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Review

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PPARα and PPARγ as main regulators of fatty acid metabolism

PPARα i PPARγ jako główne czynniki regulujące przemiany kwasów tłuszczowych

Mirosław Kucharski, Urszula Kaczor

[1]Department of Animal Biotechnology, University of Agriculture in Krakow

Summary

PPARα and PPARγ nuclear receptors are transcription factors responsible for regulating the expression of lipid, carbohydrate and protein metabolism genes. PPAR receptors are distinguished by their capability to efficiently bind a number of synthetic or natural ligands. Genes encoding PPARα and PPARγ are expressed in many tissues and organs, including in the adipose tissue. Changes in the expression of these genes are dependent on many factors, such as the impact of other genes and fatty acids. PPARα and PPARγ proteins are - due to their neuroprotective and anti-inflammatory properties, as well as the key role they play in lipid metabolism – important for human health. This is especially true with regards to neurological disorders such as Alzheimer's disease or those accompanied by a metabolic syndrome – type II diabetes, insulin resistance, obesity and hypertension.

Keywords: **fatty acid • metabolism • nuclear receptor • PPARα • PPARγ**

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Author's address: dr inz Mirosław Kucharski, ul. Redzina 1B, 30-248 Krakow; e-mail: miroslaw.kucharski@urk.edu.pl

Abbreviations: **CLA** – conjugated linoleic acid; **CRP** – C-reactive protein; **DHA** – docosahexaenoic acid; **DNA** – deoxyribonucleic acid; **EPA** – eicosapentaenoic acid; **FABP4** – fatty acid binding protein 4; **FFA** – free fatty acids; **GPR40** – G protein-coupled receptor 40; **Il** – interleukin; **LBD** – ligand binding domain; **MAPK** – mitogen-activated protein kinases; **NF-**κB – nuclear factor kappa B; **PPAR** – peroxisome proliferator-activated receptor; **PPRE** – peroxisome proliferator response element; **PUFA** – polyunsaturated fatty acids; ***RXR*** – retinoid X receptor; **SCD** – stearoyl-CoA desaturase; **TNF-α** – tumor necrosis factor alpha; **UCP1** – uncoupling protein 1; **UFA** – unsaturated fatty acids; **WAT** – white adipose tissue

INTRODUCTION

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors of the steroid receptor superfamily responsible for regulating the transcription of genes involved in metabolic or inflammatory processes pathways [76]. Three PPAR isotypes - PPARα, PPARβ/δ and PPARγ - expressed in different tissues have been distinguished [42]. PPARγ, like all nuclear receptors, is of a modular structure, and contains three major functional domains. The N-terminal region domain is responsible for the transcription activation function, while the C-terminus region domain is an LBD (ligand binding domain); between them is a conservative DNA-binding domain (deoxyribonucleic acid) [76].

Peroxisome proliferator-activated receptors alpha and gamma – genes

PPAR family proteins are encoded by genes of the same name: *PPARα, PPARβ/δ,* and *PPARγ*. In the case of *PPARγ*, two isoforms of the gene, $PPAR\gamma_1$ and $PPAR\gamma_2$ have been identified. They are generated by an alternative action of the same gene promoter, resulting in four mRNA variants: *PPARγ1, PPARγ2, PPARγ3, PPARγ4.* All four mRNA variants encode the $PPAR\gamma_1$ protein. *PPARγ2* encodes $PPAR\gamma_2$ protein that is identical to $PPAR\gamma_1$ but has an additional 30aa sequence at the N-terminus [17].

PPARα is present in the heart, liver, kidneys, muscles and brown adipose tissue. The $PPAR\gamma_1$ gene is primarily expressed in white and brown adipose tissue, as well as the large and small intestines, in immune system cells, muscle tissue, pancreas, liver and kidneys. In contrast, $PPAR\gamma_2$ expression is observed mainly in adipose tissue [42].

