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Role of the Peroxisome Proliferator-Activated Receptors (PPAR) in Atherosclerosis

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ABSTRACT. Peroxisome proliferator-activated receptors (PPAR) are ligand-activated transcription factors which form a subfamily of the nuclear receptor gene family. PPAR activators have effects on both metabolic risk factors and on vascular inflammation related to atherosclerosis. PPAR have profound effects on the metabolism of lipoproteins and fatty acids. PPARα binds hypolipidemic fibrates, whereas PPARγ has a high affinity for antidiabetic glitazones. Both PPAR are activated by fatty acids and their derivatives. Activation of PPARα increases the catabolism of fatty acids at several levels. In the liver, it increases uptake of fatty acids and activates their β-oxidation. The effects that PPARα exerts on triglyceride-rich lipoproteins is due to their stimulation of lipoprotein lipase and repression of apolipoprotein CIII expression, while the effects on high-density lipoproteins depend upon the regulation of apolipoproteins AI and AII. PPARγ has profound effects on the differentiation and function of adipose tissue, where it is highly expressed. PPAR are also expressed in atherosclerotic lesions. PPAR are present in vascular endothelial cells, smooth muscle cells, monocytes, and monocyte-derived macrophages. Via negative regulation of nuclear factor-κB and activator protein-1 signalling pathways, PPARα inhibits expression of inflammatory genes, such as interleukin-6, cyclooxygenase-2, and endothelin-1. Furthermore, PPARα inhibits expression of monocyte-recruiting proteins such as vascular cell adhesion molecule (VCAM)-1 and induces apoptosis in monocyte-derived macrophages. PPARγ activation in macrophages and foam cells inhibits the expression of activated genes such as inducible nitric oxide synthase, matrix metalloproteinase-9 and scavenger receptor A. PPARγ may also affect the recruitment of monocytes in atherosclerotic lesions as it is involved in the expression of VCAM-1 and intracellular adhesion molecule-1 in vascular endothelial cells. The involvement of PPAR in atherosclerosis, a disease with a chronic inflammatory character, suggests that they may play a role in other inflammatory-related diseases as well. BIOCHEM PHARMACOL **60**;8:1245–1250, 2000. © 2000 Elsevier Science Inc.

KEY WORDS. PPAR; lipoproteins; atherosclerosis; inflammation

The nuclear receptor subfamily of PPARs† consists of isoforms α (NR1C1), γ (NR1C3), and δ/β (NR1C2). Although these different members are encoded by separate genes, they have a similar protein structure. Like other nuclear receptors, the receptors consist of an A/B domain, a DNA-binding domain (C), a hinge region (D), and a ligand-binding domain (E). The DNA-binding domain is approximately 85% similar within the PPAR family, whereas the ligand-binding domain possesses a 70% similarity within the family members. Since the discovery of PPAR as a member of the nuclear receptor superfamily activated by peroxisome proliferators, understanding of the physiological role of PPARs has greatly expanded. We discuss here the involvement of PPARα and γ in lipid metabolism and inflammation. The role of PPARδ/β in these processes is currently unclear.

PPAR EXPRESSION

Tissue expression of PPARα, γ, and δ/β is diverse. PPARα is mainly expressed in tissues having a high metabolic rate such as liver, muscle, kidney, and heart [1, 2]. In addition, it is expressed in steroidogenic tissues such as adrenals [3]. PPARγ is mainly expressed in the intestine and in adipose tissue [1, 4, 5] and is also detectable in the mammary gland [4, 6]. Furthermore, both PPARα and γ are expressed in vascular cells including endothelial and smooth muscle cells and macrophages/foam cells [7–11].

PPAR: MECHANISM OF ACTION

PPAR bind, upon heterodimerisation with RXR, to specific PPRE in the promoter of target genes, thus regulating the transcription of these genes (Fig. 1). The PPAR consensus PPRE consists of a direct repeat of the AGGTCA sequence

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† *Abbreviations:* PPAR, peroxisome proliferator-activated receptors; RXR, retinoid X receptor; PPRE, peroxisome proliferator response elements; LDL, low-density lipoprotein; NF-κB, nuclear factor-kappa B; AP-1, activator protein-1; IL, interleukin; VCAM-1, vascular cell adhesion molecule-1; and TNF-α, tumor necrosis factor-alpha.

