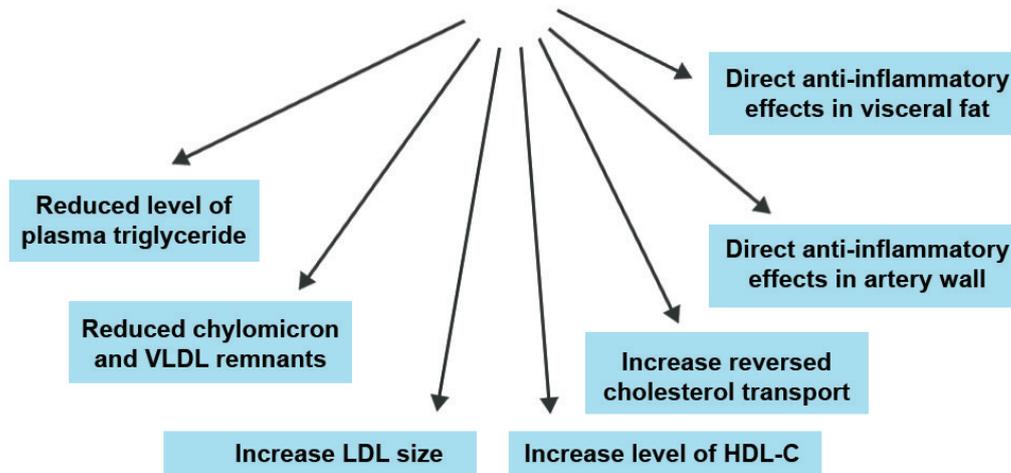
Increase LDL size

Increase level of HDL-C

Fig. 4. Effects of fibrates with the potential to protect against cardiovascular disease (Adapted from Barter PJ, 2008).

(233,234), although the magnitude of the increases in the plasma concentrations of these proteins tends to be small. Generally, the increase in plasma apoA-II is greater than that of apoA-I (234,235,236). This results in an increase in the concentration of HDL particles containing both apoA-I and apoA-II but a decrease in those containing apoA-I without apoA-II (236). Other potential mechanisms by which fibrates increase the level of HDLC include an enhancement of cell cholesterol efflux secondary to an induction of cell ABCA1 expression (237), although others have not been able to confirm this (238). Fenofibrate has been reported to decrease SR-B1 in the liver (239), an action that would contribute to an elevation of HDLC but which may not necessarily translate into a reduction in atherosclerosis. Fibrates also increase LDL particle size (142,240) and decrease the concentration of TG-rich lipoprotein remnants. These latter effects are potentially antiatherogenic and appear to be mediated equally well by all fibrates. Post hoc analyses of several of the fibrate studies have shown that people with features of the MetS, particularly overweight people with high plasma TG levels and low levels of HDL cholesterol, derive a disproportionately large reduction in cardiovascular events when treated with these agents. Thus, there is a strong case for the use of a fibrate to reduce the cardiovascular risk in overweight people with high TG and low HDLC (241).

PPARγ is essential for normal adipocyte differentiation and proliferation as well as fatty acid uptake and storage. Thiazolidinediones increase the number of small adipocytes and the subcutaneous adipose-tissue mass in studies in animal models (100,242,243). These observations, plus the high level of PPARγ expression in adipose tissue, have led to the hypothesis that thiazolidinediones exert their insulin-sensitizing actions either directly (the "fatty acid steal" hypothesis) or indirectly, by means of altered adipokine release, modulating insulin sensitivity outside adipose tissue. According to the "fatty acid steal" hypothesis, thiazolidinediones promote fatty acid uptake and storage in adipose tissue. In this way, they increase adipose-tissue mass and spare other insulin-sensitive tissues such as skeletal muscle and the liver, and possibly pancreatic beta cells, from the harmful metabolic effects of high concentrations of free fatty acids. Thiazolidinediones thus keep fat where it belongs.

