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Synthesis of DHA (omega-3 fatty acid): *FADS2* gene polymorphisms and regulation by PPARα

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Abstract – In humans, in several biological systems, in particular the nervous system, the *FADS2* gene transcribes Δ6-desaturase, which is the rate-limiting enzyme for converting α-linolenic acid into docosahexaenoic acid (an n-3 fatty acid). The peroxisome proliferator-activated receptor α (PPARα) modulates the transcription of *FADS2* gene by interacting with a second transcription factor: the retinoid X receptor α (RXRα). These transcription factors take the form of a PPARα-RXRα heterodimer and are modulated by the ligands that modify their respective structures and enable them to bind to the peroxisome proliferator response element (PPRE) located in the promoter region of the *FADS2* gene. Free estradiol induces the activation of PPARα *via* two pathways (i) transcription through genomic action mediated by an estrogen receptor; (ii) a non-genomic effect that allows for phosphorylation and activates PPARα *via* the ERK1/2-MAPK pathway. Phosphorylation is an on/off switch for PPARα transcription activity. Since Δ6-desaturase expression is retro-inhibited by free intracellular DHA in a dose-dependent manner, this position paper proposes an original hypothesis: if DHA simultaneously binds to both phosphorylated PPARα and RXRα, the resulting DHA-PPARαP-RXRα-DHA heterodimer represses *FADS2* gene *via* PPRE. The retinoic acids-RARα-RXRα-DHA heterodimer would not dissociate from corepressors and would prevent coactivators from binding to *FADS2*. We speculate that SNPs, which are mostly located on PPRE, modulate the binding affinities of DHA-PPARαP-RXRα-DHA heterodimer to PPRE. The DHA-PPARαP-RXRα-DHA heterodimer's greater affinity for PPRE results in a decreased production of D6D and DHA. *FADS2* promoter polymorphism would increase the competition between DHA and other ligands, in accordance with their concentrations and affinities.

Keywords: *FADS2* / Δ6-desaturase / DHA / PPARα / regulation

Résumé – Synthèse du DHA (acide gras oméga-3) : polymorphismes du gène *FADS2* et régulation par PPARα. Dans plusieurs systèmes biologiques humains, en particulier au niveau cérébral, le gène *FADS2* produit la Δ6-désaturase, l'enzyme qui catalyse la conversion de l'acide α-linolénique en acide docosahexaénoïque (DHA). Le récepteur activé par les proliférateurs de peroxysomes (PPARα) module la transcription de *FADS2* en interagissant avec un second facteur de transcription, le récepteur des rétinoïdes X (RXRα). Sous forme d'hétérodimère PPARα-RXRα, ces facteurs de transcription sont modulés par leurs ligands respectifs qui modifient leurs structures, et leur permettent de se lier à l'élément de réponse au proliférateur de peroxysome (PPRE) situé dans la région promotrice de *FADS2*. L'œstradiol induit l'activation de PPARα selon deux voies : (i). par transcription grâce à son action génomique *via* un récepteur œstrogénique ; (ii) par son effet non génomique qui permet la phosphorylation et l'activation de PPARα par la voie ERK1/2-MAPK. L'expression de la Δ6-désaturase étant rétro-inhibée par le DHA intracellulaire de manière dose-dépendante, cet article présente l'hypothèse originale que la liaison simultanée de DHA sur PPARαP (phosphorylé) et RXRα rendrait l'hétérodimère DHA-PPARαP-RXRα-DHA répressif pour *FADS2 via* PPRE. L'hétérodimère acides rétinoïques-RARα-RXRα-DHA ne romprait pas sa liaison avec les corépresseurs et empêcherait la liaison avec des coactivateurs sur *FADS2*. Et nous pensons que les SNP, principalement sur PPRE, modulent les affinités de liaison de DHA-PPARαP-RXRα-DHA sur PPRE. Des productions plus faibles de D6D et de DHA résulteraient d'une plus grande affinité de DHA-PPARαP-RXRα-DHA. Le polymorphisme du promoteur de *FADS2* augmenterait la compétition entre le DHA et d'autres ligands en fonction de leurs concentrations et de leurs affinités.

