Peroxisome Proliferator- Activated Receptors (PPARs): A Review on Effects on Glucose Metabolism, Energy Homeostasis and Cardiovascular System

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ABSTRACT

Background: Molecular biology and human medical genetics have introduced several novel biomarkers giving control over vital body functions, of these are transcriptional factors known as peroxisome proliferator activated- receptors "PPARs". The aim of this review is to shed light on available online information and published research works about these biomarkers. The current review will try to display those findings mainly related to energy homeostasis, glucose metabolism, insulin sensitivity and some cardiovascular interactions.

Methods: a literature review about peroxisome proliferator activated- receptors and their roles in controlling some vital body functions has been made and recorded. Search covered published investigations and research works over the last three decades as accessible.

Results: peroxisome proliferator activated- receptors have crucial roles in controlling a big deal of vital biological processes in humans.

Conclusions: Peroxisome proliferator-activated receptors are important transcriptional factors with clinical impacts. Literature shows a wide spectrum of effects and interactions through affecting many genes involved in processes of glucose homeostasis, energy balance, and peripheral insulin sensitization in addition to interfering with processes of inflammation, angiogenesis, blood pressure control and atherosclerosis.

Keywords: Peroxisome proliferator activated- receptors, PPARs, glucose homeostasis, energy balance.

مضعفات البيروكسوسومات-والمستقبلات المحفزة (PPARs): مراجعة عامة حول التأثيرات على أيض الجلوكوز و استقلاب الطاقة ونظام القلب والأوعية الدموية

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الخلاصة

الخلفية: في البيولوجيا الجزيئية وعلم الوراثة الطبية البشرية ، تم تمييز العديد من المؤشرات الحيوية الجديدة ذات الصلة بوظائف الجسم الحيوية المختلفة. من بين هذه العوامل الجينية المعروفة بروتينات (مضعفات البيروكسوسومات-والمستقبلات المحفزة). الهدف من هذه المراجعة المنهجية هو إلقاء الضوء على المعلومات المتاحة حول هذه المركبات الهامة. تركز هذه المراجعة على عرض النتائج المتعلقة بشكل أساسي بدور البروتينات محور الدراسة باستقلاب الطاقة وأيض الجلوكوز وحساسية الأنسولين وبعض متغيرات وظائف جهاز الدوران و القلب و الأوعية الدموية.

الطرق: تم إجراء وتسجيل مراجعة واسعة للمقالات المنشورة حول PPARs وأدوارها في التحكم في بعض وظائف الجسم الحيوية. تعاملت الدراسة مع البحوث المنشورة على مدى العقود الثلاثة الماضية.

النتائج: ان للمستقبلات PPARs أدوارا هامة في السيطرة على قدر كبير من العمليات البيولوجية البشرية.

الاستنتاجات: مستقبلات البيروكسيسوم المفعلة هي عوامل نسخ حيوية ذات تأثيرات سريرية هامة. أظهرت الدراسات المتعددة مجموعة واسعة من التأثيرات والتفاعلات لهذه البروتينات و ذلك من خلال التأثير على العديد من الجينات المشاركة في عمليات الجسم الحيوية بما في ذلك تلك المتعلقة بأيض الجلوكوز وتوازن الطاقة وتحسس الأنسولين المحيطي بالإضافة إلى دورها في عمليات الالتهاب وتكوين الأوعية الدموية والتحكم في ضغط الدم وتصلب الشرايين.

INTRODUCTION

In Molecular Biology and Human Medical Genetics, there are many novel biomarkers with important roles in controlling vital body functions. Among these is a group of transcriptional regulatory proteins known as "Peroxisome proliferator activated- receptors or PPARs" which were identified since early 1990s. Peroxisome proliferator- activated receptors (PPARs) are transcription factors of a nuclear hormone receptor superfamily activated by binding with certain ligands [1]. These proteins heterodimerize with retinoid X receptor (RXR) and bind to a co-repression complex of certain proteins. The heterodimers bind to a part of a gene area known as "peroxisome proliferator response elements (PPREs)" through their DNA binding domain (DBD) [2,3].

