The Effect of PPARs on Coronary Heart Disease

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Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily. PPARs play an important role in biological functions including lipid metabolism, inflammatory signaling, insulin sensitivity, and cell proliferation/differentiation. Growing evidence points to a causative relationship between PPARs and coronary heart disease (CHD). It is known that PPAR activators improve key surrogate markers of the atherosclerotic process and significantly lower the incidence of cardiovascular events by reducing circulation inflammatory status. Although PPAR activators are beneficial for the treatment of dyslipidemia and insulin sensitivity, it has been noted that there are some limitations in a population prone to congestive heart failure (CHF). There are increasing challenges of the cardiovascular safety associated with PPAR activators treatment of type 2 diabetes mellitus (T2DM). A better understanding of diverse range of physiological and metabolic processes and the relationship among inflammation, atherosclerosis, and PPARs may be helpful in elucidating more preventive avenues to manage CHD.

Key Words: PPARs • CHD • Atherosclerosis • Fibrates • Thiazolidinediones (TZDs)

INTRODUCTION

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors belonging to the nuclear hormone receptor superfamily. They act on numerous target genes following heterodimerization with the retinoid X receptor and subsequently bind to PPAR response elements of regulatory promoter regions of target genes to further modulate gene transcription. There are three subtypes of PPARs (i.e., α, β/δ, and γ), with studies having suggested their roles in biological functions including lipid metabolism, inflammatory signaling, insulin sensitivity, and cell proliferation/differentiation [Figure 1]. PPARα is mainly expressed in brown fat, heart, liver, and skeletal muscle, elevating the rates of mitochondrial/peroxisomal β- and ω-oxidation of fatty acid. PPAR β/δ is expressed ubiquitously, with a suggested role in lipid metabolism and cell proliferation/differentiation. PPARγ is expressed in adipose tissue, liver, macrophage, cardiac and skeletal muscle, and has a potential role in modulating lipid metabolism, inflammatory signaling, adipocyte differentiation, and insulin sensitivity. It is known that all three PPARs are expressed in vascular tissue, while both PPARα and PPARγ are expressed mostly in vascular endothelium, vascular smooth muscle, and macrophages/foam cells as well as human atherosclerotic lesions.

Fatty acids and eicosanoids are natural ligands of all three PPARs. Eicosanoids are a class of fatty acids mainly derived from arachidonic acid, either via the lipoxygenase pathway, leading to the formation of leukotrienes and hydroxyeicosatetraenoic acids or via the cyclooxygenase pathway, producing prostaglandins. The synthetic ligands of PPARα are lipid-lowering fibrates, such as bezafibrate, clofibrate, ciprofibrate, and fenofibrate, as well as the non-fibrate drugs, benfluorex, gemfibrozil, and probucol. The selective activators of PPARγ are insulin sensitizer thiazolidinediones (TZDs), such as pio-
glitazone, rosiglitazone, and troglitazone. The availability of PPARγ and PPARα activators has allowed many investigation of their vascular functions. Consequently, activation of both receptors can improve insulin sensitivity and proinflammatory status; it has been shown to reduce the progression of atherosclerosis and coronary heart disease (CHD).

**CHD, ATHEROSCLEROSIS, AND INFLAMMATION**

CHD, one of the most common and serious forms of cardiovascular disease, is a chronic process that begins during adolescence and slowly progresses throughout life. The major risk factors increase the likelihood for developing CHD, including cigarette smoking, hypertension, T2DM, high serum cholesterol and various cholesterol fractions, low level of high-density lipoprotein (HDL) cholesterol, advancing age, and other relative risk factors include obesity, physical inactivity, family history of premature CHD, hypertriglyceridemia, small low-density lipoprotein (LDL) particles, increased lipoprotein (a) (Lp [a]), increased serum homocysteine, and abnormalities in several coagulation factors. These risk factors accelerate or modify a complex and chronic inflammatory progress that ultimately manifests as atherosclerosis.

Atherosclerosis was considered as a bland lipid accumulation disease formerly. Actually, accumulating evidence suggests that inflammation has a causative link between risk factors and the processes of atherogenesis. Recent studies show a potential role for inflammation in the underlying cellular and molecular mechanisms that ultimately contribute to atherosclerosis and the thrombotic complications of atherosclerosis.

Atherogenesis begins with the activation of inflammation and immune cells at the endothelium, thus leading to endothelial dysfunction and eventually damage of the artery muscle and the formation of fibrous plaque. It involves endothelial cells (ECs) and vascular smooth muscle cells (VSMCs), an increasing in endothelial ad-
INFLAMMATION AND PPARS

Advances in the basic science of inflammation show a fundamental role for PPARs in mediating all stages of the atherogenesis and thrombotic complications of atherosclerosis. Recently, there has been a plausible model linking among lipids, inflammation, atherogenesis, and PPARs. LDL cholesterol retained in the intima, in part by binding to proteoglycan, undergoes oxidative modification. These modified lipids (i.e., ox-LDL) induce the expression of adhesion molecules, chemokines, proinflammatory cytokines, and other mediators of inflammation in macrophages and VSMCs, thus ultimately contributing to atherogenesis. Some other lipoprotein particles, such as very low-density lipoprotein (VLDL) and intermediate-density lipoprotein, also have considerable atherogenic potential. Studies suggest that reverse cholesterol transport (RCT) affected by HDL accounts for some atheroprotective effects. HDL transport antioxidant enzymes, such as platelet-activating factor (PAF, i.e., acetylhydrolase and paraoxonase), which can break down oxidized lipids and reduce their proinflammatory affects.

