Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors discovered for their ability to respond to xenobiotics with peroxisomal proliferation in the liver of rodents. They are encoded by 3 distinct genes: \( \alpha \), \( \beta/\delta \), and \( \gamma \). Initially believed to regulate genes involved only in lipid and glucose metabolism, the role of PPARs has more recently been increasingly associated with regulation of cell growth and migration and inflammation. PPAR-\( \alpha \) may be activated by fatty acids, fibrates, and leukotriene B4 to induce transcription of genes involved in \( \omega \)- and \( \beta \)-oxidation of fatty acids. PPAR-\( \alpha \) is mainly expressed in tissues in which fatty acid catabolism is important, such as liver, kidney, heart, and muscles. Shortly after the discovery of PPAR-\( \alpha \), PPAR-\( \beta/\delta \), and PPAR-\( \gamma \) were identified. PPAR-\( \beta/\delta \) is expressed ubiquitously, and its function remains unclear, although recent evidence suggests a role on fatty acid and lipid metabolism, particularly in the heart. PPAR-\( \gamma \) is highly expressed in adipose tissue, where it controls adipocyte differentiation and lipid storage and modulates the action of insulin. The Figure shows schematically the activation of PPARs and their transcriptional role.

PPAR structure includes an N-terminal domain that regulates PPAR activity, a DNA-binding domain that binds to the PPAR response element (PPRE) in the promoter region of target genes, a domain for a cofactor, and a C-terminal ligand-binding domain. Ligand specificity is determined by the latter. When activators bind to PPARs, they heterodimerize with retinoid X receptors (RXR-\( \alpha \)) and then may bind to PPRE in target genes to modulate gene transcription. PPAR-\( \alpha \) is activated by natural ligands such as fatty acids and eicosanoids and by synthetic ligands, the lipid-lowering fibrates. Selective activators of PPAR-\( \gamma \) are the insulin sensitizers thiazolidinedione glitazones, such as troglitazone, pioglitazone, and rosiglitazone (Figure).

**Vascular Effects of PPARs**

Since both PPAR-\( \alpha \) and PPAR-\( \gamma \) are expressed in the cardiovascular system, such as in endothelial cells and vascular smooth muscle cells (VSMC) and monocytes/macrophages, a number of studies have been carried out to elucidate the cellular and molecular mechanisms underlying PPAR actions on the vasculature. We first identified that the PPAR-\( \alpha \) ligand docosahexanoic acid (DHA) had proapoptotic effects on cultured VSMCs. This proapoptotic action was mediated by activation of p38 mitogen–activated protein kinase. PPAR-\( \alpha \) ligands inhibited IL-1\( \beta \)-induced production of interleukin (IL)-6 and prostaglandin and expression of...
cyclooxygenase-2, as a result of PPAR-α repression of transcription factor nuclear factor-κB (NF-κB) signaling. The PPAR-α activator fenofibrate significantly reduces plasma interferon-γ and tumor necrosis factor-α (TNF-α) in patients with hyperlipoproteinemia IIb, demonstrating its anti-inflammatory activity. PPAR-α activators also downregulate cytokine-induced genes, such as expression of vascular cell adhesion molecule (VCAM)-1 and tissue factor in endothelial cells. PPAR-α-deficient mice had exaggerated inflammatory response to lipopolysaccharide (LPS) stimulation, and fibrates failed to affect LPS-induced IL-6 transcription in these mice. The molecular mechanisms of the anti-inflammatory action of PPAR-α activators could involve antagonism of the NF-κB signaling pathway. Accordingly, we investigated the effect of the PPAR-α activator DHA in angiotensin (Ang) II–infused rats and demonstrated that the PPAR-α activator reduced Ang II–induced oxidative stress and inflammatory mediators in blood vessels. Systolic blood pressure elevated in Ang II–infused rats was reduced by DHA from 172±3 to 112±4 mm Hg (P<0.01). In mesenteric small arteries studied in a pressurized myograph, media/lumen ratio was increased and acetylcholine-induced relaxation impaired in Ang II–infused rats; both were normalized by DHA. NADPH oxidase activity measured by chemiluminescence and expression of adhesion molecules intercellular adhesion molecule (ICAM) and VCAM-1 were significantly increased in blood vessels of Ang II–infused rats, changes that were abrogated by DHA. Thus, DHA attenuated the development of hypertension, corrected structural abnormalities, and improved endothelial dysfunction induced by Ang II. These effects were associated with decreased oxidative stress and inflammation in the vascular wall.