Mots clés : : *FADS2* / Δ6-désaturase / DHA / PPARα / régulation

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1 Introduction

In humans, the Δ6-desaturase gene, a *FADS2* (fatty acid desaturase 2) gene is located on chromosome 11 (11q12–13.1) and is ubiquitously expressed, especially in the liver and brain (astrocytes) (Innis and Dyer, 2002; Nakamura and Nara, 2004), as well as in heart skeletal muscle, kidney, lung, prostate, testes, adipocytes, ovary, uterus and sebaceous glands (Ge *et al.*, 2003; Nwankwo *et al.*, 2003; Pédrono *et al.*, 2010). The *FADS2* gene transcribes Δ6-desaturase (D6D), which is a membrane-bound enzyme that desaturates and introduces a double bond at specific carbon positions along the chain of at least six substrates: four polyunsaturated fatty acids (PUFAs), one monounsaturated fatty acid (oleic acid) and one saturate (palmitic acid) (Guillou *et al.*, 2004; Rioux *et al.*, 2015). The same D6D acts on 18- and also on 24-carbon fatty acids in very-long-chain polyunsaturated fatty acid biosynthesis (d'Andrea *et al.*, 2002) (Fig. 1). D6D is the rate-limiting enzyme for converting α-linolenic acid (ALA) into docosahexaenoic acid (DHA) (n-3 fatty acid) (Fig. 1). Moreover, this FASD2 enzyme displays also a Δ8-desaturase activity on 20:2 n-6 and 20:3 n-3 which leads respectively to 20:3 n-6 and 20:4 n-3 (Park *et al.*, 2009).

There is a local competition between the substrates. The reactivity of the enzyme depends on the concentration of available substrates and their affinity with D6D. This is usually expressed as the enzyme's Km (Michaelis constant), an inverse measure of affinity (Ivanetich *et al.*, 1996; Rodriguez *et al.*, 1998). The conversion rate is also dependent on tissue type.

Several studies examining n-3 fatty acids have demonstrated the transcription of *FADS2*. Dietary n-3 fatty acid intake regulates D6D expression (Cho *et al.*, 1999), but conversion to DHA is limited (Burdge, 2006). D6D expression is subject to feedback regulation by dietary *polyunsaturated fatty acids* (*PUFAs*) (Nara *et al.*, 2002). Several studies in animals and *in vitro* models suggest that D6D expression and/or activity is regulated by steroid hormones (Childs *et al.*, 2008), as well as by insulin in the liver (Cho *et al.*, 1999). More 18:3n-3 is converted to 20:5n-3 and 22:6n-3 in women than in men (Burdge, 2006). However, the mechanisms regulating *FADS2* transcription have not been well established to date. This position paper aims to highlight the possible mechanisms involved – active molecules and transcription factors – while also considering the impact of single-nucleotide *FADS2* promoter polymorphisms.

2 Regulation of the *FADS2* gene

Peroxisome proliferator-activated receptor α (PPARα) modulates transcription of the *FADS2* gene (Guillou *et al.*, 2002) by interacting with a second transcription factor, retinoid X receptor α (RXRα) (Tang *et al.*, 2003). PPARα is stabilized through heterodimerization with RXRα, and there is a rapid turnover of excess protein unpaired with RXRα, unless it is bound by an appropriate ligand (Hirotani *et al.*, 2001). 17β-estradiol treatment upregulates PPARα mRNA expression and PPARα protein content (Campbell *et al.*, 2003).

Like most nuclear receptors, PPARα is organized into functional domains called A/B, C, D and E/F. The A/B domain supports an activation function that is independent of ligand binding (Activation Function-1: AF-1). The central region, which contains the DNA-binding domain (domain C), contains the best-conserved nuclear receptor: a highly conserved two-finger zinc structure that allows interaction with the DNA molecule at specific sites. The C-terminal region, which contains domain E, is the second-best conserved region and contains the E domain. This region is the repository of numerous functions, in particular, the ligand-binding-dependent activation of genes (activation function 2 (AF-2) (Bugge and Mandrup, 2010).

PPARα is a phosphoprotein. Phosphorylation is an on/off switch for transcriptional PPARα activity. The phosphorylation of serine residues (at Ser 6, 12 and 21) (Barger *et al.*, 2001) takes place in the A/B domain. It affects intramolecular communication, since the phosphorylation status of the A/B domain affects the activity of the E/F region of the protein (Burns and Vanden Heuvel, 2007).

These transcription factors take the form of a PPARα-RXRα heterodimer, located within the nucleus and are modulated by ligands that modify their tertiary structures, and enable them to bind to the peroxisome proliferator response element (PPRE) located in the promoter region of the *FADS2* gene. The PPAR contains a direct repeat sequence 1 (DR1) that assists in the regulation of human *FADS2* gene transcription (Tang *et al.*, 2003). The heterodimer bond to the PPRE modulates the transcription of the gene under highly specific conditions.

