

The peroxisome proliferator-activated receptor: A family of nuclear receptors role in various diseases

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ABSTRACT

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors of nuclear hormone receptor superfamily comprising of the following three subtypes: PPAR α , PPAR γ , and PPAR β/δ . Activation of PPAR- α reduces triglyceride level and is involved in regulation of energy homeostasis. Activation of PPAR- γ causes insulin sensitization and enhances glucose metabolism, whereas activation of PPAR- β/δ enhances fatty acids metabolism. Thus, PPAR family of nuclear receptors plays a major regulatory role in energy homeostasis and metabolic function. The present review critically analyzes the protective and detrimental effect of PPAR agonists in dyslipidemia, diabetes, adipocyte differentiation, inflammation, cancer, lung diseases, neurodegenerative disorders, fertility or reproduction, pain, and obesity.

Key words: Diabetes, dyslipidemia, peroxisome proliferator-activated receptors

INTRODUCTION

Peroxisomes are subcellular organelles found in most plant and animal cells that perform diverse metabolic functions including H₂O₂-based respiration, β -oxidation of fatty acids (FAs), and cholesterol metabolism. Peroxisome proliferator-activated receptors (PPARs) proteins belong to superfamily of phylogenetically related protein termed nuclear hormone factor.^[1] PPARs were identified in rodents in 1990 and these belong to a nuclear hormone receptor superfamily containing 48 members. But, these agents are associated with no proliferation in the human beings. Structurally, PPARs are similar to steroid or thyroid hormone receptor and are stimulated in response to small lipophilic ligands. In rodents, a large class of structurally related chemicals including herbicides, industrial solvents, and hypolipidemic drugs lead to significant increase in the number and size of

peroxisomes in the liver and may cause liver hypertrophy, liver hyperplasia, hepatocarcinogenesis, and transcription of genes encoding proximal enzymes. PPARs mainly exist in three subtypes; α , β/δ , and γ , each of which mediates the physiological actions of a large variety of FAs and FA-derived molecules. Activated PPARs are also capable of transcriptional repression through DNA-independent protein-protein interactions with other transcription factors such as NF κ B signal activators and transducers of transcription STAT-1 and AP-1 signaling.^[2]

STRUCTURE

The PPARs possess the canonical domain structure common to other nuclear receptor family members, including the amino-terminal AF-1 trans activation domain, followed by a DNA-binding domain, and a dimerization and ligand-binding domain with a ligand-dependent trans activation function AF-2 located at the carboxy-terminal region.^[3]

ISOFORMS OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS

PPARs are transcription factors that belong to the Superfamily of nuclear receptors. Other members of this family include retinoic acid, estrogen, thyroid, vitamin D, and glucocorticoid receptors, and several other proteins involved in xenobiotic metabolism PPARs act on DNA response elements as heterodimers with the retinoid X receptor (RXR). Their natural activating ligands are lipid-derived substrates. The family of PPARs is represented

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by the following three members: PPAR- α , PPAR- δ , and PPAR- γ . They play an essential role in energy metabolism; however, they differ in the spectrum of their activity—PPAR- γ regulates energy storage, whereas PPAR- α is expressed predominantly in the liver, and to a lesser extent, in muscle, in the heart, and in bone and PPAR- δ present ubiquitously expressed in whole body regulate energy expenditure; expression of PPAR- γ in endothelial cells, vascular smooth muscle cells. PPAR- γ is further subdivided in four isoforms.^[4]

- γ 1 - expressed in virtually all tissues, including heart, muscle, colon, kidney, pancreas, and spleen.
- γ 2 - expressed mainly in adipose tissue (30 amino acids longer).
- γ 3 - expressed in macrophages, large intestine, and white adipose tissue.
- γ 4 - expressed in endothelial cells.

