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Peroxisome Proliferator-Activated Receptors as sensors of fatty acids and derivatives

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Abstract. Lipid homeostasis requires a strict balance between lipid intake and consumption. This balance is controlled by different systems that regulate food intake, energy storage and energy expenditure. This review focuses on the roles of peroxisome proliferator-activated receptors (PPARs) in some of these regulatory processes. PPARs are transcription factors that bind and are activated by fatty acids and fatty acid derivatives. They act as lipid sensors and adapt the metabolism and development of various tissues to lipid availability. Due to their actions on lipid metabolism, PPARs are *bona fide* therapeutic targets in the treatment of metabolic syndrome not only by affecting gene expression patterns in several tissues but also by inducing remodeling of tissues such as adipose or skeletal muscle.

Keywords. PPAR, fatty acid, obesity, type 2 diabetes, metabolic syndrome.

Introduction

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors that belong to the nuclear receptor superfamily and play multiple physiological roles in several tissues. Three PPAR isotypes, α (NR1C1), β/δ (NR1C2) and γ (NR1C3), have been described so far. PPARα was cloned from a rodent liver complementary DNA (cDNA) library and described as activated by peroxisome proliferators, such as fibrates and fatty acids, hence its name [1]. The two other PPAR isotypes were identified in *Xenopus* [2] and mammals [3, 4]. Each of the PPAR isotypes is encoded in a separate gene and exhibits tissue-selective expression patterns. PPARα is mainly expressed in liver, heart, kidney, small intestine and brown adipose tissue [5]. Several forms of PPARγ have been identified with distinct expression patterns. PPARγ2 is almost exclusively found in white and brown adipose tissues, while PPARγ1 is expressed in several other tissues and cell types, including intestine, placenta and macrophages [3]. PPARβ/δ is the most widely expressed isotype but is found at a high level in small intestine, skeletal and cardiac muscles, brain and adipose tissue [4, 5].

As other members of the nuclear hormone receptors, PPARs are organized in different domains. The amino-terminal domain is poorly conserved between the three isotypes and contains a ligand-independent transactivation function. The central domain, which is highly conserved, brings the capacity of DNA binding, and the carboxyl-terminal region contains the ligand binding domain (LBD) and confers the ligand-dependent transactivation function. X-ray crystal structure analyses have revealed that PPAR ligand binding pockets are larger than in other nuclear receptors. Furthermore, these studies also revealed some differences in the ligand binding pocket of PPAR isotypes. For instance, it has been reported that the PPARβ/δ ligand binding cavity is smaller than the PPARα and PPARγ pockets, while the PPARα ligand binding cavity is more lipophilic than those of the other isotypes [6, 7]. These features explain why PPAR isotypes can bind a large diversity of molecules and also display a relative selectivity for both natural and synthetic ligands.

Transcriptional regulation by PPARs requires heterodimerization with the retinoid X receptor (RXR, NR2B). Such a heterodimer binds to a specific DNA responsive element called peroxisome proliferator

response element (PPRE), which is generally formed by a direct repeat of six nucleotides, AGGTCA, separated by one spacer nucleotide. Functional PPREs have been found in a large number of genes encoding proteins involved in a variety of functions, including lipid and carbohydrate metabolism, such as fatty acid transporters, fatty acid binding proteins, acyl-CoA synthetase, acyl-CoA oxidase, pyruvate dehydrogenase kinase 4 and phosphoenolpyruvate carboxykinase [8–10].

Another important step of PPAR transcriptional regulation is the interaction with cofactors. The unliganded PPAR/RXR heterodimer interacts with co-repressors that exert transcriptional repression. It has been proposed that binding of the ligand stabilizes the PPAR AF-2 helix in a conformation that is permissive for interactions with co-activator proteins, allowing nucleosome remodeling and activation of the transcription of the target genes [7, 11]. Several co-repressors and co-activators able to interact in a selective manner with the various PPAR isotypes have been described. As some of these cofactors are expressed in a tissue-specific manner and controlled by physiological status in a given tissue, this selectivity of interaction could explain why PPAR isotypes display differential tissue-specific transcriptional activities and why a specific isotype can be active or inactive depending upon the expression level of the cofactors in a given tissue.

