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Minireview: Lipid Metabolism, Metabolic Diseases, and Peroxisome Proliferator-Activated Receptors

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Lipid and carbohydrate homeostasis in higher organisms is under the control of an integrated system that has the capacity to rapidly respond to metabolic changes. The peroxisome proliferator-activated receptors (PPARs) are nuclear fatty acid receptors that have been implicated to play an important role in obesity-related metabolic diseases such as hyperlipidemia, insulin resistance, and coronary artery disease. The three PPAR subtypes, α, γ, and δ, have distinct expression patterns and evolved to sense components of different lipoproteins and regulate lipid homeostasis based on the need of a specific tissue. Recent advances in identifying selective ligands in conjunction with microarray analyses and gene targeting studies have helped delineate the subtype-specific functions and the therapeutic potential of these receptors. PPARα potentiates fatty acid catabolism in the liver and is the molecular target of the lipid-lowering fibrates (*e.g.* fenofibrate and gemfibrozil), whereas PPARγ is essential for adipocyte differentiation and mediates the activity of the insulin-sensitizing thiazolidinediones (*e.g.* rosiglitazone and pioglitazone). Recent evidence suggests that PPARδ may be important in controlling triglyceride levels by sensing very low-density lipoprotein. Thus, uncovering the regulatory mechanisms and transcriptional targets of the PPARs will continue to provide insight into the pathogenesis of metabolic diseases and, at the same time, offer valuable information for rational drug design. (*Endocrinology* 144: 2201–2207, 2003)

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. 1). Lipoproteins are composed of triglycerides (TG), cholesterol esters, phospholipids, and apolipoproteins, which modulate lipoprotein catabolism. In the forward transport system, TG-rich very low-density lipoprotein (VLDL) released by the liver delivers fatty acids to adipocytes for storage and to cardiac and skeletal muscle for energy consumption. Lipoprotein lipase (LPL), secreted by the adipocyte, muscle, and macrophage, plays an important role in VLDL fatty acid release, and its subsequent conversion to low-density lipoprotein (LDL). Cholesterol ester-rich LDL, on the other hand, delivers cholesterol to peripheral tissues for steroidogenesis and maintaining cell membrane integrity. Conversely, in the reverse transport system, high-density lipoprotein (HDL) transports excess cholesterol from extrahepatic cells, such as macrophages at the vessel wall, to liver, where it can be recycled or catabolized to bile acid (1). Disturbances in this system are integral components of life-threatening diseases, best exemplified by the metabolic syndrome, or syndrome X, which refers to patients who are insulin-resistant (hyperinsulinemic), dyslipidemic (elevated TG and decreased HDL-cholesterol levels), frequently hypertensive and at high risk for developing coronary artery disease (CAD) (2).

The identification of fatty acids as endogenous ligands for peroxisome proliferator-activated receptors (PPARs) has provided a unique approach to study lipid homeostasis at the molecular level (3–7). PPARs are members of the nuclear receptor superfamily, which contains a signature type II zinc finger DNA binding motif and a hydrophobic ligand binding pocket (8). Three subtypes, PPARα (NR1C1), PPARδ/β (NR1C2), and PPARγ (NR1C3), have been identified with distinct tissue distributions and biological activities. PPARα is expressed in liver, heart, muscle, and kidney where it regulates fatty acid catabolism (9, 10). PPARγ is highly enriched in adipocyte and macrophage and is involved in adipocyte differentiation, lipid storage, and glucose homeostasis (11–13). PPARδ is expressed ubiquitously with a less defined function. It has been implicated in keratinocyte differentiation and wound healing and, more recently, in mediating VLDL signaling of the macrophage (14–17).