MECHANISM OF ACTION OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS

PPARs function as heterodimer in association with co-activator complex that binds to DNA sequence termed peroxisome proliferators response elements (PPREs) present in promoter of target genes which leads to transactivation and transrepression of various genes.^[1] In the absence of the ligands, these heterodimers are associated with co-repressor complex which block gene transcription. Some of the agonists of various PPARs receptors are given in Balakumar P.2007.^[5] Like PPARs, RXR exists as three distinct isoforms: RXR- α , β , and γ , all of which are activated by the endogenous agonist 9-cis retinoic acid.^[6] No specific roles have yet been elaborated for these different isoforms within the PPAR: RXR complex. However, synthetic RXR agonists (rexiniids) can activate the complex and thereby obtain antidiabetic outcomes similar to those seen with PPAR agonists in mouse models of type 2 diabetes.^[7] The LBD facilitates the heterodimerization of PPARs with RXR and the resultant heterodimer subsequently binds to PPRE with the recruitment of cofactors.^[1]

Peroxisome Proliferator-Activated Receptor-Alpha

PPAR- α expression is relatively high in hepatocytes, enterocytes, vascular and immune cell types such as monocytes/macrophages, endothelial cells, smooth muscle cells, lymphocytes, non-neuronal cells like microglia and astroglia.^[8,9] In the liver, it plays a crucial role in FA oxidation, which provides energy for peripheral tissues, elevated mitochondrial and peroxisomal FAs β -oxidation rates, such as liver, heart muscle, kidney, skeletal muscle, retina, and brown adipose tissues, and have a potential role in oxidant/antioxidant pathway.^[10,11] PPAR- α ligands can be both synthetic or endogenous FAs and FA-derived compounds are natural ligands for PPAR- α .^[12] Over the last several decades, there have been a number of studies on the physiology, pharmacology, and functional genomics

of PPAR- α . *In vivo* and *In vitro* studies demonstrate that PPAR- α plays a central role in lipid and lipoprotein metabolism, and thereby decreases dyslipidemia associated with metabolic syndrome.^[13-15] In the fasting state, PPAR- α is activated by adipose-derived FAs, thereby enhancing the generation of ketone bodies through FA oxidation in liver and peripheral blood mononuclear cells.^[16]

Peroxisome Proliferator-Activated Receptor- γ

Thiazolidinediones (TZDs) are the most widely studied PPAR- γ ligands. Troglitazone was the first drug approved for this use, followed by rosiglitazone and pioglitazone. The mechanism of action of TZDs was not known until 1995, when Lehmann reported that TZDs were high affinity ligands, for Peroxisome proliferator-activated receptor gamma (PPAR- γ) is a ligand-dependent transcription factor and a member of the nuclear receptor superfamily. Acting as sensors of hormones, vitamins, endogenous metabolites, and xenobiotic compounds, the nuclear receptors control the expression of a very large number of genes. PPAR- γ has been known for some time to regulate adipocyte differentiation, FA storage and glucose metabolism, and is a target of antidiabetic drugs.^[17] PPAR- γ agonist improves insulin resistance by opposing the effect of TNF- α in adipocytes.^[18] PPAR- γ enhances the expression of a number of genes encoding proteins involved in glucose and lipid metabolism.^[19] Various modulator of PPAR- γ agonist is shown in Balakumar P. 2007.^[5]

Peroxisome Proliferator-Activated Receptor- β/δ

PPAR- δ/β is expressed in skeletal muscle, adipocytes, macrophages, lungs, brain, and skin. It promotes FA metabolism and suppresses macrophage derived inflammation.^[20] Newly synthesized compounds such as GW501516, GW610742, and GW0742X are shown to have high selectivity to PPAR δ .^[21] PPAR- δ has been noted to reduce the expression of inflammatory mediators and adhesion molecules, suggesting their potential role in attenuating atherogenesis.^[22] Few studies have shown that PPAR- δ ligands have the potential to inhibit cardiac hypertrophy due to their inhibitory activity on NF κ B, a transcription factor which produces inflammatory cytokines. Various modulator of PPAR- β/δ agonist is shown in Balakumar P. 2007.^[5]

