Roles of Peroxisome proliferator-activated receptors PPARs

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors that exert important functions in mediating the pleiotropic effects of diverse exogenous factors such as physical exercise and food components. Particularly, PPARs act as transcription factors that control the expression of genes implicated in lipid and glucose metabolism, and cellular proliferation and differentiation. In this review, we aimed to summarize recent advancements reported on the effects of lifestyle and food habits on PPAR transcriptional activity.

Introduction
Modern lifestyle characterized by unbalanced composition of the diet and poor physical activity, accompanied by the presence of environmental pollutants, has resulted in dramatic increases in the rates of metabolic disease and age-related diseases. These chronic diseases, such as diabetes, cardiovascular disease (CVD), autoimmune diseases, cancers (breast, colorectal, pancreas), and neurodegenerative diseases are all characterized by a chronic sterile systemic low-grade inflammation [11,12,13]. Moreover, these chronic diseases correlate with the metabolic syndrome (MetS), defined by a cluster of interrelated factors: dyslipidemia, hypertension, dysregulated glucose homeostasis, abdominal obesity, and insulin resistance (IR) [14]. Particularly, the obesity and insulin resistance emerge to be the heart of the pathophysiology of the MetS [15]. Different environmental factors of Western lifestyle play a key role in inducing chronic sterile systemic low-grade inflammation and, eventually, the correlated chronic disease. These factors may be divided in the unbalanced composition of the diet [16,17] and non-food related factors [18]. Regarding the diet, in Western society there is a consumption of high glycemic index foods (cookies, chocolate, pastries), thus is associated with obesity and IR [19,20,21]. This kind of diet increases inflammatory biomarkers [22] and it is related to chronic disease, such as CVD, diabetes, cancer, Alzheimer’s disease [23,24,25]. Furthermore, in Western diet there is also an elevated consumption of certain saturated fatty acids (SAFA) [26], and industrially produced trans fatty acids [27,28]. Moreover, in Western diet there is an high ω6/ω3 fatty acid ratio [29,30,31], mostly because of a low intake of long-chain polyunsaturated fatty acids of the ω3 series, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from fish, and alpha-linolenic acid (ALA) from vegetable sources [32]. Among the non-food related factors, it is possible to mention smoking habit, insufficient physical activity [33,34,35,36], and environmental pollution [37] such as exposition to endocrine disruptors [38]. Thus, these kinds of lifestyle and food habits promote a chronic inflammatory status that as mentioned above is characteristic of chronic diseases. Biochemical mediators of lipids are represented by PPARs [39]. This review provides an update of lifestyle and food habits on low grade inflammation in two main chronic diseases, polycystic ovary syndrome (PCOS) and non-alcoholic fatty liver disease (NAFLD), with particular attention on the mechanism that involve the activation of the major metabolic and inflammatory players, the PPARs.

PPARs are ligand-activated transcription factors, belonging to the superfamily of nuclear receptors (NR). PPARs act as lipid sensors; therefore, they have attracted much attention for their ability to improve metabolic syndromes [40]. They take part in nutrient and energy metabolism regulating whole-body energy homeostasis [41,42]. PPARs regulate nutrient metabolism such as lipid, glucose, and cholesterol and sustain the intraorgan metabolic flexibility (Box 1); indeed PPARs play also an important role in regulating the correct inflammation tone [43]. There are three PPARs subtypes: PPARα (NR1C1), PPARβ/δ (NR1C2), and PPARγ (NR1C3), that are highly homologous but differ for tissue distribution and biological functions (Table 1). Fatty acids and their derivatives are the main endogenous agonists of PPARs [44], while among the synthetic ligands there are the main drug utilized for counteracting MetS (Table 1). Their main activity in regulating lipid, glucose metabolism, and inflammation suggests that PPARs are the crossroad of several molecular signaling pathways, implicated in metabolism onset [45].

