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Natural product agonists of peroxisome proliferator-activated receptor gamma (PPARγ): a review

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ABSTRACT

Agonists of the nuclear receptor PPARγ are therapeutically used to combat hyperglycaemia associated with the metabolic syndrome and type 2 diabetes. In spite of being effective in normalization of blood glucose levels, the currently used PPARγ agonists from the thiazolidinedione type have serious side effects, making the discovery of novel ligands highly relevant.

Natural products have proven historically to be a promising pool of structures for drug discovery, and a significant research effort has recently been undertaken to explore the PPARγ-activating potential of a wide range of natural products originating from traditionally used medicinal plants or dietary sources. The majority of identified compounds are selective PPARγ modulators (SPPARMs), transactivating the expression of PPARγ-dependent reporter genes as partial agonists. Those natural PPARγ ligands have different binding modes to the receptor in comparison to the full thiazolidinedione agonists, and on some occasions activate in addition PPARα (e.g. genistein, biochanin A, sargaquinoic acid, sargahydroquinoic acid, resveratrol, amorphastilbol) or the PPARγ-dimer partner retinoid X receptor (RXR; e.g. the neolignans magnolol and honokiol). A number of *in vivo* studies suggest that some of the natural product activators of PPARγ (e.g. honokiol, amorfrutin 1, amorfrutin B, amorphastilbol) improve metabolic parameters in diabetic animal models, partly with reduced side effects in comparison to full thiazolidinedione agonists. The bioactivity pattern as well as the dietary use of several of the identified active compounds and plant extracts warrants future research regarding their therapeutic potential and the possibility to modulate PPARγ activation by dietary interventions or food supplements.

Abbreviations: 9-(*S*)-HODE, (9*S*,10*E*,12*Z*)-9-hydroxyoctadeca-10,12-dienoic acid; AF-2, activation function-2; CAP, c-Cbl-associated protein; Cdk5, cyclin-dependent kinase 5; DCM, dichloromethane; DIO, diet-induced obesity; DPP-4, dipeptidylpeptidase 4; EMA, European Medicines Agency; FDA, Food and Drug Administration; Glut4, glucose transporter type 4; HDL, high-density lipoprotein; HUVEC, human umbilical vein endothelial cells; LBD, ligand-binding domain; LDL, low-density lipoprotein; MAPK, mitogen-activated protein kinase; MeOH, methanol; NF-κB, nuclear factor-kappaB; PPAR, peroxisome proliferator-activated receptor; RXR, retinoid X receptor; PDB, protein data bank; PPRE, peroxisome proliferator response element; SPPARMs, selective PPARγ modulators; TCM, traditional Chinese medicine; TNF-α, tumor necrosis factor alpha.

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1. Significance of metabolic disorders

The metabolic syndrome is currently a major worldwide epidemic. It strongly associates with obesity, insulin resistance, type 2 diabetes, and cardiovascular diseases, which are major pathologies contributing to mortality and morbidity worldwide. At present the metabolic syndrome is already affecting more than a quarter of the world's adult population. Its prevalence is further growing in both adults and children due to a life style characterized by high calorie nutrition combined with low physical activity [1,2].

The metabolic syndrome represents by definition a disorder related to imbalance of energy utilization and storage. Its features include abdominal obesity, hypertension, dyslipidemia (increased blood serum triglycerides; low high-density lipoprotein (HDL) and high low-density lipoprotein (LDL) cholesterol levels), insulin resistance with elevated fasting blood glucose, and glucose intolerance as well as establishment of pro-thrombotic and pro-inflammatory states [3]. People affected by the metabolic syndrome have a greater risk of developing cardiovascular diseases and type 2 diabetes. Moreover, recent research indicates that metabolic syndrome associated obesity causes chronic low-grade local tissue inflammation and increased susceptibility to other disease conditions such as fatty liver, sleep disturbances, cholesterol gallstones, polycystic ovary syndrome, asthma, and some types of cancer [3,4].

The two main approaches in metabolic syndrome management are in the first place life style modifications that aim at restoring energy balance by reduced calorie intake and increased energy expenditure by physical activity, and on second place pharmaceutical interventions [1,3]. Employed drugs target different relevant aspects of the metabolic syndrome such as body weight and fat distribution, insulin resistance, hypertension, dyslipidemia, hyperglycemia, or the established prothrombotic and proinflammatory state [3]. For the treatment of patients suffering from type 2 diabetes, aside from life-style alterations, insulin and insulin analogs were first applied [5]. Later a number of oral anti-hyperglycemic pharmaceuticals were developed and successfully used [6] including sulfonylureas (increasing insulin secretion) [7], biguanides (insulin sensitizers; e.g. metformin), alpha-glucosidase inhibitors (slowing the digestion of starch in the small intestine), meglitinides (increasing insulin secretion), dipeptidylpeptidase 4 (DPP-4) inhibitors (increasing insulin secretion) [6], as well as thiazolidinediones (agonists of PPARγ). Recent research strategies also explore targeting the nuclear factor-kappaB (NF-κB) pathway [8], mitogen-activated protein kinases (MAPK) signaling [9], fatty acid-binding proteins [10], as well as other targets involved in fatty acid metabolism [11,12]. PPARγ, the molecular target of the thiazolidinediones, is particularly involved in the regulation of insulin sensitivity, inflammation, fatty acid storage, and glucose metabolism, and therefore represents an especially interesting pharmacological target which is able to simultaneously modulate several of the underlying pathologies of the metabolic syndrome [13,14].

