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PEROXISOME PROLIFERATOR- ACTIVATED RECEPTORS FAMILY OVERVIEW

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ABSTRACT

Nuclear receptor superfamily comprised of many receptors such as retinoic acid, thyroid hormone, steroid, and Peroxisome Proliferator- Activated Receptors (PPARs). The binding of Peroxisome Proliferator- Activated Receptor with its ligand and then with retinoid X receptor will lead to form a heterodimer complex, which has a transcription factors activity on many target PPAR responsive genes. The PPAR exist as three forms alpha (α), delta (δ) and gamma (γ) that have important roles in expression of gene that regulate many biological processes such as metabolism and deposition of lipid, metabolism of glucose, and reaction of inflammation.

KEY WORDS: Peroxisome Proliferator- Activated Receptors (PPARs), vasoprotective, insulin sensitivity, inflammation.

INTRODUCTION

Peroxisome Proliferator-Activated Receptors (PPARs) which detected in 1990 are transcriptional factors that activated when binding with their specific ligands and can control some physiological processes inside the human body. There are three kinds of PPARs family, PPAR alpha (α), delta (δ), and gamma (γ) which have various tissue disposition and various genes encoding on different chromosomes.[1,2]

PPARα is highly distributed in (liver, kidneys, heart, muscles) at which the catabolism of fatty acid is high. Whereas PPAR γ is mostly existed in adipose tissue and mammary gland. Additionally, PPARα and γ founded in many cells such as epithelial cells, smooth muscle cells, monocytes, / macrophage and in the lipid core of the atherosclerotic lesions. Actually, the expression of PPAR δ is universal; it explicated in many organs and tissues such as heart, adipose tissue, brain, intestine, muscles, spleen, lungs, suprarenal gland.[1, 3-5]

The ligands that bound with activated PPARs are differing from one type of PPAR to another. For alpha form of PPAR, leukotriene B4 and fatty acid (FA) such as linoleic acid are the most common ligands. While the prostacyclin and fatty acids are the most effective ligands for PPAR delta. Concededly, the prostaglandin-J2 (PG-J2) is the most convenient ligand for the PPAR gamma as noted in Fig.1.[5-7]

Many factors can influence on the regulation of PPARs expression. Inflammatory cytokines such as tumor necrosis factor - alpha (TNF- α), interleukin one (IL- 1), interleukin six (IL-6) can lower PPARs activation in rat adipocyte. Whereas other factors like fibrates drug derivatives or glitazones derivatives, (oral anti-diabetic drugs) can elevate PPARs activation. As well, drugs like Non-steroidal anti-inflammatory (indomethacin and ibuprofen) can enhance PPAR α and γ activation.[8,9]

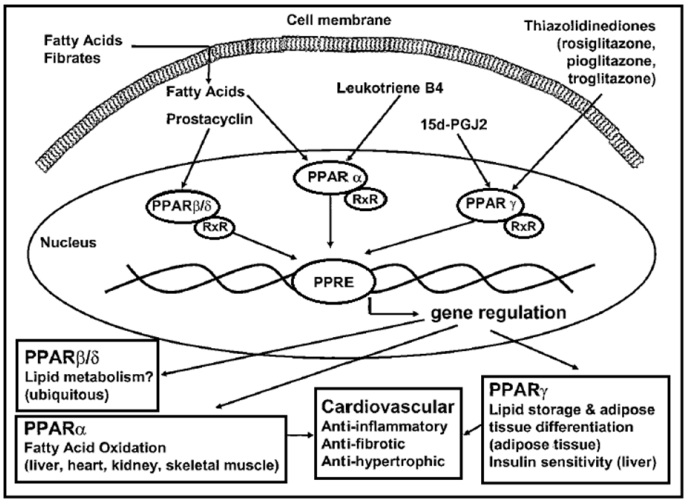

Fig. 1: Expression pathway of Peroxisome Proliferator-Activated Receptors (PPARs) family.[retinoid X receptor (RXR), PPAR response elements (PPRE)].[7]

OUTLINE OF PPAR α

PPARα has an essential role in the metabolism of lipid, this occurs by many ways like hindering the expression of many enzymes that control fatty acid re-esterification

with glycerol, lessen the expression of apoprotein C III, an inhibitor of lipoprotein lipase (LPL), leading to enhance the activity of lipoprotein lipase (LPL) and thereafter increase triglyceride hydrolyses into three fatty acid and glycerol. As well, PPARα intensifies the expression of the fatty acid transporter protein (FATP) which promotes more free fatty acids (FFA) transit into the liver as shown in Fig. 2.[1, 10]