PPARα gene in humans consists of 13 exons and is located on chromosome 22. In mice, it is located on chromosome 15 and consists of 16 exons, while porcine *PPARα* gene has 8 exons and is located on chromosome 5. In chickens, *PPARα* is located on chromosome 1 and is made of 13 exons. In ruminants, the gene encoding peroxisome proliferator-activated receptors alpha is found on chromosome 3 for sheep, while in cattle it is located on chromosome 5. It is formed by, respectively, 9 (sheep) and 11 (cattle) exons.

In humans, *PPARγ* contains 11 exons and is located on chromosome 3. In mice, the gene consists of 15 exons and is located on chromosome 6. In cattle, the gene is located on chromosome 22 and is made of 7 exons. In the case of sheep, this gene - formed by 17 exons -is located on chromosome 19. Porcine *PPARγ* consists of 13 exons and is found on chromosome 13, while in chickens it contains 9 exons and is located on chromosome 12.

The main factors influencing the expression of genes encoding PPAR proteins are fatty acids. It was found that the presence of CLA (conjugated linoleic acid) acid in the diet of mice with metabolic syndrome led to an increase in PPARγ gene expression [73]. Also, the action of docosahexaenoic acid (DHA) stimulates increased expression level of this gene [56]. In contrast, long-term action of eicosapentaenoic acid (EPA) leads to a significant decrease in *PPARγ* expression in rat adipocytes [40]. Introduction of n-3 PUFA (polyunsaturated fatty acids) into the diet of ob/ob (leptin-deficient) mice results in increased expression of the gene encoding peroxisome proliferator-activated receptors gamma [20]. However, studies demonstrating the negative effect of n-3 PUFA on the expression of this gene are available as well. Such an outcome was observed in adult obese patients on a 12-week diet rich in DHA, who experienced a significant decrease in *PPARγ* expression [44]. The use of n-3 PUFA-enriched goat meat in mice nutrition resulted in a significant increase in expression of the analyzed gene [16]. In addition, also differentiated diet of mother ewes during pregnancy induces changes in the expression of *PPARα* and -γ in the fetus, causing changes in lipid metabolism [9]. The demonstrated significant increase in *PPARγ* gene expression in skeletal muscle of fetuses of obese ewes can serve as confirmation of increased adipogenesis in muscle tissue [86].

Identification of polymorphisms of genes encoding peroxisome proliferator-activated receptors alpha and gamma in humans is relevant in studies focusing primarily on the nervous system, obesity, metabolic syndrome or, to an extent, cardiovascular diseases [49, 60, 71, 74]. In livestock, genetic variability in the *PPARα, -γ* is chiefly related to the quality of meat, due to the role these genes play in protein coding in adipogenesis and fatty tissue storage processes [36, 38].

Peroxisome proliferator-activated receptors alpha and gamma – proteins

In animal cells, PPAR proteins interact with nuclear proteins acting as co-activators or co-compressors [53]. Ligand-unbound PPAR, by interacting with a co-repressor, remains deacetylated and inhibits gene expression [55]. Ligand-bound PPAR after binding to the ligand forms a heterodimer with the retinoid X receptor (RXR) and a co-activator with intrinsic histone acetylase activity (for example PPARγ 1-α or EP300 co-activator). It then joins - in the gene promoter region - the peroxisome proliferator response element (PPRE) gene sequence, regulating its transcription.

PPAR genes change their conformation depending on the bound ligand. In the case of binding an agonist, they may interact with the co-activator. After binding a PPAR antagonist, such an interaction is impossible [55]. Wang et al. [72] indicated yet another mechanism characteristic for PPARγ. According to them, a PPARγ ligand, such as for example rosiglitazone (a drug used to treat diabetes), is capable of activating the G protein-coupled receptor 40 (GPR40). This leads to phosphorylation of p38 MAPK (mitogen-activated protein kinases), which

sequentially phosphorylates and activates PPARγ 1-α and EP300 co-activators, and causes conformational changes of PPARγ [72].

What distinguishes PPAR proteins from other nuclear receptors is their capability to bind many different ligands [29, 63]. Because of the size of the ligand binding site, PPAR – especially PPARγ – can bind a variety of natural or synthetic lipophilic acids, in particular fatty acids and their derivatives – eicosanoids [33].

