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

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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

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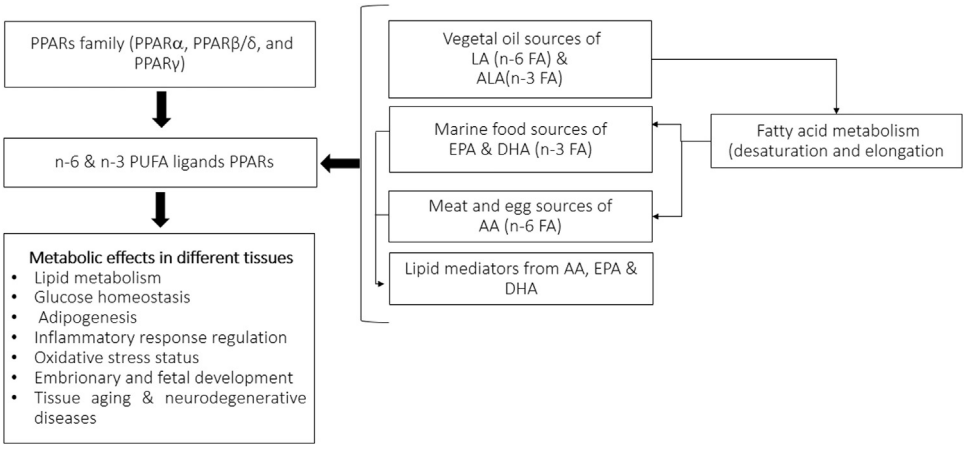

Fig. 1. Participation of LCPUFAs and lipid mediators in different actions mediated by PPARs. Abbreviations: PPARs; peroxisome proliferator-activated receptors, n-6 PUFA; n-6 & n-3 polyunsaturated fatty acid. LA; linolenic acid, ALA; alpha linolenic acid, EPA; eicosapentaenoic acid, DHA; docoxaehaenoic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

apolipoprotein genes (*APOA1*, *APOA2*, and *APOA5*) and those implicated in HDL metabolism (*phospholipid transfer protein, PLTP*) and ketone body synthesis (*hydroxy-methylglutaryl-CoA synthase 2, HMGCS2*) [3,33,35,36]. Target genes for PPARα action also comprise those for hepatic amino acid metabolism and inflammatory responses [33,35]. The activation of PPARα is known to attenuate or inhibit the production of mediators of vascular damage, lipotoxicity, inflammation, reactive oxygen species (ROS), endothelial dysfunction, angiogenesis and thrombosis [34,37–39], a feature that is achieved by (i) endogenous ligands (palmitic acid (C16:0, PA), stearic acid (C18:0, SA), oleic acid (C18:1 n-9, OA), LA, arachidonic acid (C20:4, AA), and eicosapentaenoic acid (C20:5, EPA); and (ii) exogenous agonists such as fibrates (WY-14.643, clofibrate, gemfibrozil, nafenopin, bezafibrate, and fenofibrate) [30].

Work by Poynter and Daynes [25] in C57BL/6 mice showed that PPARα, their ligands, and the respective activated genes downregulate activated nuclear transcription factor-κβ (NF-κβ) and its target genes *interleukin-6* (*IL-6*), *interleukin-12* (*IL-12), macrophage migration inhibitory actor (MIF*), *cyclooxygenase-2* (*COX-2*), and *tumor necrosis factor-α* (*TNF-α*), suggesting that PPARα signaling could have an important role in clinical practice in order to maintain redox balance during old age and its restoration after inflammatory or oxidative stress states. In addition, PPARα is known to inhibit tumor growth and angiogenesis [34,40], which seem to be mediated by direct and indirect antiangiogenic effects and by its anti-inflammatory activity [41]. A possible mechanism for PPARα-mediated tumor growth inhibition may involve suppression of signaling by hypoxia-inducible factor 1α (HIF-1α), as shown in cancer cells [40] (Table 1).

