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Fatty acids, eicosanoids and PPAR gamma

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ABSTRACT

Peroxisome proliferator-activated receptor γ (PPARγ) belongs to the family of nuclear nuclear receptors and is mainly expressed in adipose tissue, hematopoietic cells and the large intestine. Contrary to other nuclear receptors that mainly bind a single specific ligand, there are numerous natural PPARγ ligands, in particular fatty acids or their derivatives called eicosanoids. PPARγ have pleiotropic functions: (i) glucose and lipid metabolism regulation, (ii) anti-inflammatory properties, (iii) oxidative stress inhibition, (iv) improvement of endothelial function. Its role has been mainly studied by the use synthetic agonists. In this review, we will focus on the effects of PPARγ mediated through fatty acids and how these have beneficial health properties.

1. Molecular structure and function

Peroxisome proliferator-activated receptors (PPAR) are nuclear receptors belonging to the steroid receptor superfamily that regulate gene transcription of different pathways, including metabolism and inflammation (Willson et al., 2000). Like all nuclear receptors, PPAR are organized into three major functional domains: (i) a N-terminal domain harboring the transcriptional activation function, (ii) a conserved DNA binding domain and (iii) a C-terminal domain ligand binding domain (LBD).

PPAR interact with nuclear proteins which act as co-activators and co-repressors (Fig. 1). In the non liganded state, PPAR interacts with co-repressors that, in the deacetylated state, inhibit gene expression (Nolte et al., 1998). After binding to a ligand, PPAR forms a heterodimer with the retinoid X receptor (RXR), recruits co-activators such as PPARγ coactivator 1-α (PGC-1α) or E1A binding protein p300 (EP300) containing histone acetylase activity and binds to the peroxisome proliferator response element (PPRE) gene promoter, leading to regulation of gene transcription. Acetylation of histone proteins seems to relieve the tightly packed structure of the chromatin, allowing the RNA polymerase II complex to bind and initiate transcription. The nature of the ligand will also modify its conformational structure: upon binding of an agonist, PPAR structure allows its interaction with transcriptional coactivators while antagonist binding does not.

Very recently, a novel mechanism has been identified in addition to the classical PPARγ signaling. Wang et al. have shown that PPARγ ligands such as rosiglitazone can also activate G protein-coupled receptor 40 (GPR40) at the cell surface and consequently phosphorylate p38 MAPK(Wang et al., 2015). This activation of p38 MAPK leads to the subsequent phosphorylation and activation of co-activators such as PGC1α and EP300 and enables a conformational change, permitting binding between co-activators and PPARγ (Wang et al., 2015).

2. Tissue expression

The PPAR family includes three isotypes: PPARα, PPARβ/δ and PPARγ. The three isotypes are differently tissue-expressed and have different function in metabolism regulation. While PPARβ is ubiquitously expressed PPARα is mainly expressed in the heart, liver, muscles, kidney and brown adipose tissue. Both are involved in lipid metabolism. PPARγ exists into two isoforms($PPAR\gamma_1$, $PPAR\gamma_2$) that are differentially expressed. $PPAR\gamma_1$ is highly expressed in brown and white adipose tissue, large intestine and immune cells but is also found various tissues such as muscle, pancreas, liver, small intestine and kidney while $PPAR\gamma_2$ is expressed in adipose tissue. PPAR are lipid sensors and regulate the expression of genes involved in lipid and glucose metabolism and inflammation.

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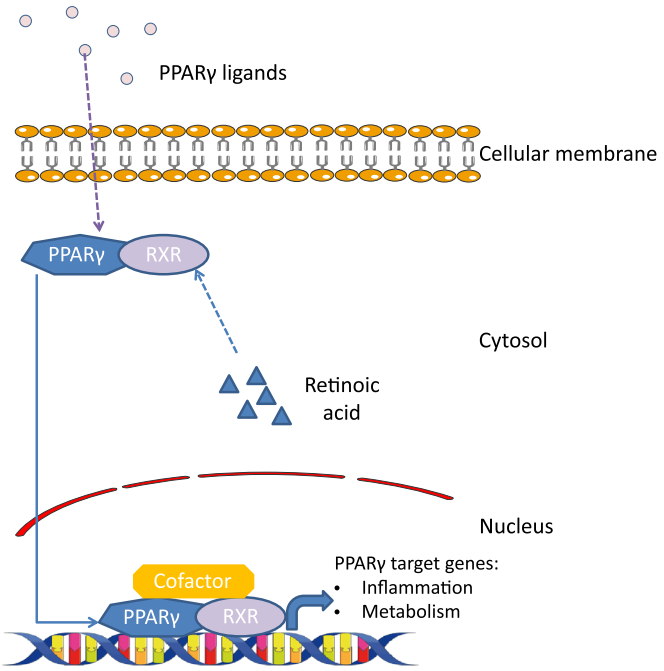

Fig. 1. PPARγ signaling. Peroxisome proliferator-activated receptor γ (PPARγ) and retinoid X receptor (RXR) belong to the superfamily of nuclear receptors. PPARγ is activated by numerous natural or synthetic PPARγ ligands. After binding to a ligand, PPAR forms a heterodimer with the retinoid X receptor (RXR) that are activated by retinoic acid and recruits co-activators. The complex then binds to the peroxisome proliferator response element (PPRE) gene promoter, leading to regulation of gene transcription of genes mainly involved in lipid and glucose metabolism, inflammation and cancer.