Various adipokines, such as adiponectin (244,245), TNFα (246), resistin (247), and 11 β-hydroxysteroid dehydrogenase 1, the enzyme that produces cortisol locally in adipose tissue (242,248), are among the genes that are regulated by PPARγ agonists in rodents. Of these, adiponectin increases insulin sensitivity, and TNFα, resistin, and 11 β-hydroxysteroid dehydrogenase 1 (249) induce insulin resistance in rodents. Adiponectin, an adipocytokine produced exclusively by adipose tissue, has both insulin-sensitizing and antiatherogenic properties in mice (244,245). PPARγ agonists increase adiponectin expression in vitro in adipose tissue (250).

In the liver and in adipose tissue, 11β- hydroxysteroid dehydrogenase 1 catalyzes the interconversion of cortisone to cortisol (251). A full-blown MetS characterized by obesity and the accumulation of visceral fat, as well as increased concentrations of cortisol in the portal vein but not of systemic cortisol, develops in mice that overexepress 11β-hydroxysteroid dehydrogenase 1 in adipose tissue (249). Thiazolidinediones down-regulate 11β-hydroxysteroid dehydrogenase 1 expression in adipose tissue (250) and might thereby alleviate features of the MetS.

Study of Samaha et al (252) found overall favorable effects of rosiglitazone on adipokines, including a significant increase in adiponectin levels. This increase in adiponectin may be attributable to a direct effect of rosiglitazone on adipocytes, and possibly macrophages (253). Adiponectin has been shown to play a role in modulating insulin sensitivity and to be increased by rosiglitazone in patients with diabetes (254). Furthermore, increasing quintiles of adiponectin levels have been associated with decreased risk of myocardial infarction (255).

Study also demonstrates that rosiglitazone lowers resistin levels in patients with MetS, as recently demonstrated in one small study of 14 patients with T2D (256). In humans, however, resistin is predominantly produced by macrophages in response to inflammatory stimuli and is almost undetectable in adipose tissue. Rosiglitazone may thus have a direct effect on resistin expression, such as through macrophage PPARγ activation. We have recently shown that resistin levels independently correlate with degree of coronary artery calcification (257).

Rosiglitazone also significantly reduced levels of CRP, IL-6, and sTNFα R2. (258). Similar responses for CRP and IL-6 were previously found in patients with diabetes (259). A significant correlation between the rosiglitazone-induced changes in resistin and changes in the inflammatory markers IL-6 and sTNFα R2. These findings are consistent with our previous findings of a significant correlation between baseline levels of resistin and sTNFα R2. (258). Rosiglitazone has been shown to lower CRP in nondiabetic patients with coronary artery disease (260) and in nonobese Taiwanese patients with MetS (261).

These findings suggest that rosiglitazone, presumably through its PPARγ agonist properties, has direct effects on inflammatory markers and adipokines in the absence of favorable lipid effects. These findings may help explain the mechanism underlying the possible antiatherosclerotic effects of rosiglitazone (252).

Current pharmacologic approaches are unsatisfactory in improving such consequences of insulin resistance as hyperglycemia, diabetic dyslipidemia, abnormal coagulation and fibrinolysis, and hypertension, each of which may require the use of at least one medication. Thus, the development of drugs targeted to reverse insulin resistance is important. The insulin-sensitizing thiazolidinediones, which are selective ligands of the PPARγ, are the first drugs to address the basic problem of insulin resistance in patients with MetS and T2D (262).

It is noteworthy that TZDs show intracellular antioxidant activity. This property may reflect 'preventative' action since these agents do not show direct antioxidant scavenging activity on free radicals, but block several mechanisms that in hyperglycaemic or hyperlipidaemic conditions lead to the generation of oxidative stress. It has been observed that PPARγ ligands inhibit the expression of inducible NO synthase (iNOS) and, consequently, ONOO− production, in mesangial cells and in cerebellar granule cells (133).

The antagonising activity of NF-ϰB is also of relevance in this setting, since it is through this mechanism that rosiglitazone and pioglitazone can reduce iNOS over-expression, and the related over-production of nitrotyrosine during experimental myocardial infarction (263).

