Review Article

Nutraceuticals as Ligands of PPARγ

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Peroxisome proliferator-activated receptors (PPARs) are ligand-activated nuclear receptors that respond to several exogenous and endogenous ligands by modulating genes related to lipid, glucose, and insulin homeostasis. PPARγ, expressed in adipose tissue and liver, regulates lipid storage and glucose metabolism and is the target of type 2 diabetes drugs, thiazolidinediones (TZDs). Due to high levels of toxicity associated with the first generation TZDs, troglitazone (Rezulin), rosiglitazone (Avandia), and pioglitazone (Actos), there is a renewed search for newer PPAR drugs that exhibit better efficacy but lesser toxicity. In recent years, there has been a definite increase in the consumption of dietary supplements among diabetics, due to the possible health benefits associated with these nutraceutical components. With this impetus, investigations into alternative natural ligands of PPARs has also risen. This review highlights some of the dietary compounds (dietary lipids, isoflavones, and other flavanoids) that bind and transactivate PPARγ. A better understanding of the physiological effects of this PPAR activation by nutraceuticals and the availability of high-throughput technologies should lead to the discovery of less toxic alternatives to the PPAR drugs currently on the market.

1. Introduction

Peroxisome proliferator-activated receptor gamma (PPARγ), or NRIC3, is a ligand-activated transcription factor that belongs to the superfamily of nuclear receptors. PPARγ plays an important role in glucose and lipid homeostasis, inflammation, and adipocyte differentiation [1]. There are three known isoforms of PPARs: PPARα, PPARγ, and PPARβ/δ, each with different tissue specificity and physiological function [2]. All three isoforms share common molecular structure and functional domains similar to other nuclear receptor superfamilies consisting of the following: a distinct N-terminal ligand-independent transcriptional activation domain (AF-1), a DNA binding domain, the hinge region, and the ligand-binding domain which contains the ligand-dependent transcriptional activation domain (AF-2). Upon ligand binding, PPARγ forms a heterodimer with the retinoic acid receptor (RXR) and controls the expression of genes that have PPAR response elements (PPRE). This transcription factor is further regulated by commonly known coactivator proteins such as CBP/p300, the SRC family, TRAP 220, and corepressors such as SMART, NCoR, and RIP140 [1]. Two isoforms of PPARγ have been identified (PPARγ1 and PPARγ2), with a wide tissue distribution among various animal species [3].

Over the past two decades, there has been a flurry of research investigating the physiological significance of PPARγ activation. It is now generally accepted that both ligand dependent and independent activation of PPARγ mediate multiple metabolic pathways in the immune system [4], cardiovascular system [5], and the adipose tissue [6], thus modulating genes related to inflammation, lipid metabolism and adipogenesis. Most of these physiological functions of PPARγ were revealed because of the discovery of thiazolidinediones (TZD). These drugs are high affinity ligands of PPARγ with insulin sensitizing effects and used in the treatment of type 2 diabetes [7]. The identification of PPARγ as the molecular target of glitazones such as pioglitazone (TZD), came from seminal work by Kliewer et al. [8], Kletzien et al. [9], and Graves et al. [10]. Troglitazone

(Rezulin), rosiglitazone (Avandia), and pioglitazone (Actos) were the three originally approved TZD drugs for diabetes. Increased hepatic toxicity, edema, and cardiovascular risk associated with the use of the TZD drugs lead to the withdrawal of troglitazone (Rezulin) from the market and black box warnings on the other two available drugs [11]. Although these drugs are known PPARγ agonists, it is still not clear if the toxicities associated with these drugs are due to their interactions with the PPARγ receptor. A new generation of PPARγ drugs with equivalent insulin sensitizing activity like TZDs, but with lower toxicity, has been in development since the withdrawal of the earlier TZDs. These include (i) non-TZD like PPARγ agonists, (ii) PPAR α/γ dual agonists, (iii) PPAR pan agonists, (iv) PPARγ antagonists, and (iv) selective PPARγ modulating drugs (SPPARγM) [12, 13]. These newer agonists seem to have similar or better insulin sensitizing effects as compared to TZDs (rosiglitazone). Still, several of these new drugs exhibit some form of toxicity [14]. Yet, SPPARγM are purported to be less toxic because they are designed based on the ligand selective regulation of receptor function [13, 15–17]. Recent studies indicate that SPPARγM are mechanistically distinct from the TZDs in that these drugs interact at a site that is different than the AF-2 region, thus altering subsequent coregulator binding and resulting in favorable cellular responses [18]. The search will continue until better alternative drugs to the currently available TZDs with equal or greater beneficial effects, but fewer adverse effects are identified.