4. PPARβ

PPARβ is highly expressed in brain, adipose tissue, skin, and skeletal and cardiac muscles [42–44]. Major ligands of PPARβ are FAs,L-165041, and the nonsteroidal anti-inflammatory drugs (NSAIDs, antagonist) [31]. The group of PPARβ target genes includes keratinocyte and sebocyte differentiation marker genes and adipocyte genes, comprising *adipose differentiation-related protein (ADRP), angiopoietin-like 4 (ANGPTL4), fasting-induced adipose factor (FIAF), epithelial membrane antigen (EMA), apolipoprotein E (ApoE), and small proline-rich protein (SPRR)* [45–47]. This nuclear receptor has been linked to *in vivo* lipid metabolism, considering that its activation stimulates β-oxidation and decreases the circulating levels of triglycerides and free FAs, which prevents adipocyte hypertrophy and hyperplasia [48].This feature and the increasing effect on HDL-cholesterol levels point to PPARβ as a suitable alternative for the treatment of dyslipidemia [43,48].

In addition, PPARβ has a role in maintaining and forming of oxidative muscle fibers (type I) [43], the activation of which leads to the transformation of muscle fibers, increasing the oxidative fibers type in relation to the glycolytic ones, which has a protector role against obesity in mice [43,49]. Besides, PPARβ expression is increased during adipocyte differentiation, specifically during the early stages, with LCPUFAs acting as PPARβ ligands being able to promote PPARγ gene expression leading to maturation and differentiation of adipocytes [50]. Interestingly, PPARβ has a critical role in epidermal maturation and healing of skin wounds, through the accelerated differentiation of keratinocytes that synthesize growth factors that promote re-epithelialization [51] (Table 1).

5. PPARγ

There are three variants of PPARγ, namely, $PPAR\gamma_1$, $PPAR\gamma_2$, and $PPAR\gamma_3$ [52,53]. The former is highly expressed in brown and white adipose tissue, large intestine, and immune system cells, and is also found in several tissues such as muscle, pancreas, liver, small intestine, and kidney; $PPAR\gamma_2$ is expressed in adipose tissue, whereas $PPAR\gamma_3$ is expressed in macrophages, large intestine and white adipose tissue [3,52–55]. Studies show that this nuclear receptor participates in pathways related with insulin sensitivity, type 2 diabetes, cell differentiation, atherosclerosis, and cancer [54]. Major ligands of PPARγ are FAs such as LA, AA, and conjugated linoleic acid (CLA), prostaglandins for instance 15-Deoxy-Delta-12,14-prostaglandin J2 (15D-PGJ2), and oxidized FAs such as 9-Hydroxyoctadecadienoic acid (9-HODE), 13-Hydroxyoctadecadienoic acid (13-HODE), and 15-Hydroxyicosatetraenoic acid (15-HETE). Exogenous ligands comprise TZDs, no TZDs (JTT-501, GW-7845), synthetic triterpenoids (CDDO; partial agonist), bisphenol A diglycidyl ether (BADGE; antagonist), and LG-100641 (antagonist) [55]. It has been shown that the pro-inflammatory cytokine TNFα expressed by adipocytes is associated with insulin resistance and with a decrease in the insulin signal transduction pathway, which are inhibited by PPARγ agonists in the adipose tissue of obese rodents [56–58]. Studies on the effect of a butter enriched with cis-9, trans-11 CLA in rats fed with high-fat diet revealed higher levels of PPARγ than controls, increasing gene transcription related to insulin signaling, glucose uptake, and uptake and storage of FAs, resulting in the prevention of hyperinsulinemia with increased HDL-cholesterol levels [59].

PPARγ is fundamental in the differentiation of adipocytes from adipocyte precursor cells [60]. Unlike PPARβ, it is expressed during final stages of differentiation process [61] and promotes adipogenesis in fibroblasts NIH-3T3 exposed to specific activators [62]. In adipocytes, PPARγ rises the hydrolysis of triglyceride-rich lipoproteins by lipoprotein lipase (LPL), with concomitant increases in the transcription of genes involved in the cellular uptake of FAs by the adipocyte protein 2 (aP2), the fatty acid transport protein (FATP), and the fatty acid transporter CD36 [3,63] (Table 1).