Such effects may explain the ability of pioglitazone to reduce oxidative stress in type 2 diabetic patients after a meal (263). It is not surprising therefore that pioglitazone can improve endothelial dysfunction in cardiovascular disease patients, both with and without T2D and MetS (265,266).

PPARγ activation by the TZDs results in an array of effects on traditional and non-traditional cardiovascular risk factors that are independent of their effects on glycaemic control. These include reduction of IMT progression and circulating platelet activity, attenuation of PAI-1 expression, inhibition of glycation, increase in plasma adiponectin and reduction of CRP, IL-6 and MMP-9 levels. There is evidence that many of the anti-atherogenic and anti-inflammatory effects of the TZDs may be attributable to the glitazone class, although no head-to-head studies have been carried out to establish comparative efficacy (267).

There continues to be uncertainty about the risk of ischemic heart disease in patients with T2D associated with the use of rosiglitazone (268). There was no evidence of any increase in death from either cardiovascular causes or all causes. Rosiglitazone was associated with an increased risk of heart failure.
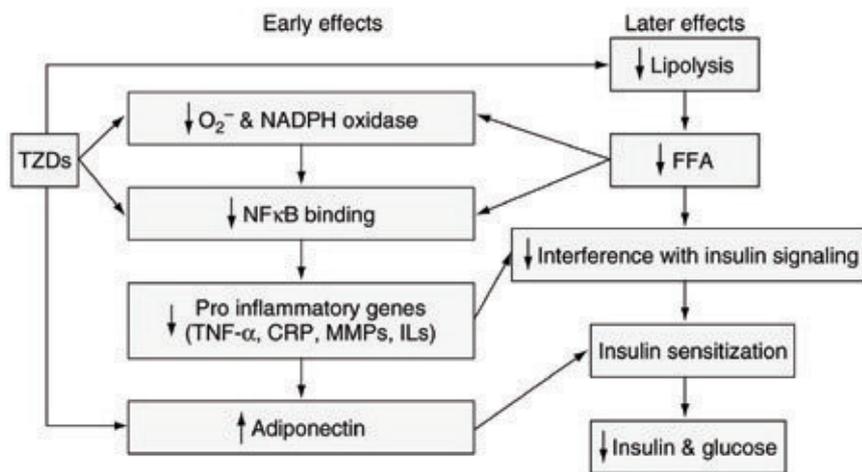
Fig. 5. TZDs affect oxidative stress and inflammation at multiple levels (adapted from Ceriello A, 2008).

The data were insufficient to determine whether the drug was associated with an increase in the risk of myocardial infarction (269). Caution should be used in patients with underlying heart disease using nitrates, and when added to ongoing insulin-based therapy (268).

A hallmark of the MetS is dyslipidemia, marked by elevated TG and low levels of HDLC. HDL is a driving force in the process of reverse cholesterol transport, reclaiming excess peripheral tissue cholesterol to the liver for excretion. Accordingly, low levels of HDL are associated with an increased risk of coronary artery disease and cardiovascular death in afflicted patients, while overexpression of apoA-I, the major apolipoprotein composing HDL particles, retards atherogenesis in animal models (270,271,272). Despite clear therapeutic need, currently marketed cholesterol-modifying drugs raise serum HDL levels only modestly.

High-affinity PPARδ ligands have revealed an important role for PPARδ in lipoprotein metabolism. Treatment of insulin-resistant obese rhesus monkeys with the PPARδ-selective agonist GW501516 resulted in a dramatic 79% increase in HDLC, a 56% decrease in TG, and a 29% decrease in LDLC (66). The profound increase in HDLC levels correlated with an increase in number, not size, of HDL particles and was accompanied by increased serum levels of the HDL-associated apolipoproteins apoA-I, apoA-II, and apoC-III. In addition, fasting insulin levels declined by up to 48% in the PPARδ drug–treated animals (66). Obese and nonobese mice similarly develop an increase of up to 50% in HDLC levels when treated with PPARδ agonists (273,274). The mechanism by which PPARδ activation

