Peroxisome Proliferator-Activated Receptors - Alpha in Chronic Inflammation - Mini-Review

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Keywords: Chronic Inflammation; PPAR α ; Metabolic Syndrome

Abstract. The pathogeny of the metabolic syndrome (MetS) is not fully elucidated, but a link between visceral obesity and the increase of the proinflammatory response was proven. Atherosclerosis, perceived as a metabolic complication, draws attention to the peroxisome proliferator-activated receptors- alpha (PPAR α). PPAR α receptors are transcription factors involved in lipid metabolism, inflammation and atheromatosis. Hence, it interferes in the pathogeny of cardiovascular diseases and other chronic diseases too (neurological, psychical, neoplasical). The study of the expression of PPAR α and its modulation on different level may be beneficial in the treatment of metabolic syndrome, intervening in the modulation of another proinflammatory factors.

Introduction

Many chronic diseases have been associated with a persistent, reduced level of pro-inflammatory factors. The discovery of insulin resistance and of type 2 diabetes is closely related to the infiltration of immune cells and chronic inflammation in the adipose tissue. The activated immune cells and chronic inflammation play a major role in cardiovascular diseases, especially in the pathogenesis of atherosclerosis [1, 2]. The peroxisome proliferator-activated receptors - PPARs - are part of the category of nuclear receptors of the protein type, similar to receptors for steroid or thyroid hormones [3-5]. Independent groups of researchers noticed in the sixth decade of the twentieth century an increase in the number of hepatic peroxisomes after administering lipid-lowering drugs (clofibrate). An increase in fatty acid oxidation in hepatic peroxisomes, as well as an increased risk of carcinogenesis in the long-term administration of these drugs was simultaneously observed [5-7]. Later, in the 90s, the nuclear receptor called PPAR (peroxisome proliferator-activated receptor) was identified and cloned in mice and later in humans and amphibians [8, 9].

PPAR - Mechanism of Action

The peroxisome proliferator-activated receptors (PPAR), which comprise three PPAR isoform: PPAR α , PPAR γ and PPAR δ (10), act as transcription factors, belonging to the nuclear receptor superfamily [4-6]. The mechanism of action of PPAR α (Fig. 1) is similar to that of other nuclear receptors (thyroid or that of vitamin D) [7-9, 11]. The activation of the PPAR receptor determines a change in the structure of the receptor complex, followed by changes in the expression of coded genes. PPAR acts as a ligand-activated transcription factor [7, 12].

Figure 1. PPAR - mechanism of action - adapted from Roberts-Thompson S J [7].

After stimulation by the ligands (“Peroxisome Proliferator-PPs”) it unites with the Retinoid Receptor X (RXR), forms a heterodimer and binds to the specific “PPAR response elements (PPREs)” in the promoter of the target genes [7, 8, 12].

PPAR Alpha in Chronic Inflammations and Diseases

Peroxisome Proliferator-Activated Receptors-Alpha (PPAR α) have a significant role in the regulation of lipids and lipoproteins metabolism, chronic inflammation and atherogenesis [14]. PPAR α can be activated by endogenous ligands (fatty acids) and pharmacological agents (such fibrates) (Table 1) [10].

Table 1. PPAR α ligands.

Endogenous	Synthetic
Unsaturated fatty acids	Fibrates (fenofibrate, bezafibrate, clofibrate)
Saturated fatty acids	WY - 14643
VLDL	Etilenoxide
Leucotriene B4	Ftalates
8- Hydroxyeicotetraenoic acid	Perfluorooctanesulfonic acid

Experimental studies [15-17] have shown that the degradation by oxidation of proinflammatory molecules such as LTB₄ (ligand of PPAR α) or arachidonic acid is enhanced after PPAR α stimulation. In animal models, in gene-modified mice PPAR α ^{-/-}, it was detected a prolonged inflammatory response and these data are related to lack of degradations of chemotactic inflammatory eicosanoids LTB₄ [16, 17]. Furthermore, in wild-type mice, but not in PPAR α ^{-/-} mice, treatment with WY-14643, a ligand of PPAR α , suppressed a number of acute phase genes such as fibrinogen, serum amyloid P-component, lipocalin 2, serum amyloid A-2, metallothioneins [15, 17].