PPAR-γ as mentioned is involved in adipocyte differentiation and insulin sensitivity. However, it has been shown to be expressed in smooth muscle and in monocytes/macrophages. PPAR-γ inhibits proliferation and migration of VSMCs. PPAR-γ is upregulated in activated macrophages and inhibits the expression of inducible nitric oxide synthase (iNOS), matrix metalloproteinase (MMP)-9, and scavenger receptor A genes in response to 15-deoxy-(Δ12-14)-prostaglandin J2 (15d-PGJ2) and synthetic PPAR-γ ligands. PPAR-γ activation inhibits gene expression in part by antagonizing the activities of these transcription factors: activator protein 1 (AP-1), signal transduction-activated transcription factors (STAT), and NF-κB. In monocytes, PPAR-γ activators inhibit the expression of TNF-α, IL-6, IL-1β, iNOS, MMP-9, and scavenger receptor A in monocytes. PPAR-γ expression has been demonstrated in atherosclerotic plaques and in endothelial cells whose function is altered in atherosclerosis, where PPAR-γ could play an antiatherosclerotic role. The PPAR-γ activators, troglitazone and 15d-PGJ2, attenuated TNF-induced VCAM-1 and ICAM-1 expression in endothelial cells, and troglitazone reduced monocyte/macrophage homing to atherosclerotic plaques in apoE-deficient mice. However, 15d-PGJ2 may stimulate the synthesis of IL-8 in endothelial cells in a PPAR-γ-independent manner. The mechanism of the anti-inflammatory effect may depend on interactions with different signaling pathways. One recently demonstrated is interaction with CCAAT/enhancer-binding protein (C/EBP)-δ, which is present in tandem repeats in the PPAR-γ gene promoter and upregulates transcription of inflammatory cytokines. The latter are negatively autoregulated by PPAR-γ in the vasculature. PPAR-γ ligands troglitazone, pioglitazone, and 15d-PGJ2 transcriptionally inhibited IL-1β–induced IL-6 expression in VSMCs. Thus C/EBP-δ may be negatively autoregulated through transactivation of PPAR-γ, downregulating inflammatory responses. PPAR-γ may also play an anti-inflammatory role in hypertensive models, such as Ang II–induced hypertension.

We recently demonstrated that the PPAR-γ activators rosiglitazone and pioglitazone prevented hypertension in Ang II–infused rats and abrogated the structural, functional, and molecular changes induced by Ang II in blood vessels by exerting direct effects on the vascular wall, leading to
inhibition of cell growth and inflammation. In mesenteric small arteries studied in a pressurized myograph, media/lumen ratio was increased and acetylcholine-induced relaxation impaired in Ang II–infused rats; both were normalized by the thiazolidinediones. In Ang II–infused rats, vascular DNA synthesis (by 3H-thymidine incorporation); expression of cell cycle proteins cyclin D1 and cdk4, Ang II type 1 (AT1) receptors, vascular VCAM-1, and platelet and endothelial cell adhesion molecule (PECAM); and NF-κB activity were increased. These changes were abrogated by pioglitazone or rosiglitazone.

PPARs may also modulate in vitro the vascular production of vasoactive peptides such as endothelin-1 (ET-1). We investigated the in vivo interaction between PPARs and ET-1 in DOCA-salt rats, which overexpress vascular ET-1. Blood pressure increase was partially prevented in the DOCA-salt hypertensive rats by coadministration of the PPAR-γ activator rosiglitazone but not by the PPAR-α activator fenofibrate. Both PPAR activators abrogated the increase of preproET-1 mRNA content in the mesenteric vasculature of DOCA-salt rats. Rosiglitazone and fenofibrate prevented the hypertrophic remodeling in DOCA-salt rats but did not affect vessel mechanics. Rosiglitazone but not fenofibrate prevented endothelial dysfunction. Furthermore, both rosiglitazone and fenofibrate prevented the vascular increase of superoxide anion production found in DOCA-salt animals.

Spontaneously hypertensive rats (SHR) have insulin resistance that has been associated with a mutation of cd36, which encodes for a fatty acid translocase, and results in decreased fatty acid translocation. cd36 is a target of PPAR-γ. We therefore hypothesized that there could be changes in expression of PPARs in blood vessels of SHR that could result in decreased inhibition of proliferation, migration, inflammation, and fibrosis in this hypertensive model. However, when this hypothesis was tested, we found the opposite, that is, increased rather than decreased expression of PPAR-α and PPAR-γ in blood vessels and in cultured VSMC from SHR. We interpret this as a possible compensatory (feedback?) response to the decreased activity of the mutant cd36 of SHR.

Cardiac Effects of PPARs

PPAR-α plays an important role in regulation of energy and lipid metabolism and accordingly in the pathophysiology of heart disease. PPAR-α is involved in mitochondrial fatty acid β-oxidation, a critical fuel-generating mechanism of the heart. PPAR-α controls myocardial lipid metabolism through the activation of transcription of the muscle carnitine palmitoyltransferase I (CPT I) gene. It serves as a molecular “lipostat” by inducing the expression of target genes involved in cardiac fatty acid metabolism. The capacity for constitutive myocardial β-oxidation of the medium and long chain fatty acids octanoic acid and palmitic acid was markedly reduced in the PPAR-α–null mice compared with wild-type mice, indicating that mitochondrial fatty acid catabolism is impaired in the absence of PPAR-α. In contrast, constitutive β-oxidation of the very long chain fatty acid lignoceric acid did not differ between the PPAR-α–deficient mice and the wild type, which suggests that the constitutive expression of enzymes involved in peroxisomal β-oxidation is independent of PPAR-α.