6. FAs: general characteristics

FAs are molecules containing a hydrocarbon chain and a terminal carboxyl group. They are an important energy source because they provide 9 kcal/g and are stored as triglycerides in the human body, being the principal reservoir of energy in the body [15]. These are classified as saturated (no double bond) or unsaturated (with at least one double bond between carbon–carbon) [16]. Unsaturated FAs are divided into two subgroups, namely, monounsaturated (with a single double bond) and polyunsaturated (with 2 or more double bonds) [15]. Furthermore, according to the length of the hydrocarbon chain FAs are classified as short chain (less than 8 carbons), medium chain (between 8 and 12 carbons), and long chain (more than 12 carbons) FAs [15]. Linolenic acid (C18:2 n-6, LA) and alpha linolenic acid (C18:3 n-3, ALA) are LCPUFAs which are the only essential FAs for many species of animals, including humans, because they cannot be synthesized by the organism and must be consumed in the diet [17]. Consuming large amounts of n-6 FAs increases the plasma concentrations of eicosanoids derived from AA metabolism, specifically prostaglandins, thromboxanes, leukotrienes, hydroxylated FAs, and lipoxins. These bioactive products contribute to the formation of thrombi and atheromas in the blood vessels, development of allergic and inflammatory disorders, and excessive cell proliferation [63]. Instead, n-3 FAs counteract the deleterious effects of n-6 FAs eliciting (i) decreases in the concentration of thromboxane A_2 (a potent vasoconstrictor and platelet aggregator); (ii) diminutions in the production of metabolites derived of prostaglandin E_2; (iii) increases in the concentration of thromboxane A_3 (a weak platelet aggregator and vasoconstrictor);(iv) enhancing the formation of leukotrienes B_5 (weak inducers of inflammation and chemotaxis); and (v) augmentations in the concentration of vasodilating prostacyclins such as prostaglandin I_3 [63].

An important aspect is the pathological process that occurs in nonalcoholic fatty liver disease (NAFLD), a condition in which oxidative stress of nutritional origin (fat and carbohydrates overload), in association with obesity, produces a significant and drastic decrease in

the activity of the Δ-5 and Δ-6 desaturase enzymes in the liver [64]. This alteration, in addition to producing lower synthesis of LCPUFAs, especially n-3 FAs, causes a decrease in hepatic levels of PPARα [65], a situation that directly increases the pro-lipogenic and pro-inflammatory status of the liver, features that are coupled to enhancements in hepatic n-6/n-3 ratios [66,67] and levels of sterol regulatory element-binding protein 1c (SREBP-1c) [65] and NF-κB [68], respectively.

In addition to the interaction of n-3 LCPUFAs with PPAR receptors as a genomic mechanism leading to upregulation of gene expression, n-3 LCPUFAs can trigger non-genomic pathways eliciting antioxidant and anti-inflammatory responses [69]. These include (i) spontaneous lipid peroxidation of n-3 LCPUFAs with formation of J_3 isoprostanes promoting nuclear factor-erythroid 2 related like 2 (Nrf2) activation, with induction of antioxidant enzymes [69,70]; and (ii) metabolism of n-3 LCPUFAs by either *cyclooxygenase-1 (COX1)* and *5-lipoxygenase (5-LOX)* pathways generating E(D) resolvins and protectin D1, or by the cytochrome P450 NADPH-dependent epoxygenase system producing epoxide derivatives, all of which constitute potent anti-inflammatory mediators [69,71].