In human cells, it was shown that activators of PPAR α inhibit the expression of *vascular cell adhesion molecule-1* (VCAM-1) gene in endothelial cells, while. In human aortic muscle cells, the nuclear receptors decrease interleukin-1 (IL-1) and induce the production of interleukine-6 (IL-6), prostaglandins and the expression of cyclooxygenase-2 (COX-2) gene [17, 20]. *In vivo*, in patients with dyslipidemia and metabolic syndrome, treatment with fibrates decreases the circulating level of systemic inflammations markers, such as high-sensitivity C-reactive protein (hsCRP), IL-6 [15, 17, 19]. This effect is independent of lipoprotein metabolism and does not change insulin sensitivity.

Figure 2. The anti-inflammatory effects of PPAR ligands - adapted from Shirinsky (2011) is mediated via NF-κB through following mechanisms [15, 17]:

- downregulation of the expression of signal transducing receptor components
- induction of Iκ-B expression
- inhibition of nuclear factor κB into nucleus
- decreasing of transcription factor expression levels
- interference with activation of the transcription initiation complex via cofactor interaction.

Recent studies [15, 17, 20]. have shown that the activation of PPARα is followed by the decrease of systemic inflammation by antagonising the Nuclear Factor κB (NF-κB) and the transcriptional activities of protein AP-1, leading to reduction on synthesis of proinflammatory molecules (Fig. 2).

The Implications of the Relation between Lipoprotein Metabolism and the Activation of PPARα *in vivo* in Inflammation and Atherosclerosis

Many studies have so far established the close relation between free fatty acids and PPARα. There is, however, relatively little information on the manner in which lipoprotein changes could be related to PPARα response at cellular level. Interestingly, PPARα actions have been defined using synthetic PPARα agonists. Lipoprotein lipase (LPL), a member of the triacylglycerol lipase family, is an important enzyme in the hydrolysis of triglyceride-rich lipoproteins (VLDL) with the release of high free fatty acid levels. The activity of this enzyme is intense both in the muscle, where it helps to provides free fatty acids for beta-oxidation and energy generation, as well as in the adipose tissue, where the free fatty acids can be stored as reserves. Recent works have shown that the hydrolysis of VLDL can activate PPARα. In macrophage, LPL activation is done by PPARδ (9), while LPL action is mediated by PPARα in the endothelial cell [13, 19]. Not all the lipases which liberate free fatty acids act on PPARα, just LPL. A complex made of LPL, lipoproteins and their lipolytic products is described to influence PPARα responses.

Relation PPAR α - Endothelial Reactivity – Atherosclerosis

The endothelial lesion determines endothelial dysfunction, manifested by altering the role of the highly selective barrier; it alters antithrombotic properties and favors pro-coagulant properties, by affecting the synthesis and secretion of vasoactive substances, growth factors (mitogens), and lipolytic enzymes. PPAR α are active in the human endothelial cell. Moreover, the PPAR activators are involved in the modulation of the endothelial function. For example, PPAR α activators prevent the recruitment and adhesion of leukocytes at the level of the vascular endothelium by lowering VCAM-1 (vascular cell adhesion molecule), ICAM-1 (intercellular adhesion molecule) and decreasing the E-selectin expression. PPAR α activators regulate the adhesion molecules due to the inhibition of NF-kB [13, 21]. The endothelial dysfunction includes alterations in any of the functional roles *in vivo*, including the maintenance of normal vascular tone, the limitation of thrombo-genesis and the protection against leukocytes adhesion [12, 20].

Relation PPAR α – Cardiovascular Diseases

The energy substrates, such as free fatty acids (FFA) and glucose, are involved in generating the energy used for normal cardiac activity. With normal conditions, the ATP is generated by the mitochondrial oxidation of fatty acids (FAO) and glucose, only 2% or less being derived from anaerobic glycolysis [22-24].

PPAR α are a major transcriptional factor of FFA metabolism in the heart [24, 25]. The activation of PPAR α in cardiac muscle by FFA, derivate from triglycerides, regulates genes that encode proteins implicated in FFA and glucose metabolism (Table 2) [25, 26].

Table 2. PPAR α target genes in cardiac muscle -adapted from Lopaschuk [25].

↑ FFA uptake (i.e Fatty acids translocate/ cluster of differentiation)
↑ FFA storage (i.e.Diacylglycerol acyl transferase - DGAT)
↑ FFA β -oxidation (i.e.carnitine palmitoyl transferase - CPT1, medium chain acyl-CoA dehydrogenase - MCAD)
↓ glucose oxidation (ie: pyruvat dehydro-genase Kinase 4 - PDK4)

Experimental studies on mice have shown that the overexpression of PPAR α in cardiomyocytes increases the uptake of FFA and beta-oxidation and decreases the glucose oxidation and cardiac lipids accumulation as a consequence of increasing the expressions of genes that are modulated by these nuclear receptors. On the contrary, the deletion of PPAR α gene (PPAR α -/- null mice), determines decrease of myocardial FFA metabolism, increase of glucose oxidation and hepatic lipid accumulation [25, 26].