Ligands binding to PPARs (through ligand binding domain (LBD)) would soon result in some conformational changes in PPAR/ RXR heterodimers, promoting an immediate dissociation of co-repressor complex (that blocks the gene activation process) and recruitment of some contradictory "co-activation protein complex"- a process resulting in activating the expression of the target gene (for example those genes participating in energy homeostasis, lipid metabolism and many other metabolic processes [4,5], Figure (1). In fact, there are three well identified kinds of PPARs; PPAR α, PPARδ (or β) and PPAR γ. The DBD of them are almost about 80% identical, with only about 65% of identity concerning their LBD. The aim of the current review is to highlight these biomarkers and analyze their biological actions. The current review will focus on PPARs effects on energy homeostasis, glucose metabolism, insulin sensitivity and some cardiovascular interactions.
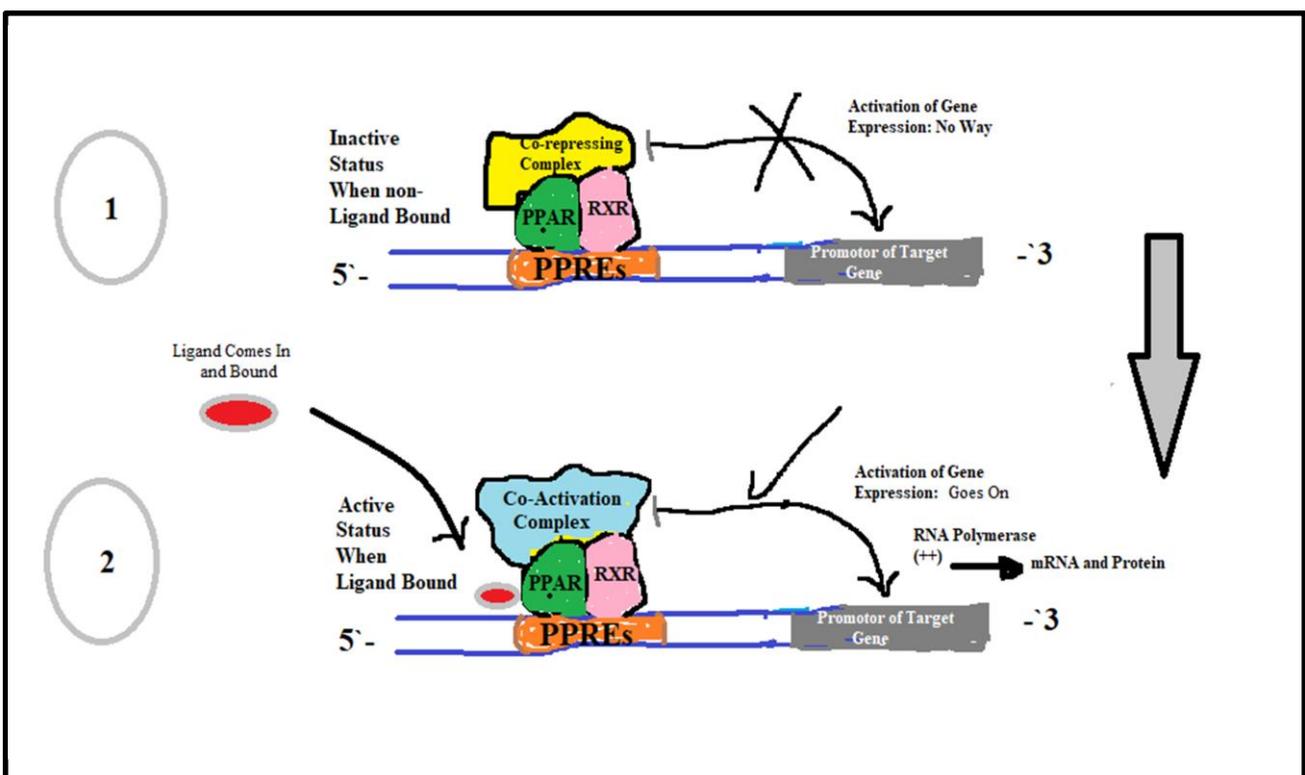

Figure (1). The PPAR/RXR heterodimer binds (PPRE) in a target gene. In status 1; the heterodimer is associated with a "co-repression protein complex" that renders the gene expression inactive. In status 2 (when a specific ligand comes in and firmly attaches the PPAR/RXR heterodimer), the co-repression complex is dismissed and a "co-activation protein complex" attaches opening the way for an active gene expression process to start up. RNA polymerase II gets stimulated & mRNA is produced .Figure's idea is adopted from [3].