7. N-3 LCPUFAs and gene expression regulation by PPARs

FAs are molecules that not only provide energy but they are also metabolic regulators [12]. These can serve as signaling molecules affecting directly intra or extracellular sensor systems or after conversion to specific fatty acid derivatives. An example of such sensor systems are PPARs [18]. When excessive lipid intake occurs, the hepatic expression of PPARα significantly decreases [65], a transcription factor controlling liver FA β-oxidation [72], whereas the expression of PPARγ increases [73,74] thus enhancing lipogenesis [61]. Therefore, search and identification of target genes has primarily focused in hepatocytes and adipocytes, where both play a key role in systemic lipid metabolism considering that PPARs exert a regulatory actions on lipid homeostasis [12].The observations that high fat diet (HFD) induces the expression of *RXR* and *fatty acid binding protein* (*FABP*), whereas LCPUFAs activate PPARs, putting forward the contention that the expression of the above genes could be mediated by PPARs [75]. Although all three PPAR isoforms have the ability to bind FAs [18], nevertheless, saturated FAs are poor ligands compared to LCPUFAs, with PPARα having the greater affinity [8,18], which is more powerful for n-3 than for n-6 [62,76]. N-3 LCPUFAs have features that allow optimal binding to PPARs, including a polar head (the carboxyl group), a binding region (the long carbon chain), and a hydrophobic tail, and because they are highly unsaturated they can be easily oxidized to activate PPARs [7]. This contention is supported by studies on PPARβ activation in mice skeletal muscle myocytes by FAs in which both OA and ALA were able to activate PPARβ compared to PA, however, by combining OA or ALA with PA, PPARβ activation was reduced to the level observed for PA alone [77]. Furthermore, mice supplemented with different doses of fish oil (7% EPA plus 24% docosahexaenoic acid (C22:6, DHA)) and safflower oil (46% OA plus 45% LA), at higher doses of fish oil lower doses of safflower were given, an inverse linear relationship between dose of fish oil and body weight was observed, concomitantly with a greater activation of the PPARα target genes *ACOX* and *medium chain acyl-CoA dehydrogenase* (*MCAD*) [76].These data suggest that PPARα activation by n-3 LCPUFAs promotes FA β-oxidation and thereby weight loss [76]. It is important to note that LCPUFAs metabolites such as like eicosanoids are also able to activate PPARα and PPARy receptors more specifically and selectively [30], with monounsaturated FAs having a strong preference for PPARα, suggesting that this receptor might have a specific roles in situations of lipid overload from the diet [8] (Table 1).

8. Role of PPARs in placental, embryonic, and fetal development: n-3 LCPUFAs participation

PPARs have been implicated in different aspects of pregnancy and development, including implantation, placentation and trophoblasts differentiation [20,21]. PPARs isoforms are co-expressed in ectodermic, mesodermic or endodermic tissues of embrionary origin with relative levels that vary among cellular types [12]. RXR and PPARγ are essential for cellular fusion from cytotrophoblast to syncitiotrophoblast and mandatory for placentation, features that are misregulated in case of a pathological placenta [78], suggesting that PPARs could be a link between energy metabolism and reproduction [22]. The three isotypes of PPAR are expressed from the seventh week of gestation in endoderm and mesoderm cells [79]. Levels of transcription of PPARα y PPARβ are similar during estrous cycle [79,80], and levels of PPARγ mRNA remain stable during the cycle [80].

The high expression levels of PPARs observed during the luteal phase and the low levels found during the follicular phase suggest an association with steroids function [22]. These receptors participate in uterine functions such as steroidogenesis, cytokine production, and angiogenesis during estrous cycle and/or pregnancy [81]. PPARs are expressed in cytotrophoblasts and syncitiotrophoblasts in the placenta and their activation can stimulate the production and secretion of some hormones such as gonadotropin, which is required during pregnancy and fetal development [82]. Consequently, PPARs are essential for the placental normal function [22]. Meher et al. observed a relation between adverse pregnancy outcomes and altered levels of nutrients in the mother, specifically, folic acid, vitamin B12, and n-3 FAs, suggesting that high levels of these nutrients in the mother could modulate the activity of key transcription factors like PPARs controlling placentation and their angiogenesis, thus representing key factors in placental growth and fetal development [83].

The exchange of nutrients through the placenta is an important factor for proper fetal development, which upon derangement constitutes one of the main causes in intrauterine growth retardation. Chen et al. [84] demonstrated that PPARγ modulates the expression of L-like amino acid transporters [LATs] in human placenta, and that a reduction in the expression of LAT1 and LAT2 in newborns that are small for their gestational age is associated with downregulation of PPARγ. This suggests that this transcription factor participates in the control of fetal development and that it could represent a therapeutic target for intrauterine growth retardation [84]. In humans, poor fetal growth is related to a higher risk of non-communicable disease (NCDs) during adulthood, particularly with diseases characteristic of metabolic syndrome and cardiovascular diseases [85]. A preclinical study showed that dietary protein restriction during gestation led to a decrease in the methylation status of PPARα genes in the liver of the descendants [86]. Furthermore, hypomethylation of PPARα genes persisted after weaning, when the direct influence of the mother's dietary restriction had ceased, pointing to a stable modification in the epigenetic regulation of the expression of this transcription factor. On the other hand, PPARγ was not altered by protein restriction, which suggests that the diet effect in the regulation of gene expression of the descendants is gene-specific [86]. It is important to note that enhanced PPARα activity is associated with an increase of ACOX expression [72] increasing the activity of peroxisomal β-oxidation pathway [86], whereas Δ6-desaturase expression is suppressed [87] in agreement with the lower DHA concentration found in the liver of the descendants [88]. In general, these changes in epigenetic regulation of the expression of PPARα as consequence of protein restriction in the mother are consistent with previous studies of hypertension development and impaired metabolism of lipids and glucose during adulthood [86].