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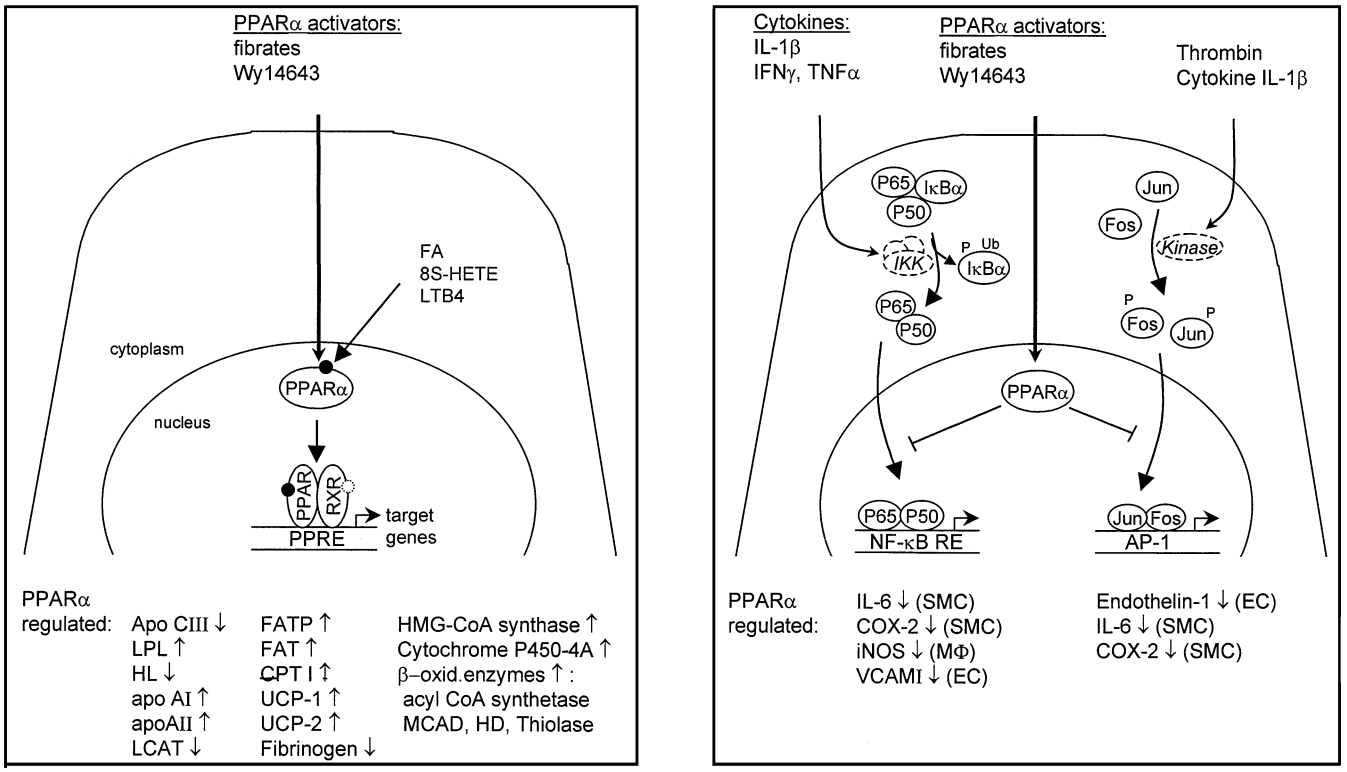

FIG. 1. Transcriptional regulation of PPARα target genes. Depicted are two mechanisms of PPARα action on the transcription of listed target genes. Abbreviations: FA, fatty acid; 8S-HETE, 8-*S*-hydroxyeicosatetraenoic acid; LTB4, leukotriene B4; APO, apolipoprotein; LPL, lipoprotein lipase; HL, hepatic lipase; LCAT, lecithin:cholesterol acyltransferase; FATP, fatty acid transport protein; FAT, fatty acid translocase; CPT, carnitine palmitoyltransferase; UCP, uncoupling protein; 3-HMG-CoA, mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase; MCAD, medium-chain acyl-CoA dehydrogenase; HD, enoyl-CoA hydratase/3-hydroxyacyl-CoA dehydrogenase; IFN, interferon; *IKK*, IκB kinase; IL, interleukin; COX, cyclooxygenase; iNOS, inducible nitric oxide synthase; EC, vascular endothelial cells; SMC, vascular smooth muscle cells; MΦ, macrophages.

spaced by 1 or 2 bases [12–15]. A PPARα-selective PPRE is further characterised by a 5′-flanking C(C/G)(A/G)A(A/T)(C/T) consensus sequence. Both the formation of the PPAR/RXR heterodimer and the subsequent transcriptional activation of the target gene are ligand-dependent. Ligand binding may evoke conformational changes within the DNA-binding domain, thereby altering the potential to stimulate transcription of target genes. The ligand may induce an alternative folding of helix 12, which contains the activation function-2 (AF-2) domain. Interaction of PPAR with RXR results in a permissive heterodimer, in which binding of 9-*cis* retinoic acid to RXR can alter activation as well [13].

