Mini Review

**PPARβ/δ in the Pathogenesis of Vascular Diseases**

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**Abstract**

Three members of PPAR family (PPARα, PPARγ, and PPARδ) have been widely studied in the past decades. Among three members of PPAR family, PPARα and PPARγ were better investigated and understood than PPARδ in various fields. However, in recent years, more and more studies revealed important roles of PPARδ in the physiology and pathology of many conditions including cardiovascular injury. In this mini review, we will introduce the roles of PPARδ in the pathology of vascular injury.

PPARδ is also termed as PPARβ which is expressed in many tissues [1-4], including vascular smooth muscle cells [5,6]. Recent evidence suggested that PPARβ/δ was involved in lipid metabolism in skeletal muscle [7,8]. In vascular smooth muscle cells [9,10] and cardiovascular tissues [11-13], PPARβ/δ is abundantly expressed. A recent study also suggested that PPARβ/δ contributes to a vasoprotective effect of a widely used antidiabetic drug metformin in obese mice [14]. Thus, PPARβ/δ is becoming an interesting novel target for the treatment of metabolic syndrome and metabolism disorder-associated cardiovascular diseases.

Although a number of studies have shown that PPARα and PPARγ exert anti-inflammatory, anti-proliferative, and antiangiogenic actions in cardiovascular cells, the role of PPARβ/δ in vascular pathophysiology is less understood [15,16]. In the past years, little evidence was reported on the relationship between PPARβ/δ and clinical complications. Moreover, the lack of PPARβ/δ-specific ligands on the market also hampered the research on the roles of PPARβ/δ in the disease conditions. However, in recent years, synthetic ligands of PPARβ/δ have been developed [17]. Furthermore, a novel subtype-selective and target gene-selective PPARβ/δ agonist, naturally occurring dimeric alkaloid picrasidine N (1) from picrasma quassioides was identified from a library consisting of plant extracts and natural compounds using a mammalian one-hybrid assay, which can selectively induce mRNA expression of PPARβ/δ target gene ANGPTL4 but not other PPAR target genes such as ADRP, PDK4, and CPT-1, suggesting its potential as an important compound for elucidating the mechanism of PPARβ/δ-regulated specific genes and the biological functions of PPARβ/δ [18].

In endothelial cells, PPARβ/δ activation inhibits inflammation [19-21], oxidative stress [14,22], and apoptosis [23,24], but stimulates angiogenesis [25]. It is a known concept that atherosclerosis is an inflammatory disease [26-28]. Studies demonstrated that the PPARβ/δ ligands including L-165041, GW0742, and GW501516 alleviated inflammatory responses by reducing the translocation of NF-kB and the subsequent inhibition on VCAM-1, ICAM-1, E-selectin, and MCP-1 [20,29-31]. PPARβ/δ activation induced by PPARβ/δ agonists GW0742 or L165041 in vitro and in vivo restored the endothelial function possibly through preserving the insulin-Akt-eNOS pathway impaired by high glucose [32]. A selective PPARβ/δ ligand GW501516 also inhibited TNF-α-induced leukocyte rolling flux, adhesion, and emigration in a dose-dependent manner [29]. PPARβ/δ agonism can directly induce endothelium-dependent relaxation when used at higher concentrations [33] and can restore the endothelial function in animal models of both type 1 [34] and type 2 [35] diabetes through increasing NO bioavailability and suppressing the generation of NADPH oxidase-derived superoxide anions. However, PPARβ/δ ligand GW0742 on lipid-related vascular injury was reported with diverse results by two independent studies. One report found that PPARβ/δ agonist GW0742 had no obvious effect on the lesion progression in fat- and cholesterol-supple-
mented Ldlr−/− mice, while another one detected a protective role of this agonist with a more aggressive dosing regimen [36,37], suggesting a dose-dependent effect.

Besides above evidence, more researches strongly supported a beneficial effect of PPARβ/δ agonist GW0742 on endothelial function [32,34,38,39]. Fan et al. reported that GW0742 protected endothelial cells against oxidative stress by upregulation of antioxidant enzymes, including superoxide dismutase-1, catalase and thioredoxin reductase [40]. GW0742 also could activate PPARβ/δ to restore the lipid-induced endothelial dysfunction by up-regulation of Carnitine Palmitoyltransferase-1 (CPT-1), thus reducing DAG accumulation and the subsequent PKC-mediated ROS production and eNOS inhibition [41]. In hypertensive rats, GW0742 prevented the development of endothelial dysfunction and hypertension by enhancing endothelial NOS activity, antioxidant genes and the regulators of G protein-coupled signaling proteins (RGS) 5, limiting NADPH oxidase activity, and reducing expressions of proinflammatory and pro-atherogenic genes [42,43]. In diet-induced obesity, treatment with GW0742 significantly prevented hypertension, vascular inflammatory and oxidative status, and endothelial dysfunction [39]. These evidences highly suggested an anti-hypertensive potential of GW0742 in the clinic.

Prostacyclin (PGI2), an endogenous ligand for PPARβ/δ, protected human endothelial cells from H2O2-induced apoptosis by inducing PPARβ/δ binding to 14-3-3ζ promoter, thereby upregulating 14-3-3ζ protein expression, which augmented Bad sequestration and prevented Bad-triggered apoptosis [44]. However, although PPARβ/δ agonists were shown to favorably modulate lipid metabolism and attenuate inflammation, thus reducing the susceptibility to atherosclerosis in both ApoE−/− and LDLR−/− mice [45,46], PPARβ/δ−/− bone marrow transplants attenuated atherosclerotic lesion area in LDLR−/− mice possibly through enhancing the inflammatory suppressor Bel-6 [47], suggesting different actions of PPARβ/δ in different cell types. Additionally, GW501516 and L-165041 enhance the recovery of blood flow in mice after hind limb ischemia and stimulate the proliferation of endothelial progenitor cells by acting on the PI3K/Akt pathway [48], indicating a protective role of PPARβ/δ under ischemic ina injury.

Vascular Smooth Muscle Cell (VSMC) proliferation is the key pathogenetic event of vascular proliferative diseases including atherosclerosis, restenosis, and vein graft failure. Activation of PPARβ/δ by GW501516 inhibited the PDGF-induced proliferation and migration of Human Pulmonary Artery Smooth Muscle Cells (HPASMC) as well as the collagen synthesis, which was associated with decreased expressions of cyclin D1, cyclin D3, CDK2, and CDK4, as well as the increased expressions of cell cycle inhibitory genes of G0S2 and P27Kip1 [49]. Furthermore, PPARβ/δ agonist GW0742 was also effective for the attenuation of neointimal hyperplasia by suppressing VSMC proliferation and accelerating recanalization after arterial injury [5]. Activation of PPARβ/δ by GW0742 or adenovirus delivery of PPARβ/δ (Ad-PPARβ/δ) significantly inhibited hemoglobin-induced VSMC phenotypic switch involved in the pathophysiology of vascular injury after aneurysmal Subarachnoid Hemorrhage (aSAH) [50]. Thus, these solid evidence also suggested a beneficial role of PPARβ/δ in antagonizing VSMC proliferation-associated diseases [13,51-53].

In summary, PPARβ/δ activation chiefly accounts for a protection against endothelial injury and dysfunction, as well as the vascular cell proliferation via diverse mechanisms. Targeting PPARβ/δ might be a promising strategy in treating various vascular diseases including atherosclerosis and high blood pressure.

References


alpha and PPARbeta/delta, but not PPARgamma, modulate the expression of genes involved in cardiac lipid metabolism. Circ Res 92: 518-524.