2. Natural Ligands of PPARγ

Although there is a renewed interest in identification of synthetic PPARγ modulators for the treatment of type 2 diabetes, developing known dietary components (nutraceuticals) that bind and activate PPARγ with more efficacy and safety, while promoting health benefits has become an absolute necessity [19]. The term nutraceutical is defined as any food (fruits, vegetables, nuts, tea, etc.) or part (extract) of a food, such as a dietary supplement that has a medical or health benefit including the prevention and treatment of disease [20]. However, there is no consensus on the definition or the regulation of nutraceuticals among scientists [21]. The majority of nutraceuticals are of plant origin. Thus, nutraceuticals are "pills" that contain concentrated forms of presumed bioactive phytochemicals extracted from the original food item (e.g., genistein from soy). Because of their plant origin, these compounds are considered safe and are popular among consumers. This review will elaborate on some of the currently well-known dietary constituents that act as PPARγ ligands, with a demonstrated ability to bind to and activate PPARγ. The subsequent biological responses that result from this activation is not the focus of this review. For the purposes of this review, any isolated dietary component used in cell based or animal studies is considered a nutraceutical. Dietary components that act as ligands of PPARγ include dietary lipids such as n-3 and n-6 fatty acids and their derivatives, isoflavones and flavonoids. Table 1 provides a partial list of dietary PPARγ ligands.

2.1. Exogenous and Endogenous Lipid Derivatives. The majority of available research has focused on understanding the physiological significance of the interactions between dietary lipids and their derivatives with PPARs [25, 32–38]. Dietary fats and oils are major sources of these ligands, which include both n-3 and n-6 lipids and their oxidized counterparts. Elegant structure-function studies have determined the binding efficiency of the dietary lipids with PPARs [25, 39–42] by comparing them to synthetic drugs (TZD). Though dietary lipids similar to synthetic ligands were able to bind to the ligand binding domain and cause conformational changes to activate the receptor, they are considered as weak PPARγ ligands because of their low physiological concentrations. One must keep in mind that most of the studies determining the binding efficiency of the nutraceuticals have been performed in either cell-free or cell-based systems. The specificity of the dietary compounds to act as ligands for PPARγ was determined by a lack of response when cells were either pretreated with a known antagonist of PPARγ or with constructs that lacked PPAR ligand binding domain. However, in cell based systems it is conceivable that a metabolite of the parent compound, not the parent compound itself, might be mediating the response through interactions with PPARγ. For example, 13-HODE (oxidized n-6 lipid), a known agonist of PPARγ, could be converted into 13-Ox-HODE prior to interacting with PPARγ.

2.1.1. Exogenous Lipids: Dietary Lipids. Many studies have demonstrated that nonesterified unsaturated fatty acids are better ligands of PPARγ as compared to saturated fatty acids [43]. Although unoxidized unsaturated fatty acids are present in abundance *in vivo*, evidence suggests that they are weak activators of PPARγ. However, there is compelling evidence that oxidized unsaturated fatty acids are potent ligands compared to their unoxidized counterparts. Using NMR spectroscopy, Itoh and colleagues [39] studied the crystal structure of PPARγ bound fatty acids. They determined that fatty acids that bound covalently to the receptor were strong activators of PPARγ and the binding was also dependent on the polar nature of the lipid. Furthermore, using a dual luciferase reporter system, they demonstrated that the oxidized forms of the docosahexaenoic acid (DHA), a dietary n-3 fatty acid, 4-hydroxy docosahexaenoic acid (4-HDHA), and 4-oxo docosahexaenoic acid (4-oxoDHA) were potent ligands (EC$_{50}$ values of 3.7 μM and 0.4 μM) as compared to DHA (>10 μM). Fatty acids that are modified by oxidation or nitration can originate in the diet or can be generated *in vivo*. Research from our laboratory [44] and by others [45, 46], has shown that dietary oxidized lipids are absorbed by the intestine and incorporated into lipoproteins and tissues. A study by Ringseis et al. [47] showed increased PPARγ DNA binding in the intestinal cells of pigs fed oxidized (heated) sunflower oil compared to pigs fed unoxidized oil. Even though it was not possible to identify the specific ligands that bound to PPARγ, the findings from this study are important because they demonstrated that dietary oxidized fats were able to increase PPARγ interactions with the DNA, even though this activation of PPARγ was not

TABLE 1: Potential dietary PPARγ ligands.