METHODS

Sixty- seven full- text papers of different types (case- control, cohort, review and meta-analyses) about peroxisome- proliferator activated receptors published in the period from 1991 through 2022 were downloaded and reviewed based on their relevance to the subject of this study. A thorough search was performed across PubMed, ResearchGate, Google Scholar and other available online sources using the keywords of peroxisome proliferator activated-receptors, PPARs, insulin sensitivity, glucose and energy homeostasis, cardiovascular system and other related words.

RESULTS AND DISCUSSION
Types of PPARs
1.PPAR α:

It is the first ever identified and cloned (in 1990). It is widely expressed in skeletal muscles, kidneys, liver, heart and small intestine of humans. In these tissues, it is known to enhance the expression of those genes related to fatty acids oxidation and lipoprotein assembly [6]. PPARα can be activated by many stimulants [7] such as:
Eicosanoids,
Unsaturated fatty acids, and
Hypolipidemic drug class-fibrates.

Activated PPAR α stimulates lipoprotein lipase expression, reduces the expression of apolipoprotein C-III, stimulates the cellular fatty acids uptake and enhances the expression of ApoA-I and II [8-10].

Fibrates are effective drugs in dyslipidemia treatment as they reduce plasma triglycerides and increase HDL-cholesterol levels [11]. Studies have shed light on the effect of PPARα activation on liver and muscle sensitivity to insulin. Although some researchers noticed that the use of gemfibrozil (a PPARα agonist) did not impact the gluco-regulatory actions of insulin among non-diabetic people with mild dyslipidemia [12], others, showed that using the same drug may significantly impose insulin sensitivity in diabetic patients with hypertriglyceridemia [13].

An organized study on experimental animals has investigated if PPARα activation can improve insulin sensitivity in rats having insulin poor responsiveness and compared these effects with PPAR-γ activation. A group of rats being on high fat diet over 3 week rats were randomly selected to be either treated or untreated with [WY14643]- a specific PPARα agonist- or [pioglitazone] a specific PPAR-γ agonist. Conclusions have been made that PPARα agonists- like agonists of PPAR γ -can noticeably manipulate the muscle cells lipid supply and improve the muscle insulin actions [14].

Studies have revealed that although being useful dyslipidemic agents in humans, PPARα agonists may produce some carcinogenicity in rodents' livers. However, the good news was that most human epidemiological studies did not detect similar findings on humans [10,15,16].These effects in animals are possibly attributable to the up-regulating effects on expression levels of peroxisomal enzymes that liberate hydrogen peroxide (H_2O_2), like acyl CoA oxidase (ACO) where the intracellular increments of H_2O_2 levels can produce DNA damages as already established [17,18].

2.PPAR δ (also called PPAR-β):

Is a member of the PPARs superfamily as well with its functions being somewhat unclear until some few years ago [19]. Oliver et al. have used some PPAR δ agonists as (GW501516) and (HS00098) to understand its metabolic actions on a group of insulin- resistant obese monkeys (Rhesus). At the end of the experiment, blood total cholesterol, triglyceride, glucose, HDL-cholesterol, LDL- cholesterol, and insulin were measured. There was a noticeable body weight gain in the GW501516 and HS00098 treated animal in comparison to the control group. There was a significant elevation in HDL-c and apo-A1 levels [20].

It has been shown that the overexpression of PPAR β (or δ) in the skeletal muscles of some transgenic mice led to increase in the proportion of oxidative myofibers and elevations of oxidative enzymes in addition to a considerable reduction of total body fats [21]. Fredenrich and Grimaldi reached a conclusion that the actions of PPAR δ involve re-distribution of non- esterified fatty acids (NEFA) flux: meaning that there will be an increased oxidative capacity which draws the NEFA flux towards the muscle to be preferentially oxidized, rather than be stored in adipocytes. This would favor a reduction in adipocytes size and increased release of "adiponectin" – an anti- atherosclerosis and insulin- sensitizing cytokine- together with promotion of lipolysis [22].

3.PPAR γ (PPAR-gamma):

This nuclear hormone receptor is a well- known vital and powerful transcriptional factor in the regulation of adipocytes differentiation and the transcription of many genes responsible for insulin signaling and lipogenesis [23]. In humans, the PPAR γ gene is located in chromosome 3 (3p25) extending over a genomic segment of about 150 thousands bases pairs. It consists of 9 exons (A1, A2, B and 1-6), from which two distinct isoforms of mRNA and proteins are derived. These are PPAR γ1 and PPAR γ2. This takes place by the use of separate promoters and exons. The PPAR γ1

mRNA specie is composed of exons A1, A2 and 1-6 and is translated from [P1] promoter; while PPAR γ2 mRNA is a combination of exons B and 1-6 and is on the contrary translated from [P2] promoter. In fact, PPAR γ2 protein is 28 amino acids longer [24].