PPAR-α is deactivated during cardiac hypertrophy. Hyper trophyed myocytes accumulate fat intracellularly in response to oleate loading, which indicates that PPAR-α deactivation reduces the capacity for myocardial lipid and energy homeostasis. PPAR-α also exerts anti-inflammatory action on the heart. PPAR-α activators inhibit cardiac expression of TNF-α and NF-κB induced by lipopolysaccharide. The PPAR-α activator fenofibrate reduced preproET-1 mRNA expression and collagen type I and type III mRNA, associated with decrease in interstitial and perivascular cardiac fibrosis after pressure overload induced by abdominal aortic banding, probably through suppression of AP-1–mediated preproET-1 gene activation. Additionally, fenofibrate reduced cardiac hypertrophy and inflammation associated with an increase in the anti-inflammatory cytokine IL-10. We recently observed that fenofibrate had beneficial effects on inflammation and collagen deposition in the heart of Ang II–infused rats. This was associated with a decrease in NF-κB activity, VCAM-1, PECAM, ICAM-1, and ED-1 (macrophage antigen) expression and downregulation of AT1 and upregulation of AT1 receptor.

The role of PPAR-γ in the heart remains unclear. This is complicated by the fact that expression of PPAR-γ in the heart is very low. PPAR-γ may act as an inhibitor of cardiac hypertrophy. Both troglitazone and the endogenous PPAR-γ ligand 15d-PGJ2 blocked hypertrophy and brain natriuretic peptide expression in cultured cardiomyocytes. PPAR-γ may function as a transducer of antihypertrophic signaling in the heart. In heterozygous PPAR-γ–deficient mice, an exaggerated hypertrophic response to pressure overload induced by aortic banding was noted. In contrast, pioglitazone significantly blunted myocardial hypertrophy in both wild-type and PPAR-γ–/– mice, although to varying degrees. Ang II–induced hypertrophic gene expression, as well increased cardiomyocyte size, may be attenuated in vitro by thiazolidinediones. Taken together, these data suggest that PPAR-γ negatively influences cardiomyocyte size. In addition, PPAR-γ improved left ventricular diastolic function and decreased collagen accumulation in diabetic rats and protected myocardium from ischemic injury. However, clinical reports have recently warned that PPAR-γ activator glitazones may lead to development or exacerbate congestive heart failure. Among molecular adaptations of the hypertrophic heart is an increase in glucose utilization and decreased fatty acid oxidation. Whether or not PPAR-γ has similar regulating effects on fatty acid metabolism as PPAR-α is unclear. Since both PPAR-α and PPAR-γ have a partially overlapping ligand binding profile, PPAR-γ could mediate to some degree similar signals as PPAR-α in cardiomyocytes. PPAR-γ signaling could attenuate cardiac remodeling through pathways not directly involved in controlling lipid and energy metabolism, such as inflammation. Inflammation is an important mechanism in the progression of cardiac remodeling and dysfunction. In macrophages, PPAR-γ is involved in regulation of inflammatory responses by antagonism of transcription factors NF-κB and AP-1. NF-κB is required for the hypertrophic response of neonatal
rat cardiomyocytes in vitro. Indeed, we recently observed that the PPAR-γ activator pioglitazone had beneficial long-term effects on cardiac hypertrophy and cardiac inflammation without affecting cardiac function in stroke-prone SHR. However, whether PPAR-γ effects on the heart are directly exerted on cardiomyocytes or occur through infiltrating macrophages and other blood-borne cells or are the result of endocrine actions mediated indirectly by other organs through hormonal effects remains unclear.

Perspectives

Based on in vivo and in vitro studies with different cell types, it is clear that PPAR-α and PPAR-γ play an important role in the modulation of inflammatory, fibrotic and hypertrophic responses (Figure). However, our knowledge of the regulatory mechanisms and signaling cascades underlying the anti-inflammatory effect of PPARs, particularly in the heart, is still limited. More research in this area is required. In addition, the discrepancy between the beneficial effect of PPAR-γ activators on the heart in experimental models and clinical reports of heart failure in a few diabetic patients treated with PPAR-γ activators needs to be further clarified. It is likely that in those patients, water and salt retention induced by the insulin-sensitizing action of PPAR-γ activators masks a latent left ventricular dysfunction and may thus precipitate cardiac failure that is not induced directly by PPAR-γ activators.

Both PPAR-α and PPAR-γ activators may interfere with signaling pathways, leading to cardiovascular damage, inflammation, fibrosis, and growth. Use of selective PPAR-α or PPAR-γ activators or dual α/γ activators may exert cardiovascular protective effects in hypertension or other forms of cardiovascular disease.

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References

4. Dreyer C, Krey G, Keller H, Givel F, Helftenbein G, Wahli W. Control of gene expression by PPARs and a group grant to the Multidisciplinary Research Group on Cardiac and Vascular Effects of PPARs

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