Ligand	Binding affinity	Type of assay	Reference
Linoleic acid	$K_i > 1\,\mu$M		[22]
Nitrolinoleic acid	$K_i = 133$ nM	Competitive radio-labeled binding assay	
9-Hydroxyoctadecadienoic acid (9-HODE)			
13-Hydroxyoctadecadienoic acid (13-HODE)			
9/10-NO$_2$-linoleic acid	$IC_{50} = 0.6\,\mu$M	Scintillation proximity	[23]
12-NO$_2$-linoleic acid	$IC_{50} = 0.41\,\mu$M	Competitive binding assay	
13-NO$_2$-linoleic acid	$IC_{50} = 0.44\,\mu$M		
Azelaoyl phosphatidylcholine (in oxidized LDL)	40 nm	Radiolabeled binding assay	[24]
Docosahexaenoic acid (DHA)	$EC_{50} > 10\,\mu$m		[25]
4-Hydroxy docosahexaenoic acid (4-HDHA)	$EC_{50} = 3.7\,\mu$m	Dual luciferase reporter system	
4-Oxodocosahexaenoic acid (4-oxo-DHA)	$EC_{50} = 0.4\,\mu$M		
Conjugated linoleic acid isomers (CLA)	$IC_{50} = 3.2$–$7.4\,\mu$M	Competitive scintillation proximity assays	[26]
Isoflavones:			
Genistein	$K_i = 5.7\,\mu$M	Membrane-bound competitive PPARγ binding assay	[27]
Daidzein	$20\,\mu$M	Luciferase reporter assay in 3T3-L1 cells	[28]
	$EC_{50} = 73\,\mu$M	Luciferase reporter assay in HeLa cells	[29]
Equol	$20\,\mu$M	Luciferase reporter assay in 3T3-L1 cells	[28]
Biochanin A	$EC_{50} = 3.7\,\mu$m	Luciferase reporter assay in HeLa cells	[29]
	$EC_{50} < 1\,\mu$M	Luciferase reporter assay in HepG2 cells	[29]
Flavonoids:			
Psi-baptigenin	$EC_{50} = 2.9\,\mu$M	Transcriptional factor activity assay in ThP-1 cells	[30]
Hesperidin	$EC_{50} = 6.6\,\mu$M		
Quercetin (from dill, bay leaves, and oregano)	$EC_{50} = 2.8\,\mu$M	Ligand screening assay	[31]
2$'$-Hydroxy chalcone (cinnamon in polymeric form)	$EC_{50} = 3.8\,\mu$M	Ligand screening assay	[31]
Rosmarinic acid (marjoram)	$EC_{50} = 16\,\mu$M	Ligand screening assay	[31]

associated with concomitant NFκB mediated inflammation. Seminal work by Schopfer et al. [22] has shown that nitrolinoleic acid (LNO2), which acts as a PPARγ ligand, is present in the plasma of healthy humans and has a K_i of 133 nM as compared to a K_i of >1000 nM for linoleic acid. Additionally, it was capable of promoting adipogenesis and glucose uptake in the 3T3-L1 cell model. Another group of isomers of linoleic acid, conjugated linoleic acid (CLA), is present in dairy products and can also be produced *in vivo* by commensal bacteria. Based on competitive scintillation proximity assays, various CLA isomers had IC_{50} values of 3.2–7.4 μM for PPARγ, but had IC_{50} values in the nM range (140–260 nM) for PPARα [26, 48]. This suggests that CLA isomers are stronger activators of PPARα as compared to PPARγ. However, in the past few years there has been a flurry of research investigating the role of CLA isomers in experimental colitis [49] because PPARγ is abundantly expressed in this tissue, and it appears that the protective effects of CLA isomers are due to the activation of PPARγ. Future investigations should consider if these protective effects are being partially mediated by other PPAR isotypes.

2.1.2. Endogenous Lipids. The identification of an endogenous physiological ligand for PPARγ has been problematic, possibly due to its low abundance. Even though it has been well established that endogenous ligand-mediated activation of PPARγ leads to adipocyte differentiation, the identification of this ligand has not yet materialized. Is there any evidence that ligands of PPARγ are generated *in vivo*? Yes, since there are endogenous enzymes that generate lipid ligands that interact with PPARs. 12/15 lipoxygenase-derived oxidized fatty acids such as 13-HODE, 12-HETE, and 15-HETE have been shown to activate PPARγ in vascular smooth muscle cells [50, 51]. In addition, ligands such as 9-HODE, 13-HODE [52], and 1-O-hexadecyl-2-Azelaoyl-sn-glycero-3-phosphocholine (AZ-PC) [24], derived from

oxidized LDL, have also been shown to activate PPARγ in cell based studies. Similarly, ligands such as 15-deoxy-Δ,12,14-prostaglandin J2 (PGJ2) generated by the action of cyclooxygenase (COX) on arachidonic acid (n20 : 4) are excellent activators of PPARγ [53] but due to their low *in vivo* abundance are considered as weak ligands.