The fact that dietary fatty acids are natural activators of this subfamily implies that lipoproteins serve as ligand carriers for PPARs, which, in turn, modulate lipid homeostasis of the body. Consistent with this, the activities of the fibrate class of lipid-lowering drugs and the thiazolidinedione (TZD) class of insulin-sensitizing drugs are believed to be mediated by PPARα and PPARγ, respectively (18, 19). In addition, these PPAR agonists have all been reported to exhibit antiinflammatory activity in macrophages and endothelial cells, which is beyond the scope of this review. Here, we will discuss how these receptors coordinately mod-

Abbreviations: CAD, Coronary artery disease; CAP, c-Cbl-associated protein; FATP, fatty acid binding protein; FFA, free fatty acids; GLUT4, glucose transporter 4; GyK, glycerol kinase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase; ox-LDL, oxidized-LDL; PDK4, pyruvate dehydrogenase 4; PEPCK, phosphoenolpyruvate carboxykinase; PPAR, peroxisome proliferator-activated receptors; TG, triglyceride; TZD, thiazolidinedione; UCP, uncoupling protein; VLDL, very low-density lipoprotein.

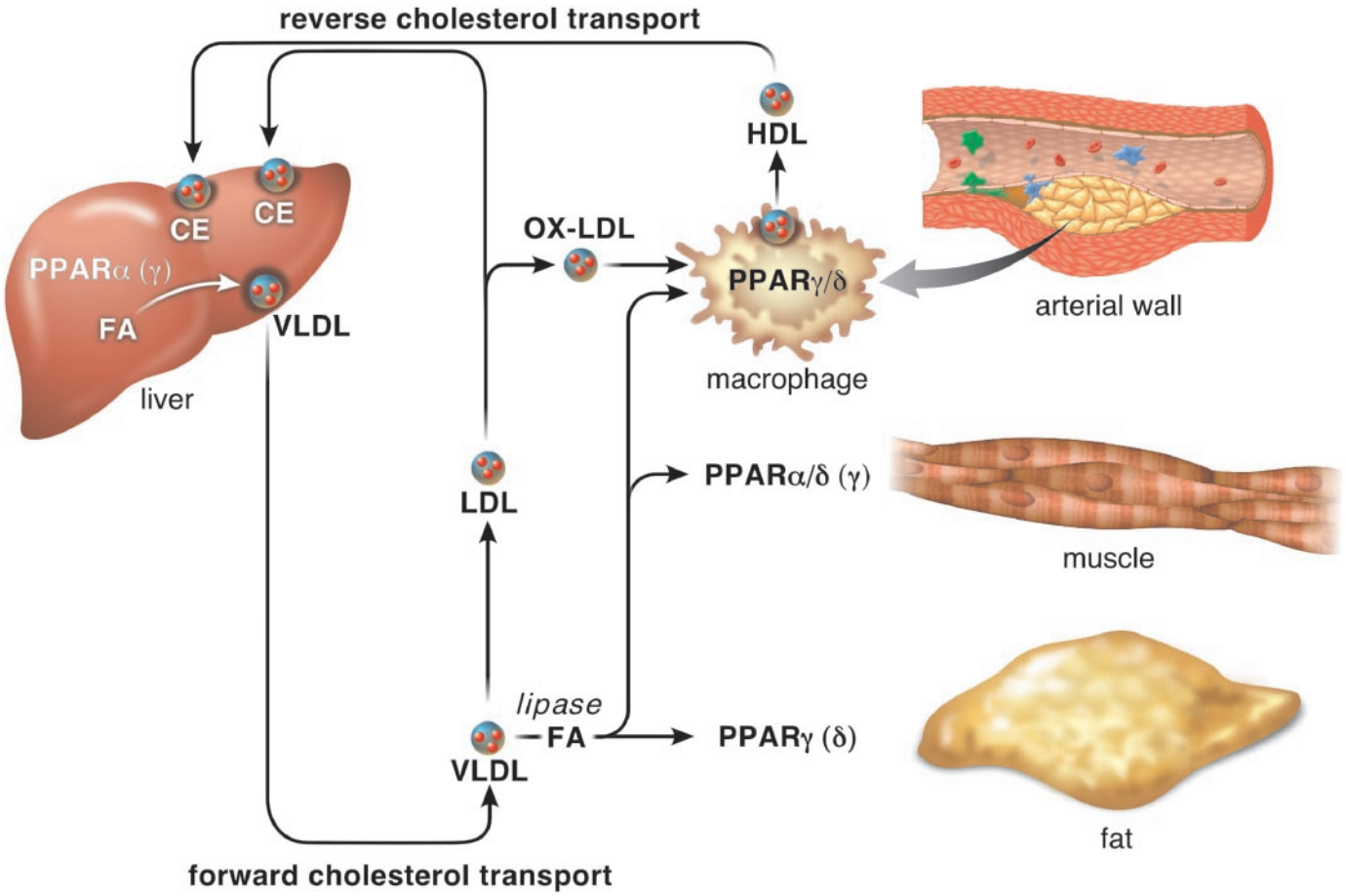

FIG. 1. Circulating lipoproteins deliver both energy substrates and endogenous activators for PPARs. In humans, TG-rich VLDL particles, released by liver, deliver fatty acids to adipocytes for storage and to muscle for energy consumption. Lipoprotein lipase, a PPARγ target gene in the adipocyte, promotes fatty acid release through its TG hydrolysis activity and conversion of VLDL to cholesterol-rich LDL. Activation of PPARα and PPARδ induces fatty acid (FA) catabolism in metabolically active tissues such as liver and muscle, whereas PPARγ is essential for lipid storage and differentiation of fat cells. Macrophages at the vessel wall also actively take up lipids such as VLDL and ox-LDL, and excess cholesterol is fluxed out through the HDL pathway. PPARγ plays an important role in the balance between lipid influx and efflux, whereas PPARδ is the major sensor for VLDL in the mouse macrophage. CE, Cholesterol esters.

ulate lipid homeostasis in metabolically active sites, including the liver, adipocytes, muscle, and macrophage, and their roles as lipid sensors in metabolic diseases.

PPARα

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 (FATP)], 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 (20, 21) or by pharmacological stimulation with synthetic ligands such as the fibrates (10, 18, 22). Although PPARα null mice have no obvious phenotype on a normal diet, these animals accumulate massive amounts of lipid in their livers when fasted or fed a high-fat diet. 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 (20, 21). 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 (23), 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.

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. When these animals are made diabetic