The PPAR γ2 is mainly expressed in adipose tissues, while PPAR γ1 is widely expressed in tissues like colon, macrophages, cardiac muscles, adipose tissue, skeletal muscles, bone tissue, kidneys, liver and others [25-27]. A study has already proved that PPAR γ is crucial for long-term survival and homeostasis of adipocytes and that its deficiency would result in substantial adipocytes losses with compensatory hypertrophies [28].

In muscles, the PPAR γ protein plays a vital role in controlling normal glucose homeostasis while liver PPAR γ is implicated in managing the systemic glucose levels and lipid metabolism [29,30]. Many PPAR γ agonists have been seen to improve insulin sensitivity in both insulin resistant animals and humans [31,32].

Vital Metabolic Effects of PPARs:

A. PPARs in Relation to Glucose and Energy Homeostasis:

Intracellular, a cascade of phosphorylations follow insulin binding to its "tyrosine kinase" receptors including tyrosine phosphorylation of insulin receptor substrate (IRS) and the resultant activation of phosphatidylinositol-3-kinase (PI 3-kinase). This phosphorylation series enhances many intracellular processes including glucose uptake, lipid metabolism and cell differentiation. Studies concluded that activation of PPARγ would significantly influence insulin signaling by interfering at a few steps in the phosphorylation cascade. The final result will be an in improvement of the overall body insulin sensitivity, enhanced lipid metabolism and increased glucose peripheral disposal [33].

The thiazolidinediones were the first group of pharmaceutical products used in clinical practices to deal with the dilemma of insulin resistance both in patients with T2DM and those syndromes of insulin resistance (obesity, metabolic syndrome and PCO syndrome). Insulin resistance is known to stimulate more insulin secretion as a compensatory regulation mechanism. However, frank clinical diabetes will be evident when insulin secretion cannot longer overcome the outstanding insulin resistance. Treatment using different PPAR-gamma agonists "TZDs" has been so effective in attenuating the insulin- stimulated disposal of glucose and the insulin- suppressed hepatic gluconeogenesis. Initial clinical trials on TZDs demonstrated their proficiency in lowering both fasting and postprandial glucose levels in addition to lowering serum insulin levels [34-36].

In metabolic syndrome, TZDs improve insulin sensitivity in addition to reducing circulating triglycerides, increasing HDL-cholesterol, lowering blood pressure and significantly reducing blood levels of Plasminogen Activator Inhibitor 1 (PAI-1) [37].

Although TZDs act through binding PPARγ and improve insulin sensitivity, there is still a controversy regarding the exact mechanism of action. The adipocytes play an important role in the pathogenesis of insulin resistance and DM. Obesity is associated with hypertrophy in adipose tissues leading to insulin resistance with the overproduction of FFAs, leptin and TNF- α [38, 39].

Among TZDs in practice, pioglitazone, troglitazone, ciglitazone, englitazone, rosiglitazone, KRP- 297 and netoglitazone (that possesses PPARα/γ agonistics) were commonly used. However pioglitazone (ACTOS) and rosiglitazone (AVANDIA) are the most widely used. Reports were made that Troglitazone produces hepatotoxicity and was thus already withdrawn from markets. In addition, the KRP- 297 has also been discontinued from clinical practice due to its carcinogenic effects [40].

In fact, it is not only PPAR γ that plays a role in improving glucose metabolism and pancreatic functions, but PPARα also that plays important roles in glucose homeostasis. Activation of PPARα has led to up-regulating glycerol-3-phosphate dehydrogenase, glycerol kinase and glycerol transport proteins, the actions that would finally promote the glucose-stimulated insulin secretion in the pancreas [41, 42].

The role of PPAR-delta in glucose metabolism is not clear enough. However, it seems to be that PPAR δ ligands may enhance insulin sensitivity through promoting FFAs oxidation mainly in skeletal muscles and adipose tissues. PPAR δ activation inhibits pyruvate dehydrogenase complex by targeting the gene [Pdk4] in addition to activating the hexose monophosphate shunt (HMP pathway) [43-45].