2.2. Dietary Isoflavones. The primary dietary sources of isoflavones that are used as supplements are extracted from legumes, especially soybeans. The isoflavones in soy are mainly daidzein, genistein, and glycitein. After hydrolysis in the gastrointestinal tract, isoflavones are further modified by intestinal microflora. Thus, the metabolites of isoflavones that end up in the circulation depend on the type of microflora that inhabits the intestine. Equol and O-desmethylangolensin (ODMA) are the most common metabolites of daidzein. Several studies have shown that genestein activates PPARγ at micromolar concentration [54, 55] but inhibits adipogenesis in 3T3-L1 adipocytes [56], primary human adipocytes [57], and in animal models [58, 59]. This antiadipogenic effect of genestein is attributed to mechanisms beyond PPARγ activation. For example, downregulation of adipocyte-specific genes such as C/EBPα and β, PPARγ, SREBP-1, and HSL has been reported [60]. A study by Dang et al. demonstrated that genistein has concentration-dependent effects on progenitor cells, that is, genistein can act as an agonist of the estrogen receptor at lower concentrations (<1 μM) but become a PPARγ agonist at higher concentrations (>1 μM) in mesenchymal progenitor cells, thus promoting either osteogenesis or adipogenesis, respectively [27]. Moreover, a role for the estrogen receptor cannot be overlooked because genistein down regulated ERα and ERβ in an animal study of ovariectomized mice [61]. Daidzein and its metabolite equol activated PPARγ [28] in luciferase reporter assays utilizing several cell types and promoted adipogenesis in 3T3-L1 cells at much lower concentrations (10–100 μm) than genistein [29].

2.3. Other Dietary Constituents. Fruits and vegetables are rich in flavonoids. By screening a natural product library, Salam and colleagues [30] identified two flavonoids, Ψ-baptigenin (EC$_{50}$ = 2.9 μM) and hesperidin (EC$_{50}$ = 6.6 μM) as strong agonists of PPARγ. Furthermore, these flavonoids promoted a strong induction of PPARγ in THP-1 cells which was abolished by treatment with the PPARγ antagonist GW9662. Interestingly, in a recent study [62], healthy humans who ingested a supplement of Red Clover had detectable levels of Ψ-baptigenin in their plasma, thus making this a plausible physiological ligand of PPARγ. The biological effects of these natural PPARγ agonists need further investigation. Other dietary components that have been studied are epigallocatechin gallate (EGCG, from green tea) and resveratrol (abundant in grapes, wine, and peanuts). Once again, there are very few studies that demonstrate the PPARγ binding ability of these compounds. Because of their ability to reduce lipid accumulation [63] by altering PPARγ expression [64], these agents are presumptive ligands of PPARγ. In an extensive review on culinary herbs and spices,

Jungbauer and Medjakovic [31] identified components of herbs and spices such as cinnamon, oregano, and marjoram with PPARγ binding affinities between 2.8 and 23.7 μM. Interestingly, most of these components seem to be very weak transactivators of PPARγ.

In summary, it is obvious that dietary components can bind and activate PPAR gamma. What is lacking, however, is the delineation of the metabolic effects that are specific to this PPAR gamma activation. Thus, future efforts should focus on study methodologies and techniques that can demonstrate a cause and effect relationship between nutraceutical activation of PPAR gamma and its physiological function.

3. Toxicology of Nutraceuticals

Nutraceuticals are increasingly being used as nutritional supplements in treatment of diseases. Due to the plant origin of these supplements they are considered safe for human consumption. However, the levels of the active substance consumed vary when taken as a whole food, as compared to a nutritional supplement [65, 66]. Very few studies have reported on long-term effects of nutrition supplements in humans. High consumption of lipids is associated with high risk of cardiovascular disease, diabetes, obesity, and cancer [67, 68]. Higher consumption of flavonoid supplements can alter the physiological levels of iron, vitamins, and other nutrients [66]. Flavonoids also interact with cytochrome P450 enzymes thus altering pharmacodynamics and pharmacokinetics of various drugs [69–71]. Similar to reports on TZDs, some of the flavonoids such as genestein have been associated with increased cancer risk [72–75]. Therefore, unless safety profiles of these nutraceutical supplements in humans are available, caution should be used in their long-term use as PPAR modulators.

4. Conclusions

The study of nutraceuticals as PPAR ligands is in its infancy. Newer insights into the role of PPARs in physiology and pathophysiology will help design better therapeutics. Future studies utilizing both high throughput screening technology and tissue specific metabolic profiling should identify nutraceuticals that modulate PPARγ activity. Subsequent cell culture and animal studies followed by rigorous clinical trials should then be able to establish the pharmacological and toxicological profiles of these nutraceuticals and their potential in influencing human health.

Acknowledgments

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