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Long-chain polyunsaturated fatty acids regulation of PPARs, signaling: Relationship to tissue development and aging

Francisca Echeverría[a], Macarena Ortiz[a], Rodrigo Valenzuela[a,*], Luis A. Videla[b]

[a] Nutrition Department, Faculty of Medicine, University of Chile, Santiago, Chile
[b] Molecular and Clinical Pharmacology Program, Institute of Biomedical Sciences, Faculty of Medicine, University of Chile, Santiago, Chile

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ABSTRACT

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors that function as ligand-dependent transcription factors that can be activated by different types of fatty acids (FAs). Three isoforms of PPARs have been identify, namely, PPARα, PPARβ/δ, and PPARγ, which are able to bind long-chain polyunsaturated FAs (LCPUFAs), n-3 LCPUFAs being bound with greater affinity to achieve activation. FA binding induces a conformational change of the nuclear receptors, triggering the transcription of specific genes including those encoding for various metabolic and cellular processes such as FA β-oxidation and adipogenesis, thus representing key mediators of lipid homeostasis. In addition, PPARs have important roles during placental, embryonal, and fetal development, and in the regulation of processes related to aging comprising oxidative stress, inflammation, and neuroprotection. The aim of this review was to assess the role of FAs as PPARs ligands, in terms of their main functions associated with FA metabolism and their relevance in the prevention and treatment of related pathologies during human life span.

1. Introduction

Peroxisome proliferator-activated receptors (PPARs) constitute a group of transcription factors that belong to the nuclear receptor superfamily [1]. Three PPAR isoforms have been identify, namely, PPARα, PPARβ/δ, and PPARγ that are fully expressed in the organisms, although the quantitative pattern of expression is characteristic of each isoform [2]. PPARs are known to regulate several metabolic and cellular processes, including lipid and glucose metabolism linked to energy homeostasis, adipogenesis, inflammatory responses or oxidative stress, besides exerting a fundamental role in embryonic and fetal development [3–6]. These nuclear receptors are dependent upon endogenous or exogenous ligands for activation [7]. Among the endogenous or natural ligands, the essential fatty acids (FAs) linoleic acid (LA, 18:2, n-6) and α-linolenic acid (ALA, 18:3, n-3) and the eicosanoids derived from n-6 and n-3 FAs are the more important [7–11]. Exogenous or synthetic ligands comprise fibrates, used in the treatment of hypertriglyceridemia, and thiazolidinediones (TZDs) employed in diabetes management, which are PPARα and PPARγ ligands, respectively [7–11]. The DNA-binding domain of PPARs is the most conserved among nuclear receptors [12]. The interaction of ligands (specific fatty acids and lipid mediators) with the ligand-binding domain results in PPAR activation due to induction of a conformational change, leading to transcription of target genes [1,14]. From the metabolic point of view, PPARα and PPARβ are mainly involved in energy expenditure, whereas PPARγ regulates adipogenesis and energy load in adipocytes [1] (Fig. 1)..

FAs, the main source of energy in the body, contain a hydrocarbon chain and a terminal carboxylic group, and are classified according to the chain length and the degree of unsaturation [15,16], AL and ALA being considered as long-chain polyunsaturated FAs (LCPUFAs) [17]. In addition, a major feature of FAs is their regulatory capability, considering that they can function as signaling molecules acting on intracellular sensing systems such as PPARs [12], with saturated FAs being considered as poor ligands in comparison with LCPUFAs [8,18]. The latter FAs can also act upon extracellular receptors such as G-protein coupled receptor 120 (GPR120, also called free fatty acid receptor 4), resulting in anti-inflammatory effects with a secondary insulin-sensitizing action [19]. Besides, PPARs have been implicated in different aspects of pregnancy and development, including implantation, placentation, and trophoblast differentiation [20,21], suggesting that these transcription factors may constitute a link between energy metabolism and reproduction [22]. Aging is a biological condition in which PPARα expression is diminished, a feature that could be of importance in the prevention of diseases associated with older age [23,24], considering that PPARα has a key role in the maintenance and

* Correspondence to: Nutrition Department - Faculty of Medicine – University of Chile, Independencia 1027, Casilla 70000, Santiago 7, Chile.
E-mail address: rvalenzuelab@med.uchile.cl (R. Valenzuela).

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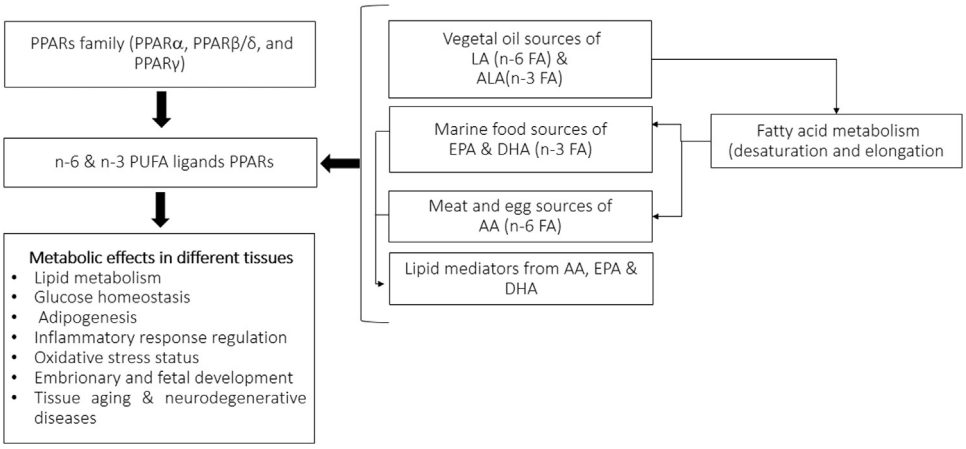