Natural PPAR receptor agonists, i.e. molecules that bind to the receptor and stimulate initiation of a cellular reaction, include mainly fatty acids, such as α-linolenic (C18:3 n-3) and linoleic (C18:2 n-6) acids, which are essential for proper functioning of the body. These acids cannot be synthesized endogenously, and thus must be supplied with food. They serve as substrates for the desaturation and/or elongation reactions that result in long-chain PUFAs. It is also known that linoleic acid, a member of the omega-6 group, is one of PPARγ ligands [77, 81]. A metabolite of this acid, 13-hydroxyoctadecadiene acid is also a PPARγ receptor agonist; it inhibits cellular signaling of inflammation and lowers secretion of Il-8 (interleukin) in colon epithelial cells [2, 11]. Vangaveti et al. [70] observed proapoptotic action of 13-hydroxyoctadecadiene acid in monocytes, while linoleic acid bound to the PPARγ receptor did not exhibit such properties [70]. In contrast, anti-inflammatory effect of lipoic acid, belonging to the omega-3 PUFA group, consists in the activation of PPARγ receptors, which leads to a decrease in Il-1, -6, and TNF-α (tumor necrosis factor alpha) synthesis [84].

Another group of PPAR ligands are eicosanoids, organic compounds that are products of oxidation of UFAs (unsaturated fatty acids) such as arachidonic acid, linoleic acid and α-linoleic acid released from the phospholipid membrane. This group of compounds includes prostaglandins, prostacyclins, leukotrienes and lipoxins [42]. Previously mentioned rosiglitazone is a synthetic eicosanoid demonstrating neuroprotective action - in rodent brain after stroke it induces 5-lipoxygenase and lipoxin A4, which has an anti-inflammatory effect [67]. Neuroprotectine D1, another PPAR ligand, also has demonstrated neuroprotective effects, and has been shown to have beneficial effects in mice with Alzheimer's disease [85]. Beneficial effects of D1 protectine have also been shown in other tissues. White et al. [75] demonstrated a significant increase in expression of *PPARγ* and *RXR* (retinoid X receptor) genes within the fatty tissue of fat-1 transgenic mice as a result of a fat-rich diet, which proves that D1 protectine may affect the adipogenesis process through PPARγ receptors [75].

By activating PPARα, conjugated linoleic acid prevents inflammation and neoplasm in the colon. Similar anti-inflammatory effects have been observed in macrophages and small and large intestine epithelium under CLA supplementation [8, 22, 30, 80, 82]. Also vaccenic acid acts via both the PPARγ and PPARα. It has been shown that this acid, present in butter, meat or milk in human diet, inhibits cardiomyocyte hypertrophy [73]. Another anti-inflammatory ligand acting via PPARγ are nitrated fatty acids generated in non-enzymatic reactions of fatty acids and nitric oxide [50].

Peroxisome proliferator-activated receptors alpha and gamma – functions

PPAR receptors have several important functions in the body. In the brain, they are involved in the differentiation of nerve cells, reduction of oxidative stress and improvement of memory. In skeletal muscles they are responsible for, *inter alia*, increased fatty acid oxidation, and, in the small intestine, for the reduction of inflammatory conditions. In fatty tissue, PPARs are responsible for the differentiation of adipocytes and triglyceride synthesis, and they stimulate insulin sensitivity [42].

ROLE OF PPAR IN LIPID METABOLISM

Polyunsaturated omega-3 fatty acids are among natural ligands bound by peroxisome proliferator-activated receptors [43]. PPARα activation by n-3 PUFA in the liver leads to strengthened expression of lipid metabolizing genes, which in turn leads to the intensification of fat catabolic processes [18].