Table 1. PPARs tissue distribution and biological functions.
### PPARs and Metabolism

All three PPARs are involved in adipose tissue homeostasis. Tissues with high rates of fatty acids catabolism, such as brown adipose tissue (BAT), liver, and skeletal muscles, present high level of PPARα activity. Most PPARα studies have been conducted on the liver [36], in which this nuclear receptor is able to increase the transcription of gene related to the fatty acid transport and catabolism [36, 37, 38], ketogenesis [37], and gluconeogenesis [36, 40]. PPARα in liver is a key factor for the adaptation of fasting and, consequently, energy switch from carbohydrate to fatty acid produced by WAT lipolysis. In the fed state, insulin-dependent PI3K pathway activates rapamycin complex 1 (mTORC1) that in turn suppresses, through nuclear receptor corepressor 1, PPARα activity [41]. PPARα agonist reduces obesity-related metabolic disorders. Experiments conducted on obese mice showed that PPARα agonist treatments improved the obesity condition and glucose homeostasis in terms of glucose intolerance, insulin resistance, and hyperglycemia [42, 43]. Goto proposes three options to explain the ability in improving glucose metabolism via adipose tissue [44]. The first option proposes that one of the PPARα capabilities is to increase the expression of a particular hepatokine, the fibroblast growth factor 21 (FGF21) [45], a cytokine able to increase the energy consumptions in white adipose tissue.