PHARMACOLOGICAL POTENTIALS

Obesity

This special issue begins with a review of key observations in human subjects harboring genetic variations in PPAR γ and a thorough overview of the metabolic effects of PPARs in genetically modified animal models. The interaction of PPARs with uncoupling proteins regulating energy expenditure is reviewed as recent developments with RXR agonists. A closely related topic addressed is the molecular and physiological functions of PPAR co-activators and co-

repressors in relationship to adipocyte energy metabolism. In addition, the potential advantages of selective PPAR agonists are discussed. The intriguing possibility that PPARs may mediate effects of caloric restriction on longevity is also considered. Finally, evidence that PPARs may be interesting therapeutic targets to modulate obesity-induced inflammation is reviewed.^[23] PPAR- α ligands such as fibrates have been used for the treatment of dyslipidemia due to their ability to lower plasma triglyceride levels and elevate HDL cholesterol levels. PPAR- α activators have been shown to regulate obesity in rodents by both increasing hepatic FA oxidation and decreasing the levels of circulating triglycerides responsible for adipose cell hypertrophy and hyperplasia. However, these effects of PPAR- α on obesity and lipid metabolism may be exerted with sexual dimorphism and seem to be influenced by estrogen. Estrogen inhibits the actions of PPAR α on obesity and lipid metabolism through its effects on PPAR α -dependent regulation of target genes.^[24]

Inflammation

Inflammatory conditions are mainly characterized by activation of macrophages and monocytes at the injury site which subsequently increase the release of proinflammatory mediators like TNF- α , IL-6, and IL-1 β which in turn stimulates the production of COX products. PPAR- α and fenofibrate reduces pain and inflammation and further inhibits the release of several pro-inflammatory and pro-angiogenic enzymes (e.g., iNOS, chymase, and metalloproteinase MMP-9), and mediators (e.g., NO and TNF- α).^[25,26] More recently, PPAR- γ has been recognized as playing a fundamentally important role in the immune response through its ability to inhibit the expression of inflammatory cytokines and to direct the differentiation of immune cells toward anti-inflammatory phenotypes. A feature of PPAR- γ is the structural diversity of its ligands, which encompass endogenous metabolites, dietary compounds, and synthetic drugs. The high and increasing incidence of inflammatory and allergic disease, coupled with encouraging results from recent clinical trials, suggest that natural PPAR- γ agonists found in foods may be beneficial to human health by acting as anti-inflammatory molecules. PPAR- γ is therefore not only a target of the pharmaceutical industry, but also of great potential interest to the food industry, since it is activated by several natural dietary constituents.^[27]

Adipocyte Differentiation

Adipogenesis refers to the process of differentiation of the pre-adipocyte precursor cells into adipocytes that are capable of lipid filling, as well as the expression of hormones and cytokines. PPAR- γ regulates the expression of numerous genes involved in lipid metabolism, including aP2, PPCK, acyl-CoA synthase, and LPL.^[28] PPAR- γ has also been shown to control expression of FATP-1 and CD36, both involved in lipid uptake into adipocytes. These genes have all been

shown to possess PPRES within their regulatory regions. PPAR- γ is mainly involved in the process of cell growth arrest, followed by progression into the fully differentiated adipocyte phenotype.^[29] PPAR- γ and PPAR- β have both been implicated in molecular signaling that mediates adipocyte differentiation, whereas the role of PPAR- γ is well established in this process. The specific role of PPAR- γ is less certain. It has been reported that in the presence of standard differentiation medium, PPAR- γ is required for maximal adipocyte differentiation as PPAR- γ null adipocytes exhibit significantly impaired lipid accumulation and expression of adipose differentiate marker mRNAs.^[30]

Anti-Cancer Effect

Peroxisome proliferator-activated receptor (PPAR) is a Double-Edged Sword in Cancer Therapy. PPAR-alpha stimulation appears to inhibit proliferation of human colon cancer cell lines and to reduce poly formation in the mouse model of familial adenomatous. PPAR- β (also referred to as PPAR δ) in epithelial homeostasis have been described including the regulation of keratinocyte differentiation, apoptosis and cell proliferation, inflammation, and wound healing.^[31] PPAR- γ not only controls the expression of genes involved in differentiations but also negatively regulates the cell cycle.^[32] TZDs induce the tumor suppressor gene PTEN, which also contributes to their antiproliferative activity. PPAR- γ activation inhibits the proliferation of malignant cells, including those derived from liposarcoma, breast adenocarcinoma,^[33] prostate carcinoma, colorectal carcinoma, non-small-cell lung carcinoma, pancreatic carcinoma, bladder cancer, gastric carcinoma, and glial tumors of the brain.^[34]