Administration of PPARγ antagonists to pregnant rats resulted in an increment of blood pressure, endothelial dysfunction, proteinuria, and an imbalance of angiogenic proteins, which are all features of preeclampsia [89]. Then, the role of PPARγ as a therapeutic target for

preeclampsia was investigated with the administration of the agonist of this nuclear receptor rosiglitazone to rats after surgery to reduce uterine perfusion [90]. It was observed a decrease in both hypertension and endothelial dysfunction, suggesting that PPARγ could have a protective role in endothelial function in preeclampsia [90]. It is known that PPARs are involved in fetal programming, development in the first years of life, and the risk of NCDs during adulthood. Although n-3 LCPUFAs are strong ligands for PPARs and trigger the expression of PPARs indifferent tissues including placenta, liver, lungs, and brain, further studies are needed to identify different factors in the mother's diet, the concentration of ligands, specially DHA, that could influence the activation of PPARs and, thereby, the placental, embryonic, and fetal development [83] (Table 1).

9. PPARs, aging, and oxidative stress

Aging is characterized by a diminution in PPARα expression in various tissues including the liver and heart, representing a key target in the prevention of diseases associated with old age [23,24]. Studies in the PPARα knockout (KO) mouse assessing the relationship between metabolism changes, aging, and the absence of this transcription factor, revealed significant changes in glucose metabolism and lipid profiles, with reduction in liver glucose and glycogen levels and subsequent steatosis development in older age [91]. Furthermore, aged rats exhibited a decrease in the activity of PPARα-regulated genes involved in β-oxidation, such as liver ACOX, which is accompanied by changes in the composition of FAs in brain, increasing the very long chain saturated fatty acids (SFAs) (C20:0, C22:0, C24:0), monounsaturated fatty acids (MUFAs) (C16:1, C18:1, C20:1, C22:1, C24:1), and decreasing the LCPUFAs AA and DHA, which are related to the progression of brain aging [92].

High levels of cellular oxidative stress contribute to the development of various pathologies and aging [93]. Old mice subjected to exogenous PPARα ligand supplementation exhibited a diminution of the nuclear activity of NF-κB to levels observed in young mice, suggesting that PPARα signaling may have a crucial role in maintaining and restoring redox balance altered by pro-inflammatory and/or oxidative stress mechanisms underlying aging [25]. In this respect, it was suggested that PPARα and their endogenous ligands have a role in neuroprotection against oxidative stress, which is key in neurodegenerative diseases, contributing to a normal brain aging [26,94]. PPARα is expressed in neuronal cells and astrocytes, and participates in cellular proliferation, apoptosis, and in differentiation and maturation of neuronal cells. [26,34]. PPARα KO mice exhibit an alteration in the age-dependent declination of progenitor neuronal cell proliferation in brain areas of major relevance, which suggests a role of PPARα in the decrease of neurogenesis as a consequence of age [95]. Deplanque et al. showed that PPARα activators decrease the negative consequences of ischemic infarction independently of their effect on lipid metabolism, a neuroprotective role that may result from PPARα activation leading to the increase in the activity of the antioxidant enzymes, with concomitant decrease in the expression of adhesion proteins [26].These considerations suggest that endogenous and exogenous PPARα agonists could be useful as a prevention measure for neurodegenerative diseases and ischemic injury, especially in the elderly and/or in patients with high cardiovascular risk [26,95] (Table 1).