The increased expression of PPAR α receptors in myocardium reproduces the metabolic profile in diabetes: increased myocardial fatty acid oxidation, increased rate of β -oxidation and decreased glucose levels [22-24]. In chronic diabetes and hypertensive hearts, studies using proteomics [27] have revealed alterations in expression of hypertrophic, metabolic and apoptotic proteins. In experimental model of chronic diabetes and hypertensive in rats, treatment with PPAR α agonists was followed by an attenuation of cell hypertrophy induced by *high-glucose*- and *angiotensin* –II levels. Furthermore, agonists of PPAR α can be used as anti-hypertrophic agents for patients with hypertension, in prevention of left ventricular hypertrophy, and beyond in prevention of cardiac remodeling [26, 27].

Many studies have shown the decrease of PPAR α expression after exposure to high blood pressure which stimulates cardiac hypertrophy. The activation of PPAR α in hypertensive animal model improves left ventricular hypertrophy and cardiac remodeling. Study of spontaneously hypertensive rats (SHR) has revealed that the treatment with fenofibrate delay ventricular hypertrophy, fibrosis, and decrease oxidative stress in young SHR with cardiac hypertrophy [28]. These effects of PPAR α stimulation are linked to interactions of PPAR α *via* proinflammatory pathways (NF kB, AP-1) (Fig. 2). On the contrary, fenofibrate *enhances* hypertrophy, fibrosis, and oxidative stress in old SHR with cardiac hypertrophy and decreased fatty acids oxidations [28, 29].

In a rat myocardial infarction (MI) model of heart failure, downregulation of PPAR α is the initial response after MI (first 4 weeks) [26, 30]. After 6 weeks, PPAR α expression increases and it returns to normal value 20 weeks after MI [31]. This suggests an overload in post MI metabolic state in other cardiac cells, including fibroblasts [26].

PPAR α expression has anti-inflammatory effects and prevents oxidative damage and treatment with PPAR α agonists may inhibit the inflammation in many cells types in chronic cardiovascular diseases [32].

The Interaction between PPAR α and Inflammation in Skeletal Muscles

The activation of PPAR α receptors at the level of the skeletal muscles is followed by an increase in lipid oxidation and decrease in triglyceride accumulation [20]. The side effects of fibrates on muscle fibers, including myopathy and rhabdomyolysis, have only been observed in rare cases (<1%). The mechanism by which these side effects occur is not very clear, the oxidative stress and the tissue alteration induced by the increase in oxidation in the peroxisomes and mitochondria being held responsible [24, 33]. The systemic inflammation, the immune system and physical activity exist in an interesting and complex correlation. Moderate regular physical exercise reduces systemic inflammation [34, 35]. The mechanism by which the PPAR α agonists determine the occurrence of myopathy is not well documented as of yet, but it appears to be the consequence of oxidative stress. To conclude, the modulation and the return to the normal level of the secretion of muscle-derived cytokines is necessary due to the fact that the high serum levels of myokines are related to the discovery of conditions associated with systemic inflammation, including cancer and other conditions entailed by aging (degenerative nervous disorders, depression, sarcopenia) [35, 36].

The Role of PPAR α in Kidney Diseases

The activity of PPAR α is manifested in the organs with a high level of mitochondrial oxidation: liver, renal cortex, heart, and bowel. PPAR α are numerous in the kidney, at the level of the proximal tubule and in the glomerular mesangial cells [37]. Due to the increased expression in kidney proximal tubules, PPAR α are involved in maintaining energy balance in the kidney [38]. PPAR α are involved in oxidative stress, inflammation, blood pressure regulation and renin-angiotensin-aldosterone system regulation, therefore influencing the pathogenesis and progression of diabetic nephropathy by indirect route, through their effects on serum glucose level and on the lipid metabolism, and by direct route, through their action on the kidney. These findings suggest that PPAR α is a therapeutic target in treating kidney complications from diabetes. The occurrence of glomerular lesions in PPAR α deficiency is followed by an increase in the production of type IV collagen as well as in the expression of *transforming growth factor beta-1* (TGF- β 1) cytokines at this level, suggesting the fact that the activation of PPAR α by its agonists could prevent the expansion of the glomerular matrix and thus the infiltration with the inflammatory cells of the renal glomerulus. The corroboration of many experimental studies resulted in the fact that PPAR α influences inflammatory conditions involving neutrophils and macrophages [38]. In diabetic patients, hyperglycemia, dyslipidemia, endothelial dysfunction, lipotoxicity as well as arterial hypertension contribute to the onset of systemic or local complications, by the activation of pro-inflammatory factors and of renin-angiotensin (RAS), the increase of oxidative stress and of cell apoptosis and the onset of vasculopathies. Furthermore, the onset and development of complications can be attenuated by PPAR α activation [38].