Neurodegenerative Disorder

PPAR- γ agonists have also shown efficacy in Parkinson disease, Alzheimer disease, brain injury, and ALS. They act on microglial cells and inhibit the microglial cells activation. The role of PPARs in modulating lipid and glucose metabolism is well established. More recently, PPARs have been demonstrated to modulate inflammation. For example, PPAR agonists inhibit the production of proinflammatory molecules by peripheral immune cells as well as resident glial cells. Furthermore, PPAR receptor agonists have proven effective in suppressing the development of animal models of CNS inflammatory and neurodegenerative disorders.^[35] *In vivo* oral administration of the PPAR- γ agonist pioglitazone reduced glial activation and the accumulation of A β -positive plaques in the hippocampus and cortex. Various neurodegenerative diseases are associated with electron transport chain enzyme activity reductions and increased mitochondrial-generated oxidative stress.^[36]

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS IN LUNG PATHOPHYSIOLOGY AND DISEASE

This special issue contains a comprehensive group of reviews

and original investigations illustrating the pivotal role of PPARs in the regulation of multiple cellular events in lung pathogenesis. Such events include lung morphogenesis, the inhibition of the release of inflammatory mediators from lung immune and stromal/parenchymal cells *In vitro*, and dampening both inflammation and damage in animal models of acute lung injury (ALI), ischemia-reperfusion injury, and allergic airways inflammation. Also covered are lung tissue remodeling and the fibro-proliferation that occur in chronic airways disease, ALI, pulmonary vascular disease, and pulmonary fibrosis. In addition, activation of key macrophage antimicrobial and reparative responses within the airspace is addressed, also data illuminating the central role of PPAR- γ in the regulation of critical aspects of lung tumor initiation, progression, and metastasis are summarized.^[23]

Peroxisome Proliferator-Activated Receptors and Diabetes

The three PPAR subtypes, alpha, gamma, and delta, have distinct expression patterns and regulate glucose homeostasis based on the need of a specific tissue. Although PPAR alpha potentiates FA catabolism in the liver and is the molecular target of the lipid-lowering fibrates, PPAR-gamma is essential for adipocyte differentiation and hypertrophy, and mediates the activity of the insulin-sensitizing TZDs. PPAR-delta may be important in regulating body weight and lipid metabolism in fat tissues.^[37]

Peroxisome Proliferator-Activated Receptors and Pain

Synthetic PPAR- α receptor agonists produce broad-spectrum analgesia in a dose-dependent manner.^[38] It was recently reported that supraspinal (intracerebroventricular) administration of PPAR- α ligands (perfluorooctanoic acid) reduced peripheral edema and/or inflammatory hyperalgesia^[25,39,40] and that intrathecal administration of PPAR γ ligands, rosiglitazone and 15d-PGJ₂, reduced behavioral signs of neuropathic pain.^[41] It was recently reported that systemic administration of pioglitazone reduced behavioral signs of neuropathic pain, raising the possibility that this FDA-approved drug can be effective as an analgesic agent.^[42]

CONCLUSION

PPAR are involved in various independent and DNA-dependent molecular and enzymatic pathways in adipose tissue, liver, and skeletal muscles. These pathways are affected in disease condition and cause the metabolic energy imbalance. Thus, intervention of PPAR can provide therapeutic targets for plethora of diseases such as dyslipidemia, diabetes, obesity, inflammation, neurodegenerative disorder, and cancer. Finally, evidence that PPARs may be interesting therapeutic targets to modulate obesity-induced inflammation is reviewed. Since its inception, a little over three years ago, PPAR Research has become a vibrant forum showcasing global effort in

this ever-expanding field of research. Then, there is a series of reviews focusing on the potentially beneficial effects of PPAR agonists on the various diseases. Examining the contents of these special issues reveals an intense interest in exploring new physiological roles of the PPARs and in the identification of new and improved PPAR agonist drugs.

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