Fibrates drugs like (fenofibrate, clofibrate) are used for the treatment of dyslipidemia and these drugs caused lowering in the blood level of triglyceride and elevating in the blood level of high density lipoprotein cholesterol (HDL-C) with or without impacting on the blood level of low density lipoprotein cholesterol (LDL-C).[11,12]

Additionally, fenofibrate may has an anti-inflammatory activity which illustrated by decreasing the blood levels of interleukin six (IL-6), fibrinogen, and C-reactive protein (CRP) in patients with hyperlipidemia likewise reducing the blood levels of tumor necrosis factor alpha (TNF-α) and intereferon- gamma (IFN-γ) in patients with type IIb hyperlipoproteinemia.[11]

Many studies founded that PPARα agonist have a role in attenuating the complication of the atherosclerotic lesions. Its decreases the activation of cytokine that interfere with the activation of other adhesion molecules such as vascular cell-adhesion molecule-one (VCAM-1),intercellular adhesion molecule-one (ICAM-1) which activated by TNF-a and endothelin-one, a vasoconstrictor peptide that after its activation by thrombin can increases smooth muscle cells proliferation.[11-15]

PPAR α inhibits the process of inflammation by inhibiting the important transcription factors for these process; nuclear factor –kappa B (NF-$_k$B) and activator protein-one (AP-1).[10,16,17] Reactive oxygen species (ROS) and free radical can activate Mitogen Activated Protein Kinase (MAPK) and Nuclear Factor - kappa B (NF-$_k$B) signaling pathways and caused cell apoptosis.[18]

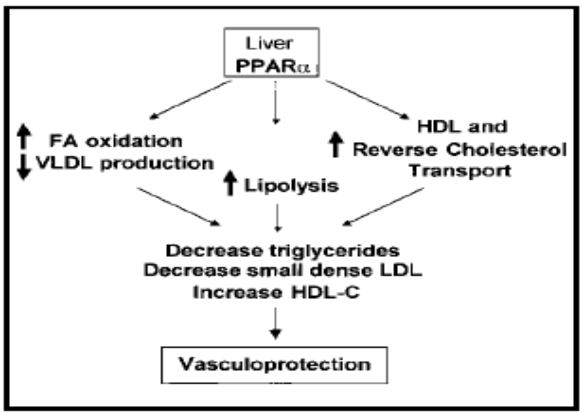

Fig. 2a: Metabolic effects of PPARα, PPAR β /δ, PPAR γ. [10]

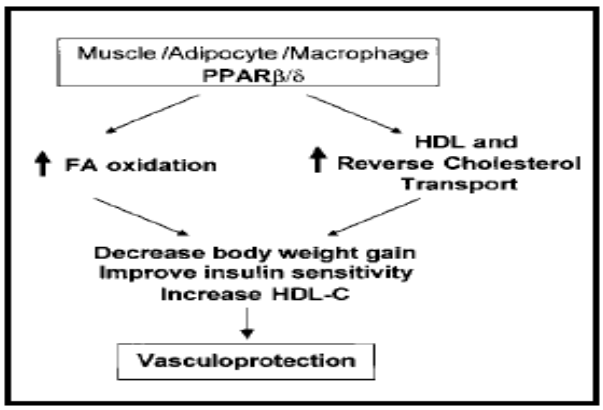

Fig. 2b: Metabolic effects of PPARα, PPAR β /δ, PPAR γ. [10]

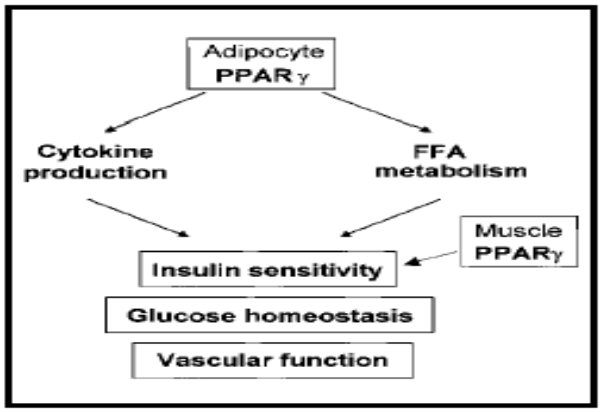

Fig. 2c: Metabolic effects of PPARα, PPAR β /δ, PPAR γ. [10]

OUTLINE OF PPAR β/δ

PPAR β/δ may has a role in the discrimination of adipose tissues at earlier stage by its effect on the expression of some enzyme and by activation of PPAR γ which has a predominant role in the discrimination of adipocyte at final stage.[5] As illustrated in Fig. 2, the PPAR β/δ increase oxidation of fatty acid in muscle and adipose tissue and resulting by many sequences in a vasoprotective effect.[10] Many researches illustrated that PPAR β/δ may mediate the expression of uncoupling protein (UCP-2) which is control the formation of reactive oxygen species (ROS) in the macrophage, lung, and intestine at where ROS formation is vital.[19]