A broad spectrum of compounds can serve as PPAR ligands and activate the receptor. PPARα ligands are fatty acids and their derivatives [16–19]. PPARα is activated by eicosanoids such as 8-*S*-hydroxyeicosatetraenoic acid (8S-HETE) and leukotriene B4 (LTB4), which are derivatives of arachidonic acid synthesised via the lipoxygenase pathway [18–20]. Well known are fibrates, the synthetic ligands for PPARα, which are widely used in the treatment of hypertriglyceridemia and combined hyperlipidemia [18]. However, other pharmacological compounds such as NSAIDs (nonsteroidal anti-inflammatory drugs) have also been identified as PPARα ligands [21].

PPARγ is activated by arachidonic acid metabolites derived from the cyclooxygenase and lipoxygenase pathways, e.g. 15-deoxy-Δ-12, 14-prostaglandin J2 (PG-J2) and 15-hydroxyeicosatetraenoic acid (15-HETE) [22–24]. In addition, fatty acid-derived compounds of oxidised LDL, such as 9- and 13-hydroxyoctadecadienoic acid (9- and 13-HODE), activate PPARγ. Furthermore, the antidiabetic glitazones (used in treatment of insulin resistance and type 2 diabetes) are high-affinity ligands for PPARγ [25], and the pharmacological NSAIDs indomethacin and ibuprofen function as ligands for PPARγ [21].

Upon binding of the PPAR/RXR heterodimer to a PPRE, this complex can recruit a diversity of cofactors (for review, see Robyr *et al.* [26]). Both cyclic AMP (cAMP) response element-binding protein-binding protein (CBP) and steroid receptor coactivator (SRC)-1 have been shown to interact with the PPARγ/RXR heterodimer, and their interaction may be mediated by initial binding of the PPARγ coactivator (PGC)-1 [27]. PPARα and PPARγ have been shown to be subjected to regulated phosphorylation, which may interfere with the recruitment of cofactors [28] and/or transcriptional activity [29–35].

Transcription of affected genes may also be indirectly modulated by PPAR via interference with other transcription factor pathways. Activation of PPARα negatively

interferes with the NF-κB, signal transducer and activator of transcription (STAT)5b, and AP-1 pathways [10, 36–38]. Similarly, PPARγ has been shown to affect the NF-κB, STAT1, and AP-1 pathways [39].

PPAR AND FATTY ACID METABOLISM

Since the first characterisation of PPAR [2], their importance in metabolic regulation has become clear. Fibrates have been shown to affect expression of genes via interaction with and activation of PPARα [40]. PPAR stimulate fatty acid catabolism at several levels: (i) PPARα alters human fatty acid and cholesterol transport in plasma by interfering with lipoprotein metabolism; (ii) it increases the transcription of apolipoproteins AI and AII and thus interferes with high-density lipoprotein (HDL)-mediated reverse cholesterol transport [41, 42]; (iii) PPARα stimulates lipoprotein lipase [43], which hydrolyses triglycerides present in very low-density lipoproteins (VLDL) and stimulates LDL uptake; (iv) PPARα inhibits expression of apolipoprotein CIII [44], resulting in increased lipoprotein lipase activity and remnant clearance; and (v) fatty acid uptake is stimulated by PPARα through increased expression of fatty acid transport protein, fatty acid translocase/CD36, and acyl CoA synthetase in mice liver and intestine [45].

After the cellular uptake of fatty acids, PPARα stimulates their transport into the mitochondria by increasing expression of carnitine palmitoyltransferase I [46–48]. Thereafter, PPARα stimulates the catabolism of fatty acid by increasing the transcription of rate-limiting enzymes in microsomal and peroxisomal β-oxidation [40]. The importance of PPARα in fatty acid and cholesterol metabolism was unequivocally demonstrated by metabolic changes, including high plasma cholesterol levels and low β-oxidation, in PPARα −/− mice [49–51]. In addition, ketogenesis, which supplies important fuels during starvation, is also affected by PPARα through activation of mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase transcription [52]. Furthermore, PPARα affects thermogenesis in adipose tissue by modulating the expression of the uncoupling protein (UCP)-2 in db/db mice and UCP-1 in rat brown adipocytes [53, 54]. UCP-1 in rat brown adipocytes is also regulated by PPARγ [53]. Thus, both PPAR play a role in uncoupling respiration from oxidative phosphorylation. The phenotype of PPARα-deficient mice after 24 hr of fasting includes hyperketonemia and hypothermia, which underlines the importance of this receptor in ketogenesis and thermogenesis [55].

An important factor in maintaining the energy balance of a body is the control of fat storage and release from adipose tissue. PPARγ plays a key role in the regulation of adipose gene expression and is essential for adipose differentiation [56–58]. Moreover, it regulates important proteins involved in glucose utilisation and insulin resistance/tolerance of adipose tissue [59]. Hence, insight into both PPARα- and γ-mediated gene regulation demonstrates a central role for PPAR in lipid and fatty acid metabolism.