PPARs decrease the expression of inflammatory genes, such as cytokines, MMPs, and acute-phase reactants by exerting anti-inflammatory activities in immunological and vascular cells, i.e., monocytes/macrophages, ECs, VSMCs, dendritic cells, and T-cells. Both PPARα and PPARγ are expressed in macrophages, which can reduce genes implicated in the inflammatory response; modulate macrophage differentiation and promote TNF-α/IFN-γ-induced apoptosis. PPARα enhances the degradation of lipid-derived proinflammatory mediators, such as LT4, or its precursor, arachidonic acid, and modulates transcription of genes’ β- and α-oxidation that catabolize LT4 itself. It also appears to reduce the synthesis of proinflammatory mediators such as IL-6 and prostaglandins by PPARα-mediated control of inflammation, via a decreased activity of nuclear factor-kB (NF-kB). PPARα activation interferes with processes involved in leukocyte recruitment and cell adhesion, with a subsequent inhibition of NF-kB activation in the VCAM-1 promoter. PPARα reduces the expression of inducible cyclooxygenase-2 (COX-2) and IL-6 in human aortic VSMCs, and cytokine-induced expression of VCAM-1 and tissue factor (TF) in monocytes/macrophages.
Studies show that fenofibrate decreases the circulating levels of IL-6, and thus can lower the levels of risk factors for cardiovascular disease, such as hs-CRP and fibrinogen. Both synthetic and natural PPAR ligands (e.g., fenofibrate, gemfibrozil, and EPA) enhance endothelial nitric oxide synthase (eNOS) expression and NO release, suggesting a vasoprotective effect.28,29

PPARγ reduces the expression of cell adhesion and chemokine receptors of the immune system, such as monocytes, leukocytes, and inducible NOS.30 PPARγ activation results in an increasing expression of CD36 gene in macrophages, whereas the transcriptional activation of scavenger-receptor (SR)-A by proinflammatory stimuli is inhibited. PPARγ modulates endothelial dysfunction in T2DM patients by increasing endothelium-dependent vasodilation with a downregulation of endothelial function and levels of inflammatory markers of atherosclerosis, such as hs-CRP, IL-6, E-selectin, SAA, and CD40L.

PPARS, ATHEROSCLEROSIS, AND CHD

Some liver X nuclear receptor-responsive target genes, cholesteryl ester transfer protein, ATP-binding cassette transporter (ABC, i.e., ABCA-1 and ABCG-1), and apolipoprotein (apo)-E, have defined roles in the RCT process.33,34 Recent studies show that all three PPARs modulate macrophage cholesterol homeostasis. By enhancing cholesterol efflux, PPARs promote the critical steps of RCT by regulating HDL cholesterol transport in plasma, macrophage cholesterol efflux, and bile acid synthesis, thus reducing the proinflammatory status. PPARα activation expresses in macrophages in transition by increasing the macrophage-free cholesterol pool available for RCT, thus reducing macrophage lipid accumulation and ensuing foam cell formation. Treatments of macrophages with TZDs can upregulate ABCA-1, thus promoting cholesterol efflux and decreasing the macrophage inflammatory responses.37 PPARα enhances lipoprotein lipase (LPL) activity directly by increasing gene transcription and indirectly by decreasing apoC-III (an inhibitor of LPL). PPARα also promote apoA-I and A-II synthesis (major apos of the HDL fraction in liver), thus contributing to a raise in serum HDL levels.38,39 Moreover, by reducing the expression of cytokines and proteins involved in monocytes/macrophages, VSMC proliferation, and inflammation, PPARα activation might reduce the progress of atherosclerosis.

Activation of PPARγ in adipose tissue can significantly increase adiponectin levels and lower resistin levels, and thus might reduce the inflammatory responses and improve glycemic control in T2DM. Rosiglitazone can raise HDL-C and lower hs-CRP, IL-6, and TNF-α levels that have been associated with decreased risks of cardiovascular disease in T2DM patients.30,41 It is known that PPARγ is expressed in the cardiovascular system (i.e., ECs, VSMCs, and monocytes/macrophages). As such, PPARγ agonists have been shown to reduce hs-CRP, fibrinogen, and regulate serum cholesterol and triglycerides, and thus might break down the constitutional risk factors for atherosclerosis and CHD.