OUTLINE OF PPAR γ

Confirmedly, PPAR γ has a central role in adjusting the discrimination of adipocytes and preserving the performance of developed adipocyte. It organizes the expression of the genes comprise in the metabolism of lipid such as acyl-co synthase, LPL, ATP, or adipocyte protein 2, Fig. 2.[20]

Many researches founded that thiazolidinedione treatments (troglitazone, pioglitazone, rosiglitazone) are synthetic ligands of PPAR γ, can activate PPAR γ, and therapeutically used for amelioration of insulin resistance. Activation of PPAR γ increases the

discrimination of adipocytes and increases the loading of fatty acids in adipose tissues this will cause weight gain and will lead to decrease the levels of lipids in the circulation making the muscles more sensitive to insulin.[21, 22]

The Troglitazone approved 1997, but retracted from market for safety problem (drug-induced liver failure) in 2000 .While Pioglitazone and Rosiglitazone accepted by FDA in 1999. Many safety issues have been illustrated with the use of PPAR-γ agonists medication such as fluid accumulation which leads to weight gain, edema and cardiac hypertrophy observed with the short period treatment (within 1-3 months). There is no data for direct cardio toxicity with the used of approved PPAR-γ agonists, but these drugs can induce heart failure and death with the long period treatment (> 6 months in animals and man).[23]

Inflammatory process can effect by PPARγ activation that lead to change the expression of many cytokines, receptors and adhesion molecules that existed in T cells, monocyte / macrophages, vascular smooth muscle cells and endothelial cells.[24] Virtually, some effect of PPAR γ ligand appeared to be oppositely to that of PPARγ agonist effect. In activated macrophages, activated PPARγ ligand prevented the activation of inducible nitric oxide synthase (iNOS) and gelatinase B, while PPAR γ agonists enhanced the production of NO from endothelial cells and increased NOS in vascular smooth muscle cells.[25, 26]

In endothelial cells, PPAR γ agonists can diminish the release of some pro-inflammatory cytokines such as TNF-α, IL-1b, IL-6, and monocyte chemotactic protein-one (MCP-1)[27] , a protein, which has an important role in triggering the inflammatory process of atherosclerosis.[28] As well, it can inhibit the release of IFN-γ, which is release after activation of T lymphocytes.[29]

As seen in Fig.3, the weakening of phosphatidylinositol 3-kinase (PI3K) /Akt pathway concomitant with the intensifying of the growth factor–stimulated mitogen-activated protein kinase (MAPK) pathway are the important properties of insulin resistance in vascular cells. The role of PPAR γ in vascular cells is deactivation of MAPK pathway, which activated by insulin, thereafter attenuates atherogenesis. While in skeletal muscle, PPARγ improves the PI3K / Akt pathway, which activated by insulin, thereafter ameliorates the metabolism of glucose and insulin sensitivity.[10]

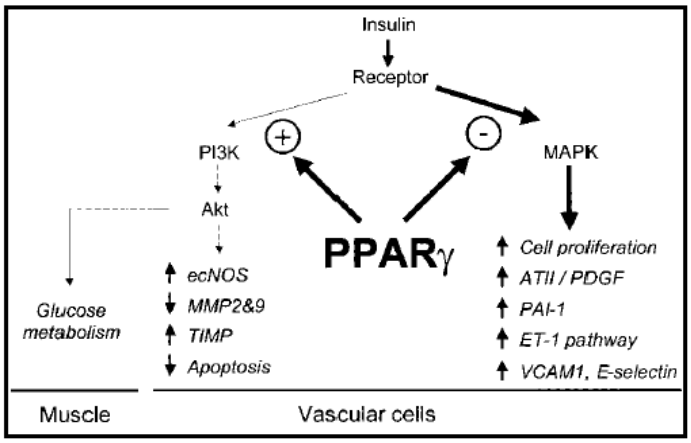

Fig. 3: Molecular pathways of PPAR γ in vascular cells and muscle and its role in improving insulin sensitivity.[10]

CONCLUSION

The foxing on the physiological and molecular activities of the PPARs and then on the pharmacological activity of the synthetic PPAR agonists and PPAR antagonists is important. Because it may give an important medical information for the treatment of many diseases that related to the cardiovascular, adipose tissue, skin or pancreas (insulin release) and for the evaluation of their safety at different durations of treatments.

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