During the last decade, it has been demonstrated that dietary lipids act, directly or after metabolic processing, as signaling molecules implicated in the regulation of lipid and of carbohydrate metabolism. It is now established that PPARs are involved in such regulatory processes by acting as lipid sensors. PPARs appear to play important physiological roles in adapting the metabolic rates of various tissues to the concentration of dietary lipids and in the management of energy metabolism in the whole body. It has been also shown that PPARs are *bona fide* therapeutic targets in the treatment of metabolic syndrome not only by affecting gene expression patterns in several tissues but also by inducing remodeling of tissues such as adipose or skeletal muscle.

Natural and synthetic PPAR ligands

PPARs are proposed to act as fatty acid sensors as it has been demonstrated that PPARs are activated by fatty acids and fatty acid derivatives [12]. Forced expression of PPARs in fibroblasts promotes fatty acid responsiveness to a variety of genes implicated in lipid metabolism. Furthermore, in several hepatocytic, adipocytic or myoblastic cell models, both genetic, i.e., expression of dominant negative forms of the various PPAR isotypes, and pharmacological, i.e., selective PPAR antagonist, approaches have confirmed that fatty acids activate PPAR-mediated transactivation. In this process, long-chain fatty acids, both saturated and unsaturated, appeared almost equally active for the three PPAR isotypes, and interestingly, the metabolism of the fatty acid is not required, as 2-bromopalmitate, a non metabolized fatty acid, appeared to be a potent PPAR agonist in preadipose cells [13]. Besides fatty acids, several fatty acid derivatives, such as branched fatty acids and eicosanoids, have been shown to be PPAR agonists. These molecules appeared to be more selective for PPAR isotypes than fatty acids. For instance, 15-deoxy-Δ12,14-PGJ2 (15d-PGJ2), a prostaglandin D2 derivative, is a selective PPARγ agonist [14], while leukotriene B4, phytanic acid or oleylethanolamide selectively activate the α isotype [15–17] and prostacyclin is more active on PPARβ/δ than on the other isotypes [18].

These fatty acids and fatty acid derivatives are also able to physically interact with PPARs. Several *in vitro* methods, including competition binding assays [7] and coactivator-dependent receptor ligand assays [19] demonstrated that PPARα and PPARβ/δ interact with both saturated and unsaturated long chain fatty acids (IC_{50} – i.e., mean inhibitory concentration – values from 1 to 30 μM), while PPARγ shows a more restricted fatty acid binding profile as interacting only with polyunsaturated fatty acids, such as linolenic or arachidonic acids (IC_{50} values from 1 to 10 μM). Furthermore, it was shown that eicosanoids bind to PPARs in an isotype-selective manner. For instance, 15d-PGJ2 interacts more efficiently with PPARγ than with PPARβ/δ or PPARα [20, 21], while 8-S-hydroxyeicosatetraenoic acid preferably binds to PPARα [21].

As it is not possible to estimate the actual concentrations of fatty acids and fatty acid derivatives within the nuclear compartment, the physiological implication of these molecules as endogenous PPAR ligands remains an open question. However, it has been proposed that the transfer of fatty acid to the nucleus may be facilitated by fatty acid binding proteins [22]. Furthermore, synthesis of some PPAR activators could occur in the nuclear compartment, as it has been shown that enzymes implicated in arachidonic acid metabolism are located in the nuclear envelope [23].

Due to their potential therapeutic interest for the treatment of metabolic disorders, several classes of PPAR synthetic ligands have been developed. The first molecules recognized as PPARα ligands/activators belong to the class of fibrates, which have been

used as hypolipidemic compounds for several years [1]. Fibrates are relatively poor PPARα activators, especially in humans, and new specific and potent PPARα ligands have been recently described [24]. Thiazolidinediones appeared to be potent and specific activators of the γ isotype [25], which is also activated by other classes of molecules [26]. More recently, compounds able to specifically bind and activate PPARβ/δ have been developed [27, 28]. Next to these classes of PPAR isotype-specific activators, pharmaceutical companies have designed dual PPAR agonists, such as the glitazar class aimed to combine beneficial effects of both PPARα and PPARγ isotypes [29]. These synthetic PPAR activators have been extensively used to investigate the roles of different isotypes in various tissues and have been useful tools for understanding the implication of PPARs in several biological mechanisms, such as regulation of energy metabolism, and inflammatory response and development.