The Relation between PPAR α and Nervous System Disorders

The idea that Alzheimer's disease is a form of the diabetic disease has gained scientific authority almost ten years ago. Many specialists are now entitled to claim that Alzheimer's disease is a type 3 diabetes mellitus [39]. Placing Alzheimer's disease in the category of type 3 diabetes mellitus should not come as a surprise for healthcare professionals, due to the fact that insulin does not only

signal the uptake of glucose in the somatic cells of the body, but also regulates brain glucose uptake. This is very important due to the fact that glucose is known as being the primary energy molecule of the brain, representing the only energy substrate for the brain [40]. Currently, it is well known that, at the level of the central nervous system, the brain in itself produces a certain quantity of insulin, and that various parts of the brain are rich in insulin receptors. Moreover, the fact that the cognitive decline is correlated with obesity and metabolic abnormalities which involve insulin is also well established [40].

The role of PPAR in modulating lipid and carbohydrate metabolism is well established [41]. More recently, the importance of PPAR in modulating inflammation has been proven. For example, PPAR α agonists inhibit the production of pro-inflammatory molecules in the peripheral immune cells as well as in the glial cells of the nervous system. Moreover, PPAR α agonists have proven to be effective in suppressing inflammation in the central nervous system in animal models, being useful in treating neurodegenerative diseases [42]. The degenerative disorders of the nervous system are related to the local pro-inflammatory response (neuro-inflammation). The tumor necrosis factor (TNF α) stimulates the apoptosis of dopaminergic neurons in the substantia nigra, neurons involved in the pathology of Parkinson's disease. The same inflammation-mediated degenerative model, in the context of dysglycemia, is also met in diabetic neuropathy. The pro-inflammatory condition is characterized by the activation of macrophages and monocytes in the lesion caused by various factors. Moreover, an accumulation of pro-inflammatory mediators is produced: TNF- α , IL-6, IL-1 β , alongside COX, generating a pro-inflammatory cascade. PPAR α and fenofibrates reduce pain and inflammation by inhibiting the NF- κ B nuclear factor, followed by the reduction of pro-inflammatory mediators, as well as by the reduced activity of certain enzymes which stimulate angiogenesis (iNOS, chymase and metalloproteinase MMP-9) [43].

The Role of PPAR α Receptors in Diabetic Retinopathy

In type 2 diabetes, the FIELD study shows a reduced need for laser treatment in diabetic retinopathy and a possible diminution in macular edema development after using a hypolipemiant agent (fibrates). These data are particularly important considering the extension of type 2 diabetes worldwide, and the fairly disappointing results of the treatment of diabetic retinopathy [44]. Fibrates (PPAR α agonist) could have anti-inflammatory and anti-oxidative/anti-apoptotic effects, and could furthermore improve vascular reactivity, thus attenuating the progression of diabetic retinopathy and the need for laser treatment. Further studies on oxidative stress and vascular inflammation in patients undergoing treatment with fibrates will define the mechanisms underlying microvascular benefits and could also prove to be useful in devising strategies for developing new drugs [44].

The Role of PPAR α Receptors in Rheumatoid Arthritis

The hypothesis that PPAR α agonists (fibrates) could be used as anti-inflammatory agents, in treating both atherosclerosis, as well as patients with chronic inflammatory diseases (rheumatoid polyarthritis) -the fibrates inducing a decrease in TNF- α , IL-1 β , IFN- γ - has been proposed [17, 45]. Experimental studies *in vivo* and *in vitro* have shown that PPAR α agonists inhibit bone resorption and reduce inflammation, the degradation of the synovial fluid, and the destruction of the articular cartilage. Consequently, PPAR α ligands reduce pain, diminish joint tumefaction and determine a decrease in inflammatory markers at systemic level [46].