raises HDLC levels remains to be elucidated, but studies to date indicate that expression of the reverse cholesterol transporter ABCA1 is enhanced in some tissues upon exposure to PPARδ agonists, including human and mouse macrophages as well as human intestinal cells and fibroblasts (66,273). Additional work suggests that PPARδ activation reduces intestinal cholesterol absorption via downregulation of the Niemann-Pick C1–like 1 gene (NPC1L1) (273). NPC1L1 is a key mediator of intestinal cholesterol absorption and a putative target for the clinically used cholesterol absorption inhibitor ezetimibe. In light of these findings, PPARδ drugs are now in clinical trial for the treatment of human dyslipidemia.

Once viewed as a bland storage depot, adipose tissue has emerged as a dynamic endocrine organ (201). Adiposity correlates with insulin resistance and is believed by some to be of primacy in the MetS (275). Even mild weight loss may improve serum lipid profiles, glycemic control, and hypertension, yet currently available weight-loss drugs are of limited effectiveness (276,277). Genetic models and ligand treatment studies have uncovered powerful regulatory functions for PPARδ in adipose tissue metabolism and weight control. Transcriptional analysis of brown fat in fat-specific VP16-PPARδmice revealed upregulation of genes involved in TG hydrolysis (hormone-sensitive lipase), fatty acid oxidation (long-chain acyl-CoA synthetase, very-long-chain acyl-CoA synthetase, acyl-CoA oxidase), and uncoupling of oxidative phosphorylation (UCP1 and UCP3). UCP1 expression was likewise elevated in white adipose tissue. Conversely, PPARδ-null mice are more susceptible to weight gain and have blunted expression of brown
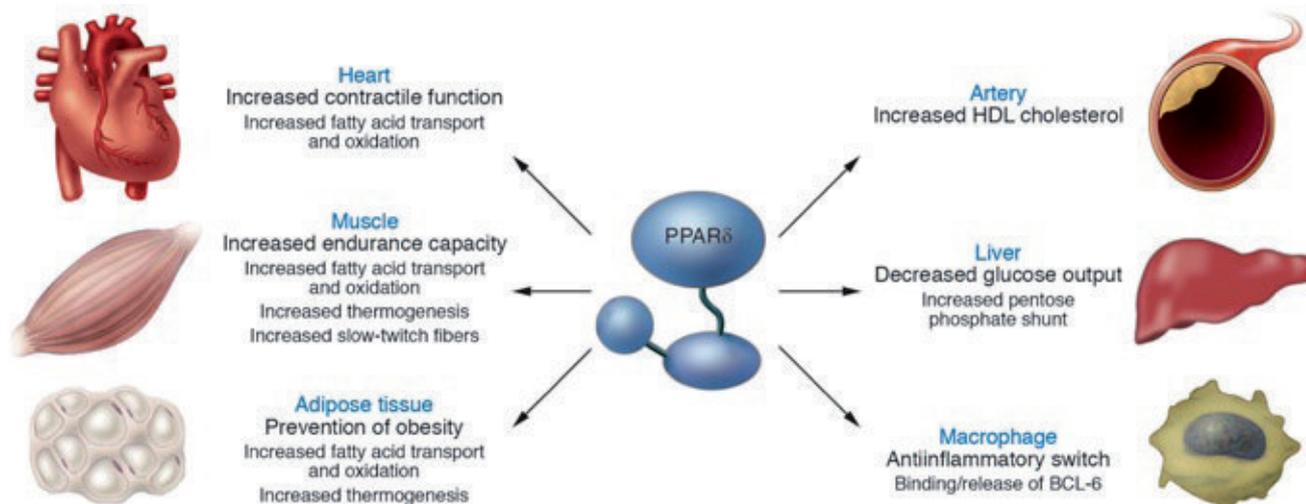
Fig. 6. Therapeutic targets of PPARδ in the MetS (Adapted from Barish GD, 2006).

fat UCP1 on a high-fat diet. These genetic models collectively suggest that activation of PPARδ protects against obesity (164).