PPAR AND ATHEROSCLEROSIS

Atherosclerosis is a multifactorial disease in which the occurrence of lesions may result in ischemia of the heart, brain, or extremities, resulting in infarction [60, 61]. The formation of atherosclerotic lesions involves attraction of monocyte/macrophages and T lymphocytes. Intermediate and advanced lesions typically consist of lipid-laden monocytes/macrophages (foam cells), migrating and proliferating smooth muscle cells, and the accumulation of cell debris and/or the presence of fibrous caps [60, 61]. Expression of PPARα and γ has been shown in atherosclerotic lesions and macrophage foam cells [7–11], which suggests that they may affect atherosclerogenic processes. Indeed, clinical observations indicate that treatment with fibrate PPARα activators lowers the progression of atherosclerotic lesions [62–64] and that the PPARγ agonist troglitazone decreases intimal thickness in human carotid arteries [65]. The accumulation of lipids and extracellular matrix in the intima of arteries elicits a local inflammatory response [61].

PPARα, which plays an important role in the metabolism of fatty acids, lipids, and lipoproteins, has also been implicated in atherogenic and inflammatory processes. PPARα-deficient mice show a prolonged response to inflammatory stimuli [20], and PPARα has been shown to inhibit transcription of several inflammatory response genes (Fig. 1). In human aortic smooth muscle cells, fibrates inhibit IL-1β-induced expression of cyclo-oxygenase (COX)-2 and IL-6 and 6-keto-prostaglandin factor 1α secretion by inhibiting the NF-κB and AP-1 signalling pathways [10, 36]. In human vascular endothelial cells, PPARα inhibits the AP-1 signalling pathway, which is involved in the thrombin activation of endothelin-1 production [37]. In addition, TNF-α-induced VCAM-1 expression in human saphenous vein endothelial cells is inhibited by PPARα activators partly via inhibition of the NF-κB pathway [66]. In addition, PPARα is present in isolated human monocytes and its expression increases upon differentiation into macrophages [67]. Furthermore, PPARα activators induce apoptosis of TNF-α-activated macrophages [67], likely by inhibiting the antiapoptotic NF-κB pathway. Recently, PPARα has been shown to affect monocytic recruitment to early atherosclerotic lesions by inhibition of TNF-α-induced VCAM-1 expression in endothelial cells [66].

Likewise, PPARγ has been shown to regulate the expression of activation-dependent genes in macrophages [68]. PPARγ activators inhibit the expression of matrix metalloproteinase (MMP)-9 of human macrophages [7] and vascular smooth muscle cells, thus interfering with vascular smooth muscle cell proliferation [66]. PPARγ inhibits the production of the inflammatory cytokines TNF-α, IL-6, and IL-1β by activated monocytes [69] and decreases the transcription of monocyte chemoattractant protein

(MCP)-1 [70]. Furthermore, PPARγ inhibits the expression of inducible nitric oxide synthase (iNOS) and the scavenger receptor A in interferon (IFN)-γ-stimulated mouse macrophages [39]. On the one hand, PPARγ agonists have been shown to enhance CD36 expression of macrophages, which may indicate that PPARγ could stimulate uptake of oxidised LDL [8, 22]. On the other hand, intracellular adhesion molecule (ICAM)-1 and VCAM-1 expression is inhibited by troglitazone in human endothelial cells [71], and the scavenger receptor CLA-1/SR-BI is induced by PPARα and PPARγ in human macrophages [11]. This suggests that PPARγ may influence monocyte recruitment and cholesterol efflux from foam cells. Further studies are required to establish the exact role of PPARγ in the formation of foam cells in the atherosclerotic lesions.

The role of PPAR in vascular inflammation related to atherosclerosis suggests that PPAR may play an additional role in other inflammatory diseases. Indeed, PPARγ activators have been shown to interfere with colon epithelial cell function and inflammatory responses [72, 73]. In addition, similar inflammatory responses in atherosclerosis and rheumatoid arthritis (reviewed in [74]) have implied a role for PPARγ in rheumatoid arthritis [39, 75].

CONCLUSION

PPAR play important roles in fatty acid metabolism and fatty acid storage in liver and adipose tissue, respectively. Furthermore, PPAR are expressed in atherosclerotic lesions and have been shown to affect transcription of genes in vascular endothelial cells, smooth muscle cells, monocytes, and monocyte-derived macrophages. Besides direct regulation of transcription via a PPRE, PPAR may negatively interfere with other signalling pathways, including NF-κB-mediated transcription. The down-regulation of several atherogenic genes by PPAR activation suggests that stimulation of PPAR expression and/or activation may have beneficial effects on the progress of atherosclerotic disease.

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