With *PPARα* knock-down in mice, it was shown that the lack of functional protein encoded by this gene results in the impairment of cellular metabolism under fasting conditions. Under the experimental nutritional conditions, this led to the accumulation of lipids in the liver and heart, hypoglycaemia, hypothermia, ketonuria and elevated levels of free fatty acids, and eventually to the death of the individual [34]. In contrast, wild phenotype mice adapted to starvation conditions by activating increased expression of the *PPARα* gene in the liver and heart, resulting in, as was found, increased FFA (free fatty acids) uptake and increased oxidation [27]. The gene also influences changes in the expression of cytochrome P450 4A11, leading to observed stimulation of β-oxidation and ω-hydroxylation [59, 64].

The paradox of PPARα action consists in increasing the intensity of fatty acid oxidation, while simultaneously engaging receptors in changes of expression of genes encoding enzymes responsible for lipogenesis, including SCD (stearoyl-CoA desaturase) [13, 47]. PPARα is also responsible for the regulation of the gluconeogenesis process in the liver by controlling the activity of enzymes involved in these processes [59, 78]. It has been shown that CLA acid, a strong PPARα agonist contained in tomato juice, is responsible for a decrease in triglyceride levels in the liver of obese diabetic mice [28].

PPARγ ligands, for example glitazones used as components of insulin sensitizers, are supplied to patients suffering from type 2 diabetes. Bogacka et al. [10] observed

that the administration of pioglitazone to patients with type 2 diabetes results in a change in the expression of genes involved in carbohydrate and lipid metabolism in the subcutaneous adipose tissue [10]. However, glitazones differ for the normal functioning of the body, as a number of side effects have a negative impact on the function of the liver and heart [12, 65].

In contrast, PPARγ stimulates the formation and differentiation of new adipocytes [18, 69] due to increased transcriptional activity of the gene resulting from it ligand-binding DHA acid [48]. The presence of rosiglitazone leads to the activation of the peroxisome proliferator-activated receptors gamma, which in the case of the WAT (white adipose tissue) precursor cells leads to the intensified creation of mitochondria and increased expression of the *UCP1* (uncoupling protein 1) gene [57]. Studies conducted on mice with *PPARγ* knockdown have shown that it is essential for adipogenesis as well as fat tissue formation [6, 31, 61]. In mature adipocytes, ligand binding and PPARγ activation lead to the increased expression of genes involved in lipid and glucose metabolism, and strengthen fatty acid oxidation and increased insulin sensitivity. In addition, PPARγ stimulates adipocytokin production [18]. Acting via PPARγ receptors, EPA stimulates the synthesis and secretion of adiponectin in adipose tissue cells [56]. The increase in adiponectin secretion, as a result of PPARγ, together with increased insulin sensitivity and reduced inflammation, is observed with omega-3 fatty acid supplementation in mice with impaired leptin synthesis [20]. Neschen et al. [51] observed that the increased production of adiponectin as a result of introduction of PUFA n-3 contained in fish oil into the diet is directly dependent on PPARγ and not on PPARα [51].

Role of PPAR in inflammation processes

PPARα receptors exhibit anti-inflammatory action by inhibiting the expression of genes encoding acute phase proteins, such as CRP (C-reactive protein) and fibrinogen. They contribute to reducing the risk of liver inflammation, cardiovascular disease and cancer [19].

PPARγ and nuclear factor kappa B (NF-κB) are also involved in the regulation of inflammatory processes: NF-κB controls the expression of a number of genes involved in the inflammatory process, and PPARγ interacts directly with NF-κB [23]. Chen et al. [14], by administrating hepatitis-inducing concanavalin (a mitogen stimulating T lymphocytes), observed a decrease in cytokine secretion and increased NF-κB activity due to high PPARγ concentration [14]. The use in the same experiment involving a 12-week n-3 PUFAs-rich diet showed an additional increase in *PPARγ* gene expression in the liver and heightened T-cell counts. These results confirm the anti-inflammatory effect of PPARγ [37]. PPARγ receptor reducing the synthesis of Il-6, -8 is activated also to prevent inflammation in the intestine [41]. Studies in mice with induced colitis showed that a diet with low n-6:n-3 PUFA ratio effectively reduces inflammation via PPARγ action [24]. Similar results have been obtained for breast cancer tumor cells [83].