Considering the different aspects discussed in this review, an important question to unravel is how preclinical evidence clearly demonstrating the metabolic benefits of LCPUFAs through activation of PPARs can be extrapolated to the clinical level. For instance, controlled clinical trials using dietary supplementation with n-3 LCPUFAs on cardiovascular health have presented conflicting results [96,97], the clinical basic background for these interventions being based on how n-3 LCPUFAs exert PPARs regulation [98]. In this context, the information obtained in animal models that can be adequately extrapolated to humans is the case of non-alcoholic fatty liver, in which low hepatic levels of n-3 LCPUFAs are directly linked to reduced activity of PPAR-α [66,99,100], but when patients with hepatic steatosis are supplemented with n-3 LCPUFAs, a significant improvement of the disease is observed [101–103]. A similar situation is observed in post-surgical liver damage prevention, as shown by the anti-inflammatory effects of n-3 LCUFA supplementation found against ischemia-reperfusion injury [104]. The beneficial effects of n-3 LCPUFA supplementation may be ascribed to PPAR-α activation, as evidenced in preclinical studies [105].

10. Conclusions

Data discussed point to signaling by PPAR transcription factors as a crucial cellular event regulating energy availability through balance in glucose and lipid metabolism, which can be triggered by ligands, mainly n-3 LCPUFAs. PPAR signaling is exerted on gene transcription involving (i) pathways of insulin action, glucose uptake, FA β-oxidation, and adipocyte differentiation; and (ii) placental and embryonic

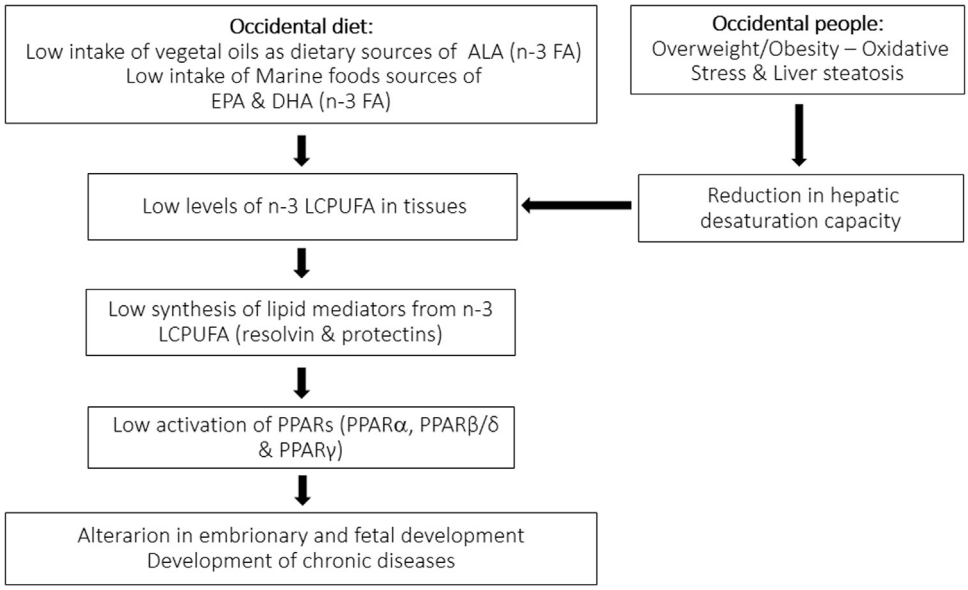

Fig. 2. Effects associated to a low tissue levels of LCPUFAs and relation with PPARs activation. Abbreviations: n-3 LCPUFA; long-chain polyunsaturated fatty acid.

development, fetal growth, and in pathologies related to oxidative stress and brain aging. Therefore, PPAR activation by n-3 LCPUFAs and the consequent promotion of gene transcription may have a fundamental role in first stages of life and in the prevention and treatment of cardiovascular, metabolic, and neurodegenerative pathologies through the life cycle (Fig. 2). Therefore, the standardization of clinical trials, namely, the selection of dosages, sources of n-3 LCPUFA, routes of administration, and intervention times, in large scale, double-blind and placebo-controlled studies, represents a major challenge to validate an efficient interaction between the role of LCPUFA in the regulation of PPARs and efficient clinical effects from development to aging..

Conflicts of interest

Authors declare no conflict of interest.

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