The “Antineoplastic” Effect of PPAR α

The role of PPAR α receptors in carcinogenesis is the subject of many discussions in the literature [5, 47, 48]. The administration of PPAR α agonists in the liver of animals has been observed to determine an increase in cell proliferation (through a PPAR α -mediated mechanism) [49], while the same effect of stimulation of the appearance of tumor formations has not been observed in human patients undergoing treatment with fibrates for dyslipidemia (50). Thus, the existence of significant

interspecies differences at the level of the liver between the effects of PPAR α stimulation in humans and animals has been suggested [50]. As regards colorectal cancer, PPAR α stimulation has been shown to inhibit the proliferation of tumor cell lines in the colon and to reduce the formation of adenomatous polyps on an animal experimental model of familial adenomatosis [51]. Moreover, in certain populations, an inverse association between the exposure to perfluorooctanoic acid (PPAR α agonist) and the prevalence of colorectal cancer has been reported [52]. The epidemiological studies have demonstrated the existence of a causal connection between chronic inflammation (occurring in the context of a microbial infection or of autoimmune diseases) and the appearance of tumor formation [52, 53]. The role of PPAR α in carcinogenesis is the result of the inhibition of the nuclear factor NF- κ B, ceasing the induction of the carcinogenic factors mentioned [54]. The antineoplastic action of PPAR α receptors is observed only in carcinogenesis with inflammatory determinism, absent in tumors in which inflammation is not involved.

PPAR α in Cutaneous Inflammation

Nuclear receptors are transcription factors that control the activity of the enzymes involved in carbohydrate and lipid metabolism and are consequently involved in regulating energy and lipid homeostasis in the skin. PPAR α agonists control the proliferation/differentiation of keratinocytes and regulate the inflammation in the tegument [55], through the inhibiting action of the nuclear factor NF κ B, followed by the inhibition of the TSLP (*thymic stromal lymphopoietin*) synthesis. Currently, TSLP protein is considered to be essential in the evolution of chronic diseases characterized by allergic inflammation, including atopic dermatitis, allergic rhinitis, and bronchial asthma [56]. The topical application of PPAR α agonists produces anti-inflammatory effects in skin disorders such as contact dermatitis, atopic dermatitis, solar erythema, consecutively improving the evolution of these disorders, irrespective of the application of topical steroids [57]. Moreover, alterations in genes involved in inflammation (MCP-1) and lipid metabolism (LXR α , PPAR α) have been observed in patients with psoriasis, thus identifying a connection between psoriasis and cardio-metabolic diseases. Consequently, an improvement in the prognosis of patients with psoriasis is expected after undergoing treatment with PPAR α antagonists [58].

The Role of PPAR α Receptors in Chronic Respiratory Diseases

Allergic bronchial asthma is characterized by bronchial hyper reactivity, eosinophilia, being associated with elevated serum of IgE immunoglobulin. On animal models of bronchial asthma [59], PPAR α nuclear receptors have been shown to reduce bronchial hyper reactivity and the release of proinflammatory cytokines, simultaneously with the decrease in levels of circulating IgE. Moreover, the decrease of eosinophil chemotaxis *in vitro* and the inhibition of antigen-induced cell cytotoxicity have also been observed. PPAR α agonists could be said to constitute a new class of drugs in inflammatory or allergic reactions through the influence which they exert on the effector and regulatory cells involved in the body's immune response. The role of PPAR α has been studied in pulmonary fibrosis [60]. In the absence of the PPAR α receptor, experimental studies carried out on animals treated with bleomycin have highlighted an increased expression of TNF α and IL-1 β , an intensified apoptosis in interstitial cells, exacerbated inflammatory phenomena and pulmonary fibrosis and, consecutively, a decreased survival rate. In the same study, the treatment with PPAR α antagonists (WY-14643) has improved the survival rate, concomitant with the reduction of the TNF α cytokine and the bleomycin-induced fibrosis. It appears that the intervention mechanism of the PPAR α receptors in COPD is related to the inhibition of NF- κ B and AP-1 pro-inflammatory factors [61].

Conclusions

The chronic diseases have been associated with a persistent, reduced level of pro-inflammatory factors. The discovery of insulin resistance and of type 2 diabetes is closely related to the infiltration of immune cells and chronic inflammation in the adipose tissue. In cardiovascular diseases, the activated immune cells and chronic inflammation play a major role, especially in the pathogenesis of atherosclerosis. Furthermore, tumor onset and progression is stimulated by the systemic increase in pro-inflammatory cytokines.

Atherosclerosis, perceived as a metabolic complication, draws attention to PPAR α receptors, transcription factors involved in lipid metabolism, inflammation and atheromatosis.

The action of PPAR α is manifested especially in energy-consuming tissues and organs, skeletal muscles, heart, liver. PPAR α activation determines a decrease in serum triglyceride and HDL-c levels and shields against an atherogenic lipid profile, by modulating the pro-inflammatory status and reducing insulin resistance.

Conflicts of Interest

The authors declare no conflicts of interest.

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