<table>
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<tr>
<th>Isoforms</th>
<th>Tissues Distribution</th>
<th>Target Genes</th>
<th>Functions</th>
<th>Synthetic Ligands</th>
<th>Natural Ligands</th>
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<tbody>
<tr>
<td>PPARγ</td>
<td>White and brown adipose tissue, the large intestine, skeletal muscle, spleen, pancreas, and brain.</td>
<td>aP2, FATP, FAT/CD36.</td>
<td>Regulation of adipogenesis, energy balance, lipogenesis, gluconeogenesis, lipid storage, glucose uptake, metabolism uptake and differentiation.</td>
<td>Rosiglitazone, Pioglitazone, Troglitazone, T3D-959, DBZ.</td>
<td>9-HODE, 13-HODE, 15d-PGJ2, EPA.</td>
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<tr>
<td>PPARβ/δ</td>
<td>Liver, intestine, kidney, abdominal white and brown adipose tissue, skeletal muscle, heart, pancreas, and brain.</td>
<td>Genes involved in lipid uptake, metabolism, and efflux, Lpin2, St3gal5.</td>
<td>Fatty acid oxidation, fatty acid metabolism, regulates blood cholesterol, glucose uptake, glucose utilization, insulin secretion, ketogenesis and inflammation.</td>
<td>L-796449, L-783483, GW-2433, MBX-8025, T3D-959, GW501516, GW610742.</td>
<td>Dihomo-γ-linolenic acid, Arachidonic acid, Methyl palmitate, 2-bromopalmitic acid, prostacyclin I2, 4-HNE.</td>
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(WAT) via the enhancement of the brown adipose tissue (BAT) activity (generally called “browning”) \(^{45},^{46}\). In fact, the authors showed that fibrate treatment increases the energy consumptions and adipocyte dysfunction and improve glucose homeostasis in WAT of high-fat diet (HFD) wild-type mice, but not in fibroblast growth factor (FGF21)-deficient mice \(^{42}\). The second option is the PPARα-mediated enhancing of the production and the release of a particular lipokine, 1-palmitoyl lysophosphatidylcholine, by the liver \(^{42}\). This lipokine is able to recover the glucose uptake in insulin-resistant adipocytes, and is an endogenous ligand of PPARα, suggesting a positive feedback loop between PPARα activation and 1-palmitoyl lysophosphatidylcholine production in the liver \(^{42}\). Finally, the last option is the improvement of glucose metabolism, via direct action of PPARα on adipose tissue. In fact, transgenic mice that express in adipose tissues constitutive active human PPARα, presented under HFD, recovered insulin sensitivity \(^{49}\), suggesting an important role of this NR in attenuating obesity-induced insulin resistance in WAT. Two isomeric forms of PPARγ exist, PPARγ1 and PPARγ2; PPARγ1 is most copious in WAT, but it presents also in other tissue (Table 1), while the expression of PPARγ2 is restricted in BAT and WAT \(^{49},^{50}\). Both isoforms are able to induce adipocytes differentiation although PPARγ2 appears more potent in this function \(^{51}\). In adipose tissue PPARγ plays key roles in adipocytes differentiation and survival, in the same time, this NR regulates insulin sensitivity and lipogenesis \(^{52},^{53}\). In BAT, the activation of PPARγ triggers the expression of genes linked to thermogenic program, comprising PPARγ coactivator protein 1α (PGC1A) and uncoupling protein 1 (UCP1) \(^{53}\). Regarding MetS, PPARγ is the most studied NR since 1995; it was recognized as a molecular target of thiazolidinediones, a class of antidiabetic and insulin-sensitizing drugs \(^{54}\). The activation of PPARγ, inducing adipocytes differentiation and strengthening the capacity of lipid accumulation in WAT \(^{50}\) protects the body from IR and free FA release leading to the attenuation of lipotoxicity. In fact, negative regulation of adipogenic transcription factors, such as PPARγ in adipose tissue, has been demonstrated to cause visceral obesity \(^{55}\). Under over-nutrition, the increase of adipose tissue has a protective role in preventing the release of free fatty acids in the systemic circulation. This is possible because in WAT there are stem cells that can differentiate in adipocytes, thus increasing its ability in lipids storage; in this mechanism PPARγ plays an essential role. The fact that fat is not always bad is derived from the evidence that a significant part of obese individuals (healthy obese) do not show dysmetabolism while a significant percentage of lean individuals do \(^{56},^{57}\). Healthy WAT is composed by different adipocytes, showing an increase of hyperplasia and a decrease of hypertrophy; the latter is a definite feature of pathologic obesity \(^{58},^{59},^{60},^{61},^{62},^{63}\). Recently, it has been demonstrated that the recruit of new adipocytes from PDGFRβ+ pre-adipocytes determines the visceral WAT health in obesity \(^{64}\). Notably, in the hypothalamicus of HFD rodents, by inhibiting PPARγ in the central nervous system (CNS), the sensitivity of the leptin pathway was improved. Another study demonstrated that transgenic mice knockout for PPARγ in hypothalamic neurons had enhanced energy consumption; on the contrary, food intake and body weight were decreased. In addition, these mice had improved glucose metabolism upon High Fat Diet (HFD) \(^{55}\). Thus, PPARγ signaling in the brain influence the energy balance and stimulate the obesity phenotype \(^{65}\). Although the same obesogenic effects have been reported for activation of PPARγ in the brain, the PPAR β/δ isotype appears to exert opposite role. Mice with PPAR β/δ deleted showed a strong expression of PPARγ and PPARα in the hypothalamus \(^{67}\). Regarding PPAR β/δ, in genetic models, it has been demonstrated that the activation of this NF protects against obesity \(^{68}\). Transgenic mice encoding an active form of PPAR β/δ specifically in adipose tissue, fed with a standard chow diet, showed decrease of body weights (20%), of inguinal fat pad masses (40%), and less circulating free FAs and triglycerides compared to control animals \(^{68}\). The same mice upon HFD or genetically predisposed to the obesity are protected against weight gain, adipocyte hypertrophy, hypertriglyceridemia, and steatosis \(^{68}\). Moreover, an increase of browning was observed in these mice \(^{68}\). In opposite, the loss of PPARβ/δ function rendered mice more prone to weight gain and had reduced expression of brown fat UCP1 upon HFD \(^{68}\). While PPARα is the most present isoform in the liver, PPARβ/δ isoform is the most expressed in muscle and it is preferentially found in oxidative rather than glycolytic myofibers \(^{69},^{70},^{72}\). In muscle cells, the activation of PPARβ/δ switches energy production from glycolysis to fatty acid oxidation enhancing muscle endurance \(^{72}\). Moreover, the activation of this NF increases the fatty acid uptake and catabolism via oxidation in skeletal muscle cells \(^{73}\). PPARβ/δ expression in muscle has several physiological implications such as decreased skeletal muscle fatigability and increased resistance to HFD-induced obesity \(^{72}\). In insulin-resistant obese monkeys treated with GW501516; a ligand PPARβ/δ showed an increased serum high-density lipoprotein cholesterol and a decrease of low density lipoprotein, fasting triglycerides, and insulin \(^{74}\). The activation of PPARβ/δ, during HFD, increases consumption of lip in skeletal muscles, avoiding hypertrophy of adipocytes and IR \(^{68},^{80},^{75}\). Finally, physical exercise and fasting increase the expression of PPARβ/δ in muscles \(^{78},^{76},^{77}\), demonstrating that PPARs act as an interface between lifestyle and health.
Striated muscle plays central roles in MetS, since it is a regulator of total body mass and energy consumption. A surplus of glucose, free fatty acid, and triglycerides concomitant with physical inactivity altered muscular metabolism, that in turn contributes to the onset of obesity and IR \([28]\). In a healthy-weight individual, skeletal muscles represent ~40% of the total human body mass, and with the cardiac tissue, use almost 30% of the resting energy and nearly 100% of energy utilization during physical exercise \([28]\). Skeletal muscle is composed of heterogeneous myofibers, slow-, mixed- and fast-twitch, that differ in the composition of contractile protein apparatus and metabolism. In particular, slow-twitch (Type I) has high oxidative aptitude using fatty acids as substrate for ATP production; mixed oxidative/glycolytic fast-twitch (type IIA) with both phenotype, and type IIB display high strength of contraction but lower oxidative ability doing anaerobic glycolysis \([28]\). Thus, systemic energy is impacted mostly by fiber type composition \([29, 30]\). Physical activities, especially aerobic exercises, increase the amount of slow fiber type, while the opposite is observed in obesity and diabetes in which there is an enhance of caloric intake without an increase of metabolic demand \([32]\). Instead, in both diabetic and obese patients, physical activity improve IR and lean mass \([83, 84]\). Similar to adipose tissue, the muscle secretes factors, named myokines, that act in an autocrine and/or paracrine manner \([85, 86]\). Myokines panel production depends on exercise and may modulate, as adipokines, glucose and lipids metabolism \([87, 88, 89]\). Among these myokines, myostatin regulates glucose and lipid metabolism, and myostatin-deficient animal are not susceptible to diet-induced obesity \([89]\).