Roles of PPARs in lipid metabolism

Fatty acids are essential as substrates or signaling molecules for several aspects of cell biology and physiological functions. For instance, they are crucial components of cell membranes and substrates for energy metabolism. Fatty acid homeostasis requires a strict equilibrium between lipid intake and lipid consumption. It is now acknowledged that PPAR isotypes play important regulatory roles to maintain such equilibrium under normal conditions by acting in several tissues. PPARs are involved in regulation of lipid intake, lipid storage and lipid utilization depending upon the tissue and the physiological situation. PPARα and PPARβ/δ have been shown to control lipid absorption in the small intestine by upregulating various genes, such as L-type fatty acid-binding protein and fatty acid translocase/CD36 [30]. These gene regulations are thought to increase lipid absorption, but, interestingly, PPARα is also involved in eating behavior. It was recently demonstrated that activation of intestinal PPARα by oleylethanolamide, a naturally occurring lipid, induces satiety in mice [17]. Adipose tissue is the main reservoir of lipids in mammals through its capacities of triglyceride storage and lipolysis. Depending upon the level of substrate supply, adipose tissue can adapt its storage capacity by modulating both the size and the number of adipocytes. Adipose tissue also plays an important endocrine role by secreting adipocytokines, such as leptin and adiponectin, which regulate eating behavior and lipid catabolism by targeting brain, liver and muscle. As circulating concentrations of adipocytokines are directly related to adipose mass cellularity, i.e., the number and size of adipose cells, adipose tissue can, in this way, inform other tissues about lipid storage levels [31]. PPARs are expressed in white adipose tissue, and it has been clearly established that PPARγ2 and PPARβ/δ are involved in regulation of adipose tissue mass. Several lines of evidence coming from both pharmacological and genetic approaches demonstrated that, when activated by 15d-PGJ2 or thiazolidinediones, PPARγ2 triggers expression of a typical adipose program and adipogenesis [32]. PPARγ2 is also involved in the regulation of triglyceride storage levels in adipose cells [33]. PPARβ/δ is not directly involved in the regulation of adipose terminal differentiation, but is implicated in control by long chain fatty acids of both preadipocyte proliferation and PPARγ gene expression. Based on these observations it has been suggested that PPARβ/δ and PPARγ modulate the number of adipose cells and the amount of stored triglycerides to adapt total adipose tissue storage capacity to the level of fatty acid supply [34]. In the healthy organism PPARs, and more especially α and β/δ isotypes, play important roles in the regulation of fatty acid oxidation during certain physiological situations, such as fasting and physical exercise. During fasting, fatty acids are released from adipose tissue and used in liver and skeletal muscle as an energy source. It has been shown that fasting increases hepatic expression of PPARα in liver [35] and of PPARβ/δ in skeletal muscle [36], and that such increases in PPAR activities upregulate genes involved in fatty acid oxidation in these tissues. The crucial role of PPARα during fasting is also evidenced by the fact that PPARα-null mice cannot sustain long-term food deprivation [37]. Endurance exercise requires an increase in fatty acid oxidation in oxidative myofibers. This is physiologically achieved by upregulation of genes encoding proteins implicated in fatty acid catabolism and, on a long-term basis, by increment of both type 2a (fast-oxidative) and type 1 (slow-oxidative) myofiber numbers. Recent studies have implicated of PPARs in these metabolic and adaptive responses of skeletal muscle to physical exercise. It has been reported that endurance training upregulates expression of PPARα [38] and PPARβ/δ [39] in skeletal muscle and that PPARβ/δ is required for the control of fatty acid oxidation in mouse cultured myotubes [36]. Furthermore, muscle-specific overexpression of PPARβ/δ promotes a phenotype reminiscent of that induced by long-term endurance exercise characterized by increment in oxidative myofiber number, increase in muscle fatty acid oxidation, resistance to muscle fatigue and resistance to deleterious actions of high-fat feeding [39, 40].