SAFETY AND FUTURE

Although PPARγ activators show benefit for insulin sensitivity and have kindled much hope for the prevention of atherosclerosis, it is important to recognize some limitations, such as hepatotoxicity, edema, and weight gain, are annoying in a population prone to these adverse drug reactions.42,43 Ignoring troglitazone, which was withdrawn due to severe hepatotoxicity, it is known that both rosiglitazone and pioglitazone are now available and show no clear evidence of hepatotoxicity. The major cause of weight gain is that PPARγ is involved in fluid retention and adipocyte proliferation/differentiation. Conceivably, PPARγ is expressed in the renal medullary-collecting duct with PPARγ-dependent activation of sodium transport and thus underlies TZD-induced fluid retention.44 By showing vascular leak syndrome, TZDs also cause edema by selectively increasing capillary permeability in adipose tissue through protein kinase C-β isoform activation.45 TZDs upregulate apoA-II and cause an increase in VLDL-C (the most triglyceride-rich remnant lipoprotein) and further loading in adipocytes. As the result of the edema and weight gain being dose-dependent, and due to more severe adverse effects with combination therapy of TZDs, insulin, and insulin secretagogues (e.g., sulfonylureas), FDA approval was sought only for lower dosages of TZDs.46

A monotherapy with TZD is associated with adverse
edema in approximately 3%-5% of patients, but is seen in approximately 12%-15% of patients treated with TZD and insulin combination.\textsuperscript{44,46} Congestive heart failure (CHF) is less than 1% in patients treated with a single TZD, but is seen in approximately 1%-3% of patients treated with TZD and insulin combination. Edema and CHF were also seen as adverse effects of muraglitazar, a novel “glitazar” dual (PPAR\_\textsubscript{\alpha} and PPAR\_\gamma) agonist.\textsuperscript{47} Compared with pioglitazone or placebo, muraglitazar was associated with excess incidences of death, adverse cardiovascular events (i.e., nonfatal MI, stroke, or transient ischemic attack), and CHF.\textsuperscript{48} As the result of these safety concerns and increased scrutiny, muraglitazar delayed its filing target for additional safety trials.

Angiotensin II receptor blockers (ARBs) have been approved for the treatment of hypertension for years. Recently, animal model have indicated that two ARBs, telmisartan and irbesartan, also show PPAR\_\gamma partial activation.\textsuperscript{49} Telmisartan is particularly similar to PPAR\_\gamma as a partial agonist in pharmacologically relevant concentrations. Metabolic syndrome includes hypertension and insulin resistance as well as lipid profiles; these findings with telmisartan and irbesartan suggest the potential for developing safe and effective drugs that treat aspects of the syndrome.

Recently, a meta-analysis raised concern about an increased risk of MI and death from cardiovascular causes associated with rosiglitazone treatment of T2DM.\textsuperscript{50} The underlying assumption represents a physiological argument: Controlling glycemia by keeping glycated hemoglobin levels as low as possible improves health benefits in T2DM. Since a PPAR\_\gamma agonist activates many of the genes, what is the overall balance of risks and benefits? Although an increasing incidence of CHF was demonstrated in most studies, the cardiovascular safety of rosiglitazone or other TZDs is still not clear.\textsuperscript{51-54}

**CONCLUSION**

It has been demonstrated that all three PPARs modulate lipid metabolism, inflammatory signaling, and insulin sensitivity. Although the precise role of PPAR \_\beta/\delta\ remains to be clarified, PPAR\_\alpha and PPAR\_\gamma ligands are in widespread clinical use for the treatment of dyslipidemia and insulin resistance, respectively. Indeed, more recent studies have shown that PPAR activators improve key surrogate markers of the atherosclerotic process and significantly lower the incidence of cardiovascular events and new diabetes in patients with features of metabolic syndrome.

**REFERENCES**


40. Desvergne BA, Michalik L, Wahl W. Be fit or be sick: peroxisome proliferator-activated receptors are down the road. Mol Endo 2004;18:1321-32.


43. Nesto RW, Bell D, Bonow RO, et al. Thiazolidinedione use, fluid...


質疑聲中 PPARs 在冠心病的角色

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過氧小體增殖活化受體 (PPARs) 屬於核激素受體超級家族的成員，PPARs 主要的生理作用，包括脂質代謝、發炎機制、胰島素敏感性與細胞增殖/分化等。證據顯示，PPARs 與冠心病之間有相當的因果關係：藉由減低循環系發炎反應，PPARs 激活劑能明確地改善動脈粥樣硬化的病程，同時顯著地降低心血管事故。PPARs 激活劑雖有益於血脂異常與胰島素敏感性改善，然而對於罹患鬱血性心衰竭的特定族群病人，則需謹慎使用。儘管 PPARs 激活劑的心血管安全性，受到日益增多的質疑，但無論如何，多瞭解發炎反應、動脈粥樣硬化與 PPARs 之間細胞生理及新陳代謝作用的關聯性，對於冠心病的預防與治療，是有正面意義的。

關鍵詞：過氧小體增殖活化受體 (PPARs)、冠心病、動脈粥樣硬化、纖維酸類 (Fibrates)、唑烷二酮類 (Thiazolidinediones)。

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