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Review

Vascular effects of PPARγ activators – From bench to bedside

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Abstract

Activation of the nuclear transcription factor peroxisome proliferator-activated receptor-gamma (PPARγ) plays an important role in adipogenesis, insulin resistance, and glucose homeostasis. Activators of PPARγ include the anti-diabetic thiazolidinediones (TZDs), drugs that are in clinical use to treat patients with type 2 diabetes mellitus. Experimental as well as clinical data gathered over the last decade suggest that PPARγ activators may exert direct modulatory function in the vasculature in addition to their metabolic effects. PPARγ is expressed in all vascular cells, where its activators exhibit anti-inflammatory and anti-atherogenic properties, suggesting that PPARγ ligands could influence important processes in all phases of atherogenesis. Results from clinical trials demonstrated that TZDs reduce blood levels of inflammatory biomarkers of arteriosclerosis, improve endothelial function, and directly influence lesion morphology and plaque stability, underscoring that PPAR activators may have direct effects in the vasculature in humans. This review will focus on the vascular effects of PPARγ activators and summarize the current knowledge of their modulatory function on atherogenesis and vascular disease.

Keywords: PPARγ; Vascular cells; Arteriosclerosis; Diabetes; Inflammation

Abbreviations: ADMA, asymmetric dimethylarginine; CIMT, carotid artery intima-media thickness; CRP, C-reactive protein; DHA, decosahexanoic acid; DR-1, direct-repeat-1; EC, endothelial cell; EPA, eicosapentanoic acid; ET, endothelin; HDAC3, histone deacetylase; HDL, high density lipoprotein; ICAM-1, intracellular adhesion molecule; IFNγ, interferon gamma; IL, interleukin; iNOS, inducile nitric oxide synthase; IP-10, inducible protein 10; I-TAC, inducible T cell alpha chemoattractant; IVUS, intravascular ultrasound; LDL, low density lipoprotein; LDL-R, low density lipoprotein receptor; MIG, synonyme for the chemokine CXCL-9; MMP, matrix metallo proteinase; NCoR, nuclear receptor corepressor; oxLDL, oxidized low density lipoprotein; PPARα, peroxisome proliferator-activated receptor-alpha; PPARβ, peroxisome proliferator-activated receptor-beta; PPARδ, peroxisome proliferator-activated receptor-delta; PPARγ, peroxisome proliferator-activated receptor-gamma; PPRE, PPAR response element; RXR, retinoic X receptor; SAA, serum amyloid A; sCD40L, solubile CD40 ligand; SMC, smooth muscle cell; SOD, Cu/Zn-super oxide dismutase; SUMOylation, post-translational modification by the smallubiquitin-related modifiers (SUMO); TNFα, tumor necrosis factor alpha; TXA2, thromboxane; TZD, thiazolidinedione; VCAM-1, vascular cell adhesion molecule.

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Contents

1. Introduction . . . 284
2. PPARs . . . 284
2.1. Metabolic effects of PPARγ activators . . . 285
2.2. PPARγ activators and arteriosclerosis . . . 286
2.2.1. Inflammation and atherogenesis . . . 286
2.3. PPARγ and atherogenesis – in vitro data . . . 286
2.3.1. Endothelial dysfunction . . . 286
2.3.2. Fatty streak formation and advanced lesions . . . 287
2.4. PPARγ and atherogenesis – results in animal models . . . 288
2.4.1. Endothelial function . . . 288
2.4.2. Lesion development and thrombus formation . . . 288
2.4.3. Neointima formation after vascular injury . . . 288
2.5. Clinical data . . . 288
2.5.1. Biomarkers . . . 288
2.5.2. Endothelial function . . . 289
2.5.3. Intima-media thickness . . . 289
2.5.4. Restenosis after coronary intervention . . . 289
2.5.5. Plaque stability . . . 290
2.6. Cardiovascular outcome studies . . . 290
2.7. Cardiovascular side effects of TZDs . . . 290
2.7.1. Fluid retention . . . 290
3. Conclusion . . . 291
Acknowledgements . . . 291
References . . . 291

1. Introduction

Over the last decade, activation of the nuclear transcription factor peroxisome proliferator-activated receptor-gamma (PPARγ) has emerged as a promising concept to modulate vascular function and the development of arteriosclerotic lesions. Initially characterized as a regulator of gene expression in various metabolic pathways, it soon became clear that PPARγ might be of interest in arteriosclerosis research, given its presence in vascular cells in vivo and in vitro. In addition, since PPARγ can be activated by the group of clinically used anti-diabetic thiazolidinediones (TZDs), it has been speculated that PPARγ activation might be a novel tool to influence arteriosclerosis in treated patients. The following review will focus on the vascular action of PPARγ activators and elucidate the effects of these PPARγ ligands on vascular processes in vitro and in vivo.

2. PPARs

Peroxisome proliferators-activated receptors (PPARs) are ligand activated transcription factors belonging to the group of nuclear hormone receptors like the vitamin D or steroid receptors [1]. Upon activation PPARs build heterodimers with another nuclear receptor, the retinoic X receptor (RXR), and these heterodimers bind to PPAR response elements (PPRE) in the promoter region of target genes, thus regulating their expression. These PPREs consist of a direct-repeat-1 (DR-1) sequence, meaning two half consensus motifs separated by one spacing base pair (Fig. 1) [2]. Initial work considered these PPREs canonical for each PPAR-regulated gene, but subsequently it became clear that PPREs demonstrate a high variability thus allowing fine-tuned specific modulation of gene expression. In addition, coactivators and corepressors, which are recruited or released by different ligands, are critical determinants of the cellular PPAR response [3–5] PPARs can also repress gene