3. PPARγ ligands

Contrary to other nuclear receptors that mainly bind a single specific ligand, there are numerous natural PPARγ ligands (Kliewer et al., 1997; Salam et al., 2008; Yu et al., 2004) (Table 1). By the size of its binding cavity, PPARγ is able to bind a variety of natural or synthetic lipophilic acids, in particular fatty acids or their derivatives called eicosanoids (Krey et al., 1997). Fatty acids can bind PPARα and PPARγ at a micromolar levels: IC50 = 1.2 μM, 1.6 μM for arachidonic acid (AA), 1.2 μM, 6.2 μM for linoleic acid (LA), 1.2 μM, 6.0 μM for α-linolenic acid (ALA), 1.1 μM, 1.6 μM for eicosapentaenoic acid (EPA) for PPARα and γ respectively (Xu et al., 1999).

3.1. Natural agonists

3.1.1. Polyunsaturated fatty acids

3.1.1.1. n-6 series. The position of the first double bond from the methyl end defined unsaturated fatty acids as n-3 or n-6 PUFA. ALA (C18:3n-3) and LA (C18:2n-6) are considered as essential fatty acids because they cannot be endogenously synthetized and thus must come from food. They are converted into long chain PUFA by elongation and/or desaturation steps of the respective n-3 or n-6 series. LA is an essential n-6 fatty acid and it has been demonstrated by a docking approach to bind human PPARγ (Yu et al., 2004).

LA derivatives can inhibit inflammatory signaling (Bull et al., 2003). For example, eicosadienoic acid (C20:2n-6), can be elongated from LA and is able to down-regulate inflammatory responses such as nitric oxide, PGE_2 or TNFα production by LPS-treated murine macrophage cell line RAW264.7 (Huang et al., 2011).

As previously described, LA is a natural PPARγ agonist (IC50 = 6.2 μM (Xu et al., 1999)) and its metabolites such as hydroxyoctadecadienoic acid (HODE) can also act through PPARγ. LA can be oxidized by several enzymes including 15-LOX into 13-HODE which can be dehydrogenated into 13-oxoHODE. Both these LA-derived metabolites are able to transactivate PPARγ in a dose dependent manner as demonstrated in an enterocyte-like cell line transfected with a PPRE (Bull et al., 2003). Similarly, pre-treatment with 13-oxoHODE was more potent to decrease IL-8 secretion in colonic epithelial cells compared to synthetic PPARγ agonist troglitazone and is an endogenous PPARγ ligand (Altmann et al., 2007). In atherosclerosis, there is an accumulation of HODE in the plaque. While HODE are mainly considered as a marker for lipid accumulation and oxidative stress, HODE are also signaling molecules. In a recent cell culture study, Vangareti et al. have investigated the role of HODE on apoptosis in monocytes and macrophages compared to other C18 fatty acids such as LA or ALA (Vangaveti et al., 2014). They found that 9-HODE and 13-HODE at 30 μM regulate apoptosis in human THP-1 cells. By the use of T0070907, a specific PPARγ antagonist, they have shown that the pro-apoptotic effect of HODE in monocytes is mediated through PPARγ (Vangaveti et al., 2014). They found no evidence of GPR32 involvement by a siRNA approach (Vangaveti et al., 2014). By contrast, ALA or LA had no significant effect on apoptosis markers in THP-1 cells (Vangaveti et al., 2014).

Compelling studies have observed an association between alterations in intestinal microbiota composition and several chronic conditions, including obesity and inflammatory diseases.

Table 1
List of natural and synthetic PPARγ ligands.

Natural ligands					Synthetic	
Unsaturated FA	**Oxidized PUFA derivatives**	**Nitrated fatty acids**	**Flavonoids**	**Other nutrients**	**Man-made environmental**	**Drugs**
LA	$15dPGJ_2$	Nitrolinoleic acid (Narala et al., 2014)	Curcumin (Zhang et al., 2006)	Glutamine (Fiatte et al., 2008; Sato et al., 2006)	Phthalates	Glitazones
EPA (Marion-Letellier et al., 2008)	$15dPGJ_3$				Bisphenols	
DHA (Marion-Letellier et al., 2008)	PGJ_2					
CLA (Yu et al., 2002)	9-HODE					
	13-HODE	Nitrooleic acid (Narala et al., 2014; Schopfer et al., 2005)	Capsaicin (Kim et al., 2004)			
	15-HETE					
	LTE_4 (Paruchuri et al., 2008)			Arginine (Liu et al., 2008)		
	NPD1(Zhao et al., 2011)					
	RvD1 (Liao et al., 2012)		Resveratrol (Ulrich et al., 2006)	Butyrate (Kinoshita et al., 2002; Wachtershauser et al., 2000)		
			EGCG			
			genistein			