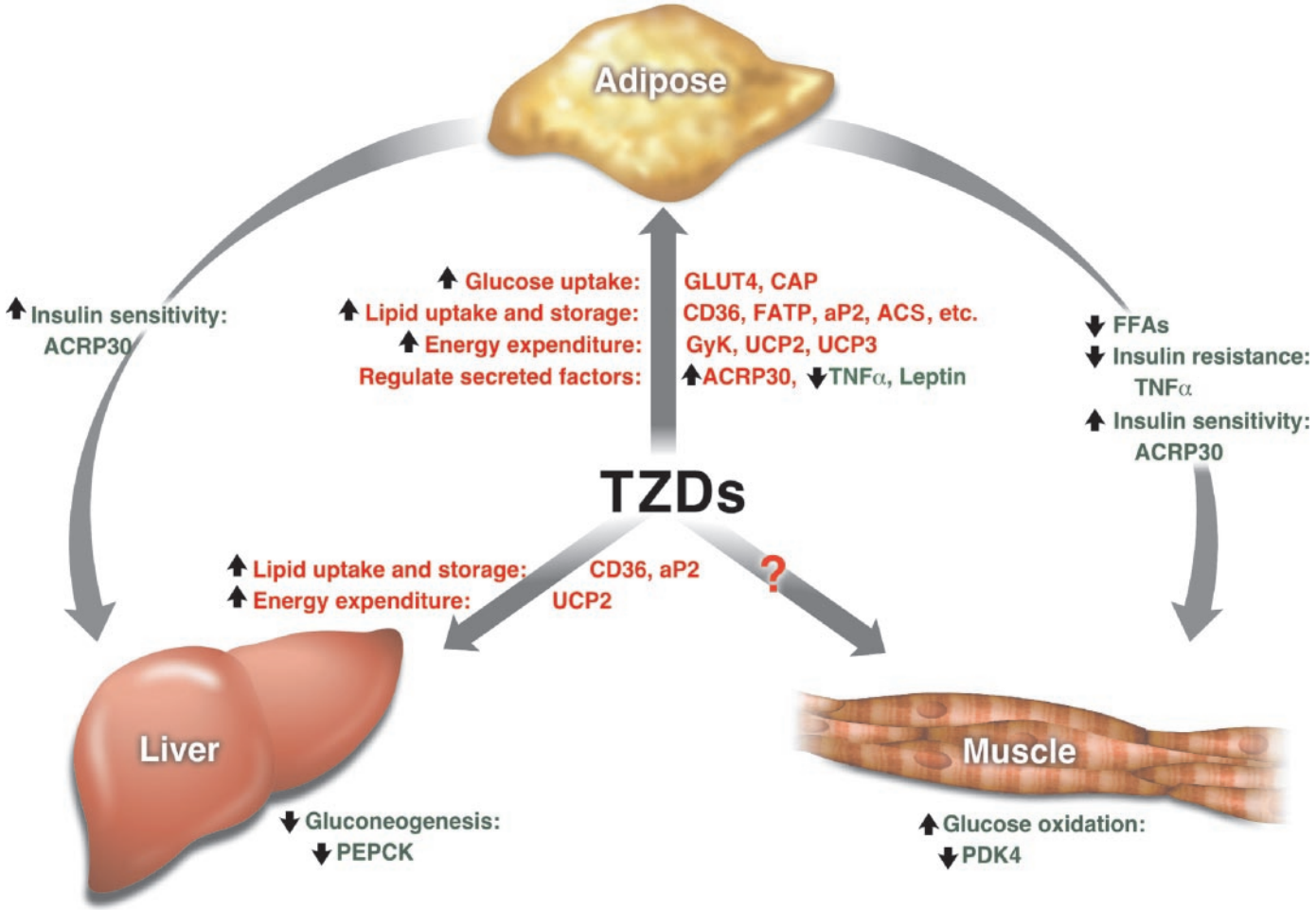

FIG. 2. Effects of TZDs on the three primary insulin-responsive tissues. Changes listed in *red* are mediated directly through the nuclear fatty acid receptor, PPARγ. This receptor is most abundantly expressed in adipose tissue where the largest transcriptional effect is seen. Direct effects have also been observed in liver; however, it is unclear whether or not PPARγ is activated in muscle. Alterations in adipocyte physiology as well as modulation of adipokines results in secondary effects denoted in *green* in other tissues. These include decreased gluconeogenesis in the liver through the down-regulation of PEPCK and increased glucose oxidation in muscle due, in part, to the down-regulation of PDK4. ACS, Acyl-CoA synthetase.

through streptozocin treatment, they develop more severe cardiomyopathy than wild-type controls, whereas PPARα null mice do not exhibit this phenotype (24, 25). Similarly, PPARα and apoE double knockout animals are protected from high cholesterol and high-fat diet-induced insulin resistance and develop less atherosclerotic lesions (26). These results strongly 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.

PPAR γ

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 (27). In humans with type II diabetes, pharmacologic activators of this receptor, such as TZDs, significantly improve insulin sensitivity (28); however, the mechanism of how these compounds work remains elusive. Considering the fact that muscle is the major tissue accounting for up to 80% of insulin-stimulated glucose disposal, one of the main issues yet to be resolved is how does a receptor that has high expression in fat, low expression in liver, and very low expression in muscle improve insulin sensitivity? Attempts to answer this question have proven difficult. PPARγ null embryos die at gestation d 10 due to a defect in the placenta, and tetraploid rescue only proves that PPARγ is essential for adipogenesis (11). Gene expression profiling by microarray suggests that the detectable changes in expression by TZDs are mostly in the adipocyte (29). These include genes involved in glucose uptake [c-Cbl-associated protein (CAP) and glucose transporter 4 (GLUT4)], lipid uptake and storage (CD36, aP2, LPL, FATP, and acyl-CoA synthetase), and energy expenditure [glycerol kinase (GyK), uncoupling protein (UCP) 2 and UCP 3; Refs. 29–37]. From these transcriptional changes, several plausible insulin-sensitizing mechanisms emerge (Fig. 2). The increase in CAP