Collectively, these findings point out the roles of different PPAR isoforms in the control of lipid homeostasis in the normal situation. However, the characteristics of western lifestyle, i.e., excessive intake of lipids and carbohydrates, lack of fasting periods and reduction of physical activity, seriously impair the balance between lipid supply and degradation, leading to the development of metabolic syndrome. Yet, the actual sequence of events linking the imbalance of lipid homeostasis and metabolic syndrome is not fully clarified. It may be that the increased availability of lipids results in fat deposition in adipose tissue, liver and muscle, predisposing to insulin resistance. Furthermore, development of obesity and adipocyte hypertrophy alter adipocytokine production and disrupt the normal crosstalk between adipose tissue and other organs. Different nutritional or pharmacological strategies are used to correct metabolic disorders. Treatments with specific agonists for PPAR isoforms appear to be efficient for the normalization of several biological parameters perturbed during metabolic syndrome. PPARα agonists, such as fibrates, are efficient in treating hyperlipemia, dyslipidemia and atherosclerosis. Hypolipidemic effects of fibrates are related to PPARα-mediated upregulation of genes implicated in hepatic fatty acid oxidation, while upregulation of apolipoprotein A-I and A-II explains some of the protective effects of fibrates on cardiovascular diseases by increasing reverse transport of cholesterol [41, 42].

The antidiabetic action of thiazolidinediones in obese mice [43] and humans [44] is paradoxically related to their adipogenic potency through PPARγ activation. It has been established that the insulin-sensitizing effect of thiazolidinediones is related to the recruitment of new and metabolically active adipocytes, allowing both increment of lipid storage capacity and restoration of normal secretion of adipocytokines. In addition, PPARγ activation also reduces fatty acid efflux from adipocytes by upregulation of genes, such as phosphoenolpyruvate carboxykinase [45] and glycerol kinase [46], that enhance glycerol-3-phosphate production and triglyceride synthesis.

Recently, several studies revealed that PPARβ/δ is also a potential target for treatment of metabolic syndrome. In insulin-resistant obese monkeys, a 4-week treatment with a specific PPARβ/δ agonist normalizes insulin and triglyceride blood levels, increases high-density lipoprotein (HDL) cholesterol and reduces low-density lipoprotein (LDL) cholesterol [47]. The PPARβ/δ agonist also partially reverses excessive adiposity in diet-induced and genetically obese mice [48]. Some of these effects are related to an increase in fatty acid oxidation in skeletal muscle. As previously discussed, it has been established that PPARβ/δ activation promotes fatty acid oxidation in cultured myotubes and skeletal muscle *in vivo*. Furthermore, as the phenotypes induced by muscle-specific PPARβ/δ overexpression, i.e., increment of oxidative myofiber number, reduction of body fat mass, and protection against deleterious effects of high-fat diet [39, 40], are very reminiscent of that provoked by endurance training [49], it is tempting to speculate that activation of PPARβ/δ mimics the actions of physical exercise on muscle remodeling and metabolism. Although these observations can explain the hypolipidemic and antidiabetic actions of PPARβ/δ agonists, further studies are required for a complete understanding of the mechanisms involved in the other beneficial effects of these compounds, such as the improvement of the HDL/LDL ratio.

Conclusions

During the past decade, genetic and pharmacological studies have considerably improved our knowledge of the physiological roles of PPARs in regulation of lipid metabolism. It is now established that, in the healthy organism, these nuclear receptors play crucial roles in adaptive responses of several tissues to lipid supply, leading to a very efficient and physiologically pertinent utilization of such energetic substrates. This newfound understanding of the different physiological roles of PPAR isoforms has been helpful in explaining the beneficial actions of the specific synthetic agonists in obese and diabetic patients. However, some questions are still incompletely answered. First, the nature and synthetic pathways of the natural PPAR ligands are still a matter of debate. Second, the mechanisms involved in regulation of the tissue content of both PPARs and cofactors, which determine transcriptional activity of the system, must be identified. Finally, our knowledge of the functions of PPAR isoforms in certain tissues is still very modest. For instance, the role of PPARs in the brain remains to be clarified. Such information would be of great interest, as growing evidence suggests that fatty acid metabolism functions as a sensor for nutrient availability in brain regions involved in eating behavior, such as the hypothalamus [50].

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