Several fatty acids prevalent *in vivo*, including palmitoleic acid (de Souza *et al.*, 2017; Bolsoni-Lopes *et al.*, 2013); oleic acid; linoleic acid (LA); α-linolenic acid (ALA); arachidonic acid (ARA) (Popeijus *et al.*, 2014; Kliewer *et al.*, 1997); eicosapentaenoic acid (EPA); and docosahexaenoic acid (DHA) (Diep *et al.*, 2002; Deckelbaum *et al.*, 2006; Dziedzic *et al.*, 2018) function as ligands for PPARα at concentrations consistent with those found in human serum. 8-HETE (8-hydroxyeicosatetraenoic acid) is also a natural agonist of PPARα (Yu *et al.*, 1995). This eicosanoid metabolite is a lipoxygenase product of arachidonic acid. It is believed to have tissue concentrations that are too low to be a ligand for PPARα.

In their free form, unlinked to binding proteins, these ligands compete with PPARα in accordance with their relative concentrations and dissociation constants.

Competing free-form DHA ligands (de Urquiza *et al.*, 2000); arachidonic acid (less efficiently) (Egea *et al.*, 2002); and 9-cis-retinoic acid (9-cis-RA), an active metabolite of vitamin A (Lengqvist *et al.*, 2004) activate RXR-mediated transcription. The crystal structure of DHA bound to the ligand-binding pocket of RXRα indicates that, despite its higher affinity, 9-cis-RA displays a significantly lower number of ligand-protein contacts than DHA, when positioned in the ligand-binding pocket (Egea *et al.*, 2002). By contrast, EPA (another n-3 fatty acid) fails to activate RXR-mediated transcription even though both DHA and EPA activate PPARα (Deckelbaum *et al.*, 2006).

Alternatively, transcription factor Elk-1, an ETS domain transcription factor encoded by the *ELK1* gene, could be one of the proteins that binds to the promoter region of the *FADS2* gene (Lattka *et al.*, 2010). Elk-1 is known to play a role in transcription regulation by forming ternary complexes with serum response factor (SRF) on the serum response elements (SRE) of gene promoters (Hipskind *et al.*, 1991). Elk-1