Fig. 1. Participation of LCPUFAs and lipid mediators in different actions mediated by PPARs. Abbreviations: PPARs; peroxisome proliferator-activated receptors, n-6 PUFA; n-6 & n-3 polyunsaturated fatty acid. LA; linolenic acid, ALA; alpha linolenic acid, EPA; eicosapentaenoic acid, DHA; docoxaehaenoic acid, AA; arachidonic acid.

re-establishment of the redox balance that can be altered by the pro-inflammatory status related to aging [25], exerting preventive neuro-protection to achieve normal brain aging [26]. In view of these considerations, the aim of this review was to assess the role of FAs as PPARs ligands, in terms of their main functions associated with FA metabolism and their relevance in the prevention and treatment of related pathologies during human life span, particularly embryonic development and aging (Fig. 1).

2. PPARs: general characteristics

The three PPAR isoforms, namely, PPARα (NR1C1), PPARβ/δ (NR1C2), and PPARγ (NR1C3) [27], are coded by individual genes with a high degree of similarity [1]. These isotypes have been identified in vertebrates including *xenopus,* mice, rats, hamsters, and humans [12]. In mice, the respective genes are localized in chromosomes 15, 17, and 6, and in chromosomes 22, 6, and 3 in humans [12,28]. The three isoforms act as sensors not only for FAs but also for FAs derivatives (eicosanoids and docosanoids) [12,29–31], steroid hormones, glucocorticoids, retinoic acids, and vitamin D, regulating diverse metabolic pathways [1,8].

The DNA binding domain of PPARs is the best conserved domain of all nuclear receptors, and is what characterizes this superfamily of nuclear receptors. This domain is composed of 2 zinc finger-like motif that forms a globular structure able to recognize a domain of 6 nucleotides in DNA [12]. Ligand binding to PPAR is followed by heterodimerization with 9-cis retinoic acid receptor (RXR) to achieve full activation as transcription factors [12]. The activated receptor binds to specific DNA sequences called PPAR response element (PPRE) present in genes under their control, which induces a conformational change in the nuclear receptor that allows transcription of coactivator proteins and their recruitment, with concomitant loss of transcription repressor proteins (Table 1) [1,13]. The size of the ligand binding domain of PPARs is 3–4 times bigger than in other nuclear receptors, thus explaining the greater binding capacity to a variety of endogenous and synthetics ligands [7].

3. PPARα

PPARα is expressed in tissues with a high FA oxidation activity, such as liver, brown adipose tissue, kidney, small intestine, heart, skeletal muscle, and nervous system cells [25,32–34]. In the liver, PPARα is fundamental in the regulation of (i) mitochondrial, peroxisomal, and microsomal FA oxidation systems [32] that ensure energy bioavailability in stress conditions such as fasting [33]; these include genes encoding for acyl-CoA oxidase (*ACOX*), carnitine palmitoyltransferase I (*CPT-I*), and carnitine palmitoyltransferase II (*CPT-II*) [33]; (ii) genes required for fatty acid desaturation (Δ*6-desaturase*); and (iii)

Table 1
General characteristics of peroxisome proliferator-activated receptor (PPAR) isoforms.

	PPARα	PPARβ/δ	PPARγ
Tissue where it is expressed	Adipose tissue, liver, kidney, small intestine, heart, skeletal muscle, neuron	Brain, adipose tissue, skin, skeletal and heart muscle	PPARγ$_1$: White and brown adipose tissue, large intestine, cells of the immune system, muscle, pancreas, liver, small intestine, kidney. PPARγ$_2$: adipose tissue PPARγ$_3$: white adipose tissue, macrophagues, large intestine
Endogenous ligands	Palmitoleic acid, PA, SA, OA, AL, AA, EPA	Fas	AL, AA, 15D-PGJ2, 9-HODE, 13-HODE, 15-HETE
Exogenous ligands	WY-14.643, clofibrate, gemfibrozil, nafenopin, bezafibrate, fenofibrate	L-165041, NSAIDs (antagonist)	TZDs, JTT–501, GW–7845, CDDO, BADGE (antagonist), LG–100641 (antagonist)
Target genes	APOA1, APOA2, APOA5, ACOX, CPT-I, CPT-II, gen de Δ6-desaturasa, PLTP; HMGCS2	ADRP, ANGPTL4, FIAF, EMA, ApoE, SPRR	LPL, fatty acid transport proteins, CD36 transporter, aP2
Function	– Regulates lipid metabolism – Regulates amino acids metabolism – Regulates lipoprotein synthesis – FAs oxidation – Energy availability during fasting – Mantainance of redox balance – Inhibits tumor growth and angiogenesis	– Stimulates β-oxidation and decreases circulating levels of free FAs and triglycerides – Raises HDL cholesterol – Role in maintaining and forming oxidative muscle fibers – Adipocyte differentiation – Epidermal maturation and skin wounds healing	– Inhibits the expression of TNFαin adipose tissue – Adipogenesis – Participates in pathways related to insulin sensitivity, type 2 diabetes mellitus, atherosclerosis, cancer – Increases hydrolysis of triglyceride-rich lipoproteins – -Promotes FAs uptake by the adipocyte