2. PPARγ and the metabolic regulation

PPARs belong to a subfamily of the nuclear receptor superfamily of ligand-inducible transcription factors [15]. To date, three PPAR isotypes encoded by separate genes have been identified, PPARα [16], PPARβ/δ, and PPARγ [17].

PPARs mainly control the expression of gene networks involved in adipogenesis, lipid metabolism, inflammation, and the maintenance of metabolic homeostasis. As they can be activated by dietary fatty acids and their metabolites, they act as lipid sensors that, upon activation, are able to markedly redirect metabolism [18–20]. The gene transcription process is identical in all three

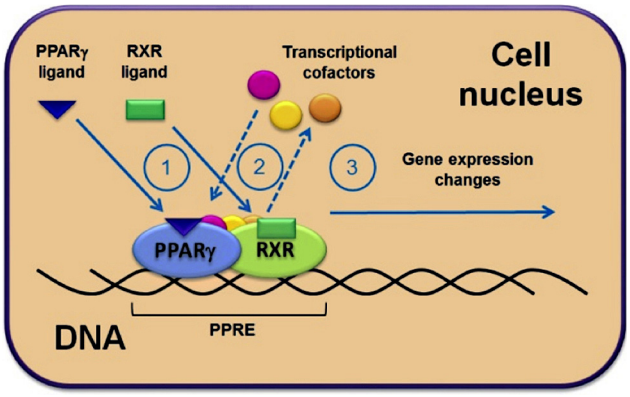

Fig. 1. PPARγ transcriptional activation. (1) Binding of activating ligands to PPARγ and to its dimer partner RXR; (2) following the ligand binding there are conformational changes of the receptors, resulting in re-arrangement of the transcriptional complex and changes in the associated transcriptional cofactors; (3) resulting from this reorganization, the transcriptional complex is activated and initiates changes in the expression of the regulated PPARγ target genes.

PPAR subtypes (Fig. 1): After ligand binding, PPARs form heterodimers with another ligand-activated nuclear receptor, the retinoid X receptor (RXR). The PPAR-RXR heterodimer binds to peroxisome proliferator response elements (PPREs) in the promoter region of the respective target genes. The transcription process is then initiated upon recruitment of different transcriptional cofactors [21–24] (Fig. 1).

The three PPAR isotypes possess a distinct tissue distribution and have different functions in the regulation of energy metabolism. PPARα is highly expressed in muscles, liver, heart, and kidney, and mainly regulates genes involved in the metabolism of lipids and lipoproteins [20,25–27]. PPARβ/δ is abundantly expressed throughout the body but at low levels in the liver. It has emerged as an important regulator of lipid metabolism and energy balance primarily in adipose tissue, skeletal muscle, and the heart [25,28,29]. The PPARγ protein exists in two isoforms that are expressed from the same gene by utilizing distinct promoters and 5′exons. PPARγ2 differs from PPARγ1 by the presence of an additional stretch of 30 amino acid residues in the ligand-independent domain at the *N*-terminal end resulting in a higher transcriptional activity compared to PPARγ1 [30–32]. The two PPARγ isoforms also show a distinct expression pattern: PPARγ1 is abundantly expressed in adipose tissue, large intestine, and hematopoietic cells, and to a lower degree in kidney, liver, muscles, pancreas, and small intestine. PPARγ2 is restricted to white and brown adipose tissue under physiological conditions [25,33,34].

Endogenous ligands for PPARγ include fatty acids and prostanoids [19,35] that act as weak agonists compared to the strong synthetic thiazolidinedione agonists [36,37]. The question of whether PPARγ has some highly specific endogenous ligands or whether it operates as a rather promiscuous physiological lipid sensor activated in concert by a variety of fatty acids and eicosanoids is still not clearly resolved [38–43].

In the human body, PPARγ is the master regulator of adipocyte differentiation, plays an important role in lipid metabolism and glucose homeostasis, modulates metabolism and inflammation in immune cells, as well as controls cell proliferation [44–46]. PPARγ is induced during the differentiation of preadipocytes into adipocytes [47–49]. The fact that PPARγ null mice are completely lacking adipose tissue clearly demonstrates that PPARγ is essential for adipocyte differentiation [50]. Furthermore, PPARγ directly activates many genes involved in adipocyte lipid storage [51,52]. Adipose tissue is also the primary tissue responsible for the