and GLUT4 may alleviate some of the hyperglycemia, however, because adipose tissue is responsible for only a very small percentage (<5%) of total glucose disposal; this alone cannot explain the profound drug activity. On the other hand, sequestering lipids into fat stores through the induction of CD36, LPL, and aP2 should reduce the metabolic burden on liver and muscle and promote glucose use. Free fatty acids (FFA), in particular, cause insulin resistance in muscle, so lowering this metabolite is likely beneficial (38). GyK up-regulation also results in decreased FFA release by adipocytes, while at the same time increasing energy expenditure. In the fasting state, TG hydrolysis is stimulated, yielding FFAs and glycerol. These molecules normally enter the blood stream to be taken up by the liver, but GyK converts glycerol into glycerol-phosphate. The presence of glycerol-phosphate allows FFA recently hydrolyzed from TGs to be reincorporated back into TGs at an energetic cost. Similarly, UCPs allow protons to cross the mitochondrial membrane bypassing the ATPase, thus diverting potential energy into heat instead of ATP formation. Increased energy expenditure should be therapeutically beneficial in diabetic patients, especially in those with obesity. Other than genes that are directly involved in lipid and glucose homeostasis, TZDs also modulate the expression of secreted signaling molecules, or adipokines in fat. This includes down-regulation of leptin (39, 40) and TNF-α (41, 42) and up-regulation of Acrp30 (43–45). TNFα induces insulin resistance, whereas low levels of Acrp30 have been correlated with insulin resistance in mice, and injection of this protein improves insulin sensitivity.

In addition to the actions of PPARγ ligands on adipose tissue, these compounds exert some of their effects, either directly or indirectly, on other tissues. This has been shown in principle by the administration of TZDs to fatless mice. These mice develop hyperglycemia, hyperinsulinemia, and hyperlipidemia that is relieved, to varying extents, by TZD treatment (46, 47). Furthermore, the expression of PPARγ is up-regulated in the liver of genetically obese mice, and TZDs induce several PPARγ target genes involved in lipid uptake and storage in liver (48). PPARγ activation also appears to increase glucose oxidation in the muscle and decrease gluconeogenesis in the liver, in part, by down-regulating pyruvate dehydrogenase 4 (PDK4) and phosphoenolpyruvate carboxykinase (PEPCK), respectively (29). However, whether this is a direct TZD activity or secondary effect from changes in adipocyte physiology requires further studies using tissue-specific knockout animals.

Because diabetic patients are often at high risk for cardiovascular disease, the activity of PPARγ in lipid-laden macrophages has also been extensively studied. Earlier findings suggested that activation of PPARγ by modified fatty acids 9-hydroxyoctadecadienoic acid (9-HODE) and 13-HODE, components of oxidized-LDL (ox-LDL), might increase lipid accumulation through the induction of the scavenger receptor CD36 (49, 50). This observation raised the question as to whether TZDs exhibit a similar activity. However, a follow-up study demonstrated that 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 (51–54). 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. Indeed, a decrease in lesion formation has been observed with drug intervention in several mouse models of atherosclerosis (55–59). Reciprocally, macrophages lacking PPARγ are defective in their efflux program and display an accelerated lesion progression (51). In aggregate, these results suggest that therapeutic intervention is beneficial in treating CAD.