Different scientists have investigated whether there is any link between some common SNPs or other genetic variations of PPARs-mainly the common (Pro12Ala) variant of PPARG2 with T2DM. Results are conflicting and researchers like (Al-Naemi AH and Ahmed AJ, 2018) did not prove such association [46]. However, Sarhangi et al., Sanghera et al. and Ho et al. revealed significant associations [47-49].

B. PPAR and Effects on Cardiovascular System:

PPARs, besides being key regulators in adipocytes differentiation, lipid and glucose metabolism, also play an essential role in the control over inflammation and the pathophysiology of many cardiovascular events (like hypertension, atherosclerosis, congestive heart failure and cardiac hypertrophy) [50]. All PPARs have been found to be widely expressed in the endothelial lining cells of blood vessels. However, it is only the PPAR γ and PPARα that are expressed in the vascular smooth muscle fibers. The way how PPARα and PPAR-δ affect the vasculature appears to be multi-fascinated. The mechanisms may include regulating endothelial cell functions, smooth muscle cells apoptosis and anti-inflammatory properties of these proteins [51-53].

In the last two decades, roles of PPARγ and α in the modulation of blood pressure have emerged, the issue that expanded the therapeutic range of PPARα and PPARγ synthetic ligands. PPARγ-regulated gene expression has been found to play a critical role in the development of systemic hypertension through controlling the rennin angiotensin aldosterone axis. However, the role of PPARα in controlling this axis is still unclear [54].

A study has demonstrated that telmisartan - a partial PPARγ agonist may inhibit the activity of the vascular enzyme (ACE) leading to a reduction in the oxidative stress and endothelial dysfunction [55].

Venegas-Pont and their co-workers have used "Roziglitazone"- a known PPARγ agonist in the management of hypertension in some animal models having systemic lupus erythematosus (SLE). They have concluded that rosiglitazone can reduce blood pressure and shows some reno-protective actions [56].

The thiazolidinediones (TZDs), have been shown to reduce blood pressure in diabetic subjects side by side with improving insulin sensitivity and glucose homeostasis. Some studies revealed that TZDs may produce their antihypertensive actions in diabetic patients through working on the vascular endothelial cell lining and through suppressing the VSMC L-type Ca^{2+}-channels [57, 58].

In terms of understanding the pathogenesis of some cardiac problems, the concept of cardiac "metabolic dysfunction" has emerged. This concept was supported by several workers who revealed that the mitochondrial DNA disorders are significantly impacting cardiac health and cause problems like cardiomyopathies and cardiac conduction defects [59,60]. PPARs have been of value in this aspect because cardiac metabolism is transcriptionally regulated by PPARs. The PPARα expression is somewhat high in those organs having an elevated capacity for FFAs oxidation and the heart is among them certainly [61]. The cardiac-high levels of the co-activator [PGC-1α] play an important role in managing heart metabolism as well. It seems to work through several transcriptional proteins in the cardiac muscles- mainly PPARα- to balance the heart metabolic demands with energy metabolism in cardiac muscles [62].

A group of researchers have generated mice deficient in [PGC-1α] and tested the role of this co-activator in maintaining normal cardiac energy metabolic capacity through conducting mitochondrial function experiments on saponin-permeabilized myocardial fibers. It was revealed that these mice would have lower cardiac power, decreased FFAs oxidation capacity and promoted reliance on glucose oxidation. These findings support the conclusions already made by others that PGC-1 α is essential in maintaining normal cardiac metabolism [63]. As mentioned above, all PPARs are expressed in the vascular endothelium. In general, both PPAR γ and PPAR α in the vascular endothelial cells show anti-proliferative, anti-inflammatory and anti-angiogenic actions [64].

PPAR δ liganding was thought to stimulate apoptosis in a study done on lung cancer growths [65]. However another study suggested that PPAR δ activation by one of its ligands can induce proliferation of cultured endothelial cells [66]. It was demonstrated that using the PPAR-γ agonist [GW501516] would support the human endothelial cell proliferation and morphogenesis- in vitro and in vivo. It also induces the expression of adipose differentiation-related protein, and the [VEGF] [67].

CONCLUSIONS

Peroxisome proliferator-activated receptors (of all types) are vital transcription factors that belong to a superfamily of nuclear hormones receptors. Literature shows their wide range of effects and interactions with a big deal of genes related to several vital body functions including those of glucose homeostasis, energy balance, peripheral insulin sensitivity in addition to those related to inflammation and angiogenesis. Ligands to these biomarkers are therapeutic agents in clinical practices over a long period of time.

Conflict of Interest: This review paper has no any conflicts of interest.

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