Other myokines involved in systemic metabolism are angiopoietin-like protein 4 (ANGPTL4) \([90]\), irisin, FGF-21, Interleukin-15 (IL-15), \([85]\), meteorin-like protein \([91]\) and Growth differentiation factor 11 (GDF11) \([92]\). Finally, \(\beta\)-aminoisobutyric acid (BAIBA), belongs to a recent class of factors called “myometabokines,” is able to regulate systemic metabolism crosstalk \([86]\), and to induce browning phenotype in white adipose tissue \([93]\). These last discoveries highlight the importance of muscle on energy homeostasis and thus the influence of moderate physical activity on human health.

### Conclusions

It is becoming noticeable that the primary cause of most Western chronic diseases, with systemic low-grade inflammation as the common denominator, is not following a correct lifestyle and improper food habits. Ruiz-Núñez and Colleagues 2013 \([84]\) deduce as human predisposition to develop IR depends on the rapid brain growth in the past millennium. During this period, the interaction between our immune system and metabolism was strongly conserved, indeed, with the advent of the agricultural and industrial revolutions, leads to chronic inflammation. Lifestyle modifications in Western countries are necessary especially in the first years of life. However, during pathology onset, since improving lifestyle is not that easy, pharmacotherapy is required. PPARs represent the interface between environment metabolism and immune system; moreover, their presence in all metabolic tissues suggests that they play an important role in regulating the fine crosstalk between them. Thus, these receptors are targets for the therapy of metabolic syndrome and the low-grade inflammatory state. Because of the collateral effects induced by fenofibrates and TZDs, new therapeutic approaches are necessary in order to obtain new PPARs ligands characterized by minor negative effects and increased positive effects. Recently, more attention is pointed toward the possible use of natural compounds, such as PUFAn3, oleylethanolamide and \(\beta\)-aminoisobutyric acid, natural and endogenous ligands of PPARs. Finally, the development of PPAR\(\gamma/\delta\) pan-agonists or PPAR\(\alpha/\gamma\) dual agonist \([94]\) could be a potential therapy for a concomitant pharmacological activity on carbohydrate and lipid metabolism.

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