PPARδ

Muscle is one of the most metabolically demanding tissues and relies heavily on fatty acids as an energy source. PPARδ is the most abundant receptor in the muscle among the PPARs (60). It was first implicated in fatty acid metabolism from studies using the knockout animals. Most PPARδ null embryos die at an early stage due to a placental defect. The small percentage of PPARδ null mice that survive exhibit a reduction in fat mass (61, 62). However, this phenotype is absent in adipocyte-specific knockout animals suggesting that PPARδ may regulate systemic lipid metabolism rather than adipocyte functions (61). This idea is further strengthened by the observation that treatment with the synthetic compound GW501516 in insulin-resistant rhesus monkeys dramatically improves their serum lipid profile. The effects include a decrease in fasting TG and insulin and an increase in HDL cholesterol, while lowering the levels of small dense LDL (63). Although it is unclear which tissue is the major target for this activity, the identification of PPARδ as a VLDL sensor (see below) suggests that muscle could be one of the potential candidates. In support of this, a selective PPARδ ligand is capable of regulating genes important for fatty acid catabolism such as malonyl-CoA decarboxylase, CPT1, and UCP3, and increasing the fatty acid oxidation rate in muscle cells (Ref. 60; Wang, Y., and R. M. Evans, unpublished data). Furthermore, exercise- or starvation-induced up-regulation of these genes in muscle, but not in heart or liver, remains intact in the PPARα null mice. Thus, PPARδ activity appears to be more relevant than PPARα in the adaptive response of the muscle.

As mentioned earlier, PPARδ has recently been shown to mediate VLDL signaling in the macrophage (17). 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 (64). 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. Accordingly, VLDL induction of this gene is abolished in the PPARδ null macrophage, whereas this regulation remains unchanged in the PPARγ null cells. This intriguing result has raised the question as to how receptor activation affects atherosclerotic lesion progression, because it is becoming clear now that high TG and VLDL levels may be independent risk factors for CAD (65). With regard to foam cell formation, *in vitro* cholesterol-loading studies using

structurally distinct synthetic PPARδ activators have generated inconclusive results. In one study, PPARδ activation potentiated cholesterol efflux through induction of the ABCA1 pathway, whereas the other demonstrated enhanced lipid accumulation using a different agonist (63, 66). This discrepancy is likely due to differences in the experimental system, or the fact that PPARδ activates both lipid uptake and oxidation, a scenario similar to the cholesterol influx and efflux activities of PPARγ. Future studies in mouse models of atherosclerosis with either drug treatment or PPARδ-deficient bone marrow transplantation will help clarify the role of this receptor in CAD.

Conclusion

The use of loss-of-function mutants and high-affinity ligands for the PPARs has provided a unique opportunity to identify genes regulated by these receptors and correlate these regulatory events in the nucleus to the physiology of the animal. 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.

Given the intimate relationship between the activity of the PPARs and lipid homeostasis, continuing the study of the regulatory mechanisms mediated by PPARs will provide valuable information for designing drugs that target these receptors in metabolic diseases. Three major challenges remain to be addressed. The first will be to define metabolic pathways regulated by these receptors and which tissues they are activated in. The apparent task will be to decipher the actual site of action for TZDs. Future experiments with tissue-specific knockout of PPARγ should shed light on where the drug works and, importantly, whether loss of receptor in a specific tissue is sufficient to cause insulin resistance. PPARδ is another promising candidate as a lipid and insulin modulator due to its potential role in muscle. Given the wide tissue distribution of this receptor, research focusing on its activity in other metabolically active tissues will grow exponentially, and its therapeutic value will be unmasked in the near future. The next challenge will be to identify ligands that retain their effectiveness without adverse side effects. Substantial progress has already been made in designing selective PPAR modulators and dual agonists that modulate receptor activity. For example, several reported PPARγ partial agonists or PPARα/γ dual agonists retain insulin-sensitizing activity without causing weight gain (67–71). Finally, the role of PPARγ and PPARδ (or/and PPARα) as lipid sensors (ox-LDL verses VLDL) in the regulation of macrophage function deserves thorough investigation. It is known that macrophages at the vessel wall actively take up lipids, and this process is essential for the formation of atherogenic foam cells. Understanding these mechanisms in conjunction with the identification of selective modulators will extend the therapeutic value of PPARs to other metabolic diseases such as CAD.

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