Administration of the synthetic PPARδ agonist GW501516 to genetically obese (db/db) mice reduced intracellular TG accumulation in the brown fat and liver, analogous to the effects of VP16-PPARδ. Moreover, PPARδ agonists enhanced β-oxidation in 3T3-L1 preadipocytes by 50% (164). Most importantly, PPARβ ligands retard weight gain in models of high-fat diet–induced obesity (128,164). These results suggest that PPARβ synthetic drugs may be therapeutic as antiobesity agents.

PPARβ has emerged as a powerful metabolic regulator in diverse tissues including fat, skeletal muscle, and the heart. Its transcriptional program enhances fatty acid catabolism and energy uncoupling, resulting in decreased TG stores, improved endurance performance, and enhanced cardiac contractility, respectively. PPARδ receptor activation mitigates macrophage inflammatory responses and modulates lipoprotein metabolism to lower TG and robustly raise HDLCl. Additionally, recent studies reveal that PPARδ activation in the liver suppresses hepatic glucose output, contributing to improved glucose homeostasis (278). These aggregate effects suggest that high-affinity PPARδ synthetic drugs may uniquely target multiple components of the MetS, including obesity, insulin resistance, hyperglycemia, dyslipidemia, and atherosclerosis, or other diseases such as cardiomyopathy (Figure 6) (198).

Research programs to develop agonists that combine the therapeutic effects of both PPARα and

PPARγ selective agonists, creating the expectation of synergy in the treatment of T2D and the MetS, have therefore been undertaken. Among these dual PPARα/γ agonists, compounds belonging to the glitazar class have been advanced to clinical development (Phases II and III). These trials clearly demonstrate superior efficacy of these compounds in correcting abnormalities associated with T2D and the MS, improving both lipid and glucose homeostasis to a greater extent than did selective PPAR agonists. However, safety remains a critical issue for glitazars, as the development of several promising candidates was halted because of adverse toxicity profiles (279).

The discovery and preliminary biological and pharmacokinetic properties of muraglitazar (BMS-298585), a novel oxybenzylglycine dual (α/γ) PPAR activator, have been recently described. Muraglitazar binds with high affinity to both human PPARγ and PPARα ligand binding domain protein (IC50 for binding = 0.19 and 0.25 μmol/l, respectively) and potently transactivates full-length human PPARγ- or PPARα-mediated reporter gene activity (EC50 for transactivation = 0.11 and 0.32 μmol/l, respectively). Harrity et al (280) assessed the effects of muraglitazar treatment on diabetes and other metabolic abnormalities in genetically obese, diabetic, and hyperlipidemic db/db mice.

Tesaglitazar, a Novel Dual PPAR α/γ agonist, dose – dependently improves the metabolic abnormalities associated with insulin resistance in a non – diabetic population (281). Macelignan, a natural compound isolated from Myristica fragrans, enhanced insulin sensitivity and improved lipid metabolic disorders

by activating PPARα/γ and attenuating ER stress, suggesting that it has potential as an antidiabetes agent for the treatment of T2D and MetS (282).

However, current safety standards with compounds for T2D and the MetS are high, and few adverse effects are currently tolerated. We believe that the best solution would be to screen for compounds that combine an intermediate PPARα affinity with selective PPARγ - modulating activity (279).

Conclusion

The MetS is diagnosed by a cluster of clinical parameters including central obesity, atherogenic dyslipidemia, raised blood pressure and hyperglycemia. Visceral obesity, hepatic steatosis and insulin resistance have been proposed as unifying mechanisms, yielding a prothrombotic and proinflammatory state. Consequently, patients with MetS are at increased risk of CAD and T2D.

The discovery of the crucial role of peroxisome proliferator–activated receptors (PPARs) as regulators of lipid and glucose metabolism has raised interest in the development of synthetic ligands as potential tools for therapeutic intervention in T2D and the MetS.

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