Role of PPAR in cardiovascular diseases

Due to PPARγ function in the regulation of inflammation, lipid metabolism, oxidative stress and cellular apoptosis, these receptors interact with the cardiovascular system [26]. Activation of PPARγ by vaccenic acid and of PPARα, -γ by conjugated linoleic acid favorably impacts the development of cardiomyocytes, inhibiting their hypertrophy [1, 73]. Beneficial effects of PPAR receptors on the cardiovascular system have also been demonstrated in patients following a diet rich in n-3 PUFA [52]. Anderson et al. [3] reported that the administration of a fluid enriched in DHA and EPA to patients three weeks prior to cardiac surgery increased PPARγ activity in the myocardium atrium. In addition, increased fatty acid oxidation in the mitochondria and intensified activity of key enzymes catalyzing antioxidant and anti-inflammatory processes have both been demonstrated [3].

Tian et al. [68] observed that a decreased expression of the *PPARγ* gene causes changes in expression of genes responsible for the development of pulmonary hypertension. Thus, this decline in gene expression is linked to the induction of hypertension in pulmonary circulation [68]. Changes in PPARγ activity are not only associated with changes in blood pressure, but also with the occurrence of vascular diseases [53, 54]. Studies in lambs have confirmed that irregularities in PPARγ activity may lead to damage to blood vessels [66].

Protective role of PPAR

Krämer et al. [32] demonstrated that *PPARα* expression is directly related to the quantity of type I fibers in skeletal muscles [32]. These receptors are, through signaling pathways, responsible for increased resistance to damage caused by ischemia of the heart, liver, or muscle tissue [5]. Studies in post-liver transplant patients have demonstrated that polymorphisms within the donor's *PPARα* gene increase susceptibility to metabolic disturbances [39].

PPAR family receptors are a very important factor in the proper functioning of the nervous system and cell signaling. Active PPARγ exhibits neuroprotective properties – such action has been demonstrated in experiments where microglial cells were treated with a toxic lipopolysaccharide, as well as in studies focused on the action of neuroprotectin D1 [4, 67, 85]. Recent study findings also indicate the possible uses of PPARγ in post-traumatic neuronal regeneration [35]. Attempts are made to make use of PPARα and -γ neuroprotective properties in interaction with various agonists in the treatment of degenerative neurological diseases – Parkinson's and Alzheimer's [7, 15, 58, 62]. In addition,

PPARα activity has been shown to be associated with sleep modulation [46].

Studies focused on age-related macular degeneration in humans suggest that increased expression of the *PPARγ* gene influences the development of this disease [21]. *In vivo* studies show that the use of n-3 PUFA-rich diet leads to an increased expression of this gene in the mouse model of age-dependent macular degeneration [79].

ROLE OF PPAR IN SHAPING FAT CONTENT AND QUALITY OF PRODUCTS OF ORIGIN PRODUCTS

Activation of PPARγ receptors by chloroformic multicloride extract (*Lolium multiflorum*) induces cell proliferation and differentiation of adipocytes as well as fat deposition, which directly influences the quality of animal meat [25]. Also, a link between the expression level of the gene encoding peroxisome proliferator-activated receptors gamma and fat deposition has been observed [44]. Evaluation of transcriptome profile of bovine muscle tissue has demonstrated that an increase in intramuscular fat content in beef [38] is connected to expression levels of 10 genes, including *SCD* and *FABP4* (fatty acid binding protein 4) that are regulators in the PPAR signaling pathway.

CONCLUSION

Peroxisome proliferator-activated receptors, due to their functions, seem to be one of the key factors responsible for the conversion of fatty acids and lipid metabolism, and thus also for the energy balance of the body. Particular emphasis should be placed on their effects in the case of the metabolic syndrome and its associated conditions: diabetes, obesity or hypertension, increasingly widespread in the twenty-first century. The significant number of studies and publications focusing on the role of expression and genetic variability of the genes, proteins and ligands of PPAR receptors in the metabolism of animal and human fat is thus a natural response to their significance for these processes.

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