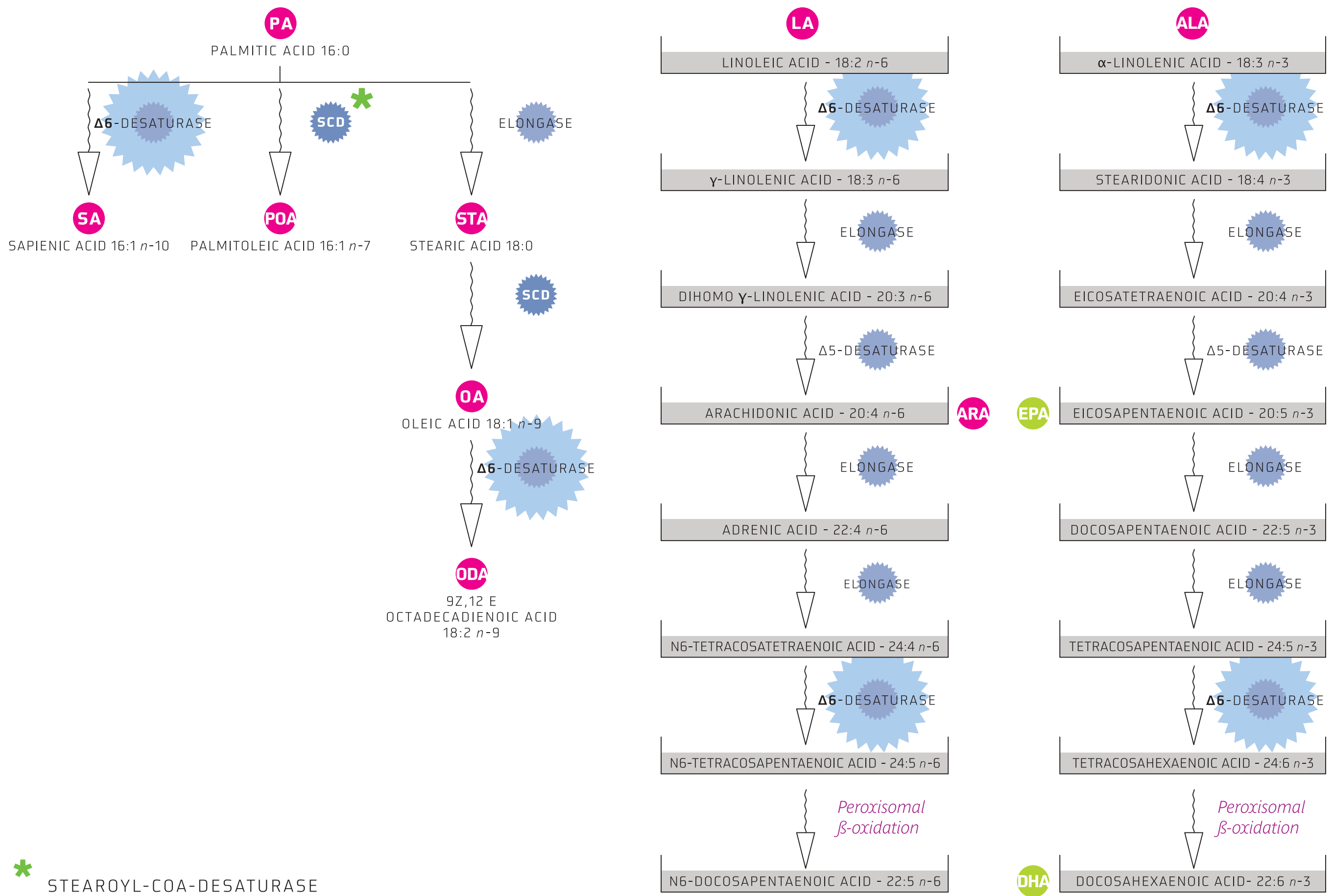

Fig. 1. The role of Δ6-desaturase in human fatty acid biosynthetic pathways.

contains a MAPK-binding motif (Yang *et al.*, 1998). Its activation and nuclear translocation require phosphorylation of serine 383–389, located in the C-terminal region of Elk-1, *via* the ERK-MAPK pathway, which results in a conformational change to Elk-1 (Lavaur *et al.*, 2007). *In silico*, phosphorylated ELK-1 would act as a coactivator.

Does biological sex affect the regulation of the *FADS2* gene? Observational evidence suggests that in populations that consume low levels of n-3 highly unsaturated fatty acids, women have higher blood DHA levels than men (Kitson *et al.*, 2010). Women of reproductive age are known to convert more ALA into DHA than men (Burdge and Wootton, 2002). Estrogens cause higher DHA concentrations in plasma cholesteryl esters in women than in men, by upregulating synthesis from ALA. This difference is independent of dietary differences. It has also been suggested that estradiol may increase the activity of the desaturation pathway because DHA synthesis has been shown to be almost 3 times greater in women who take oral contraceptive pills that contain ethinylestradiol than in women who do not, while testosterone stimulus decreases DHA status (Giltay *et al.*, 2004). This difference in conversion appears to be associated with estrogen and some evidence indicates that the expression of enzymes, including desaturases, involved in synthesizing DHA from ALA is higher in females. PPARα may mediate an estrogen-associated effect. However, because estrogens are weak ligands for PPARα, estrogen-mediated increases in PPARα activity probably occur through an indirect mechanism involving membrane-bound estrogen receptors (Kitson *et al.*, 2010). What is the relationship between the regulation of the *FASD2* gene by estradiol and by PPARα?

3 PPARα-RXRα regulation mechanisms governing the *FADS2* gene

As we mentioned above, at least two key molecules are involved in the regulation of the *FADS2* gene: free 17β-estradiol, when not bound to its binding protein SHBG (sex hormone-binding globulin) – when bound to SHBG it is not biologically active – and PPARα.

Free estradiol induces PPARα activation *via* two pathways. First, by transcription, through its genomic action on the *PPARα* gene, which is mediated by an estrogen receptor (ER) (Campbell *et al.*, 2003). Then, *via* its non-genomic effect, mediated by ERα, which allows phosphorylation and activates PPARα *via* the extracellular signal-regulated kinase/mitogen-activated protein kinase pathway (ERK1/2-MAPK) (Moreno *et al.*, 2010), as we will show below. This is also true of ELK-1.

Free estradiol has a synergistic effect with insulin-like growth factor 1 (IGF-1) (Majou, 2015). For example, several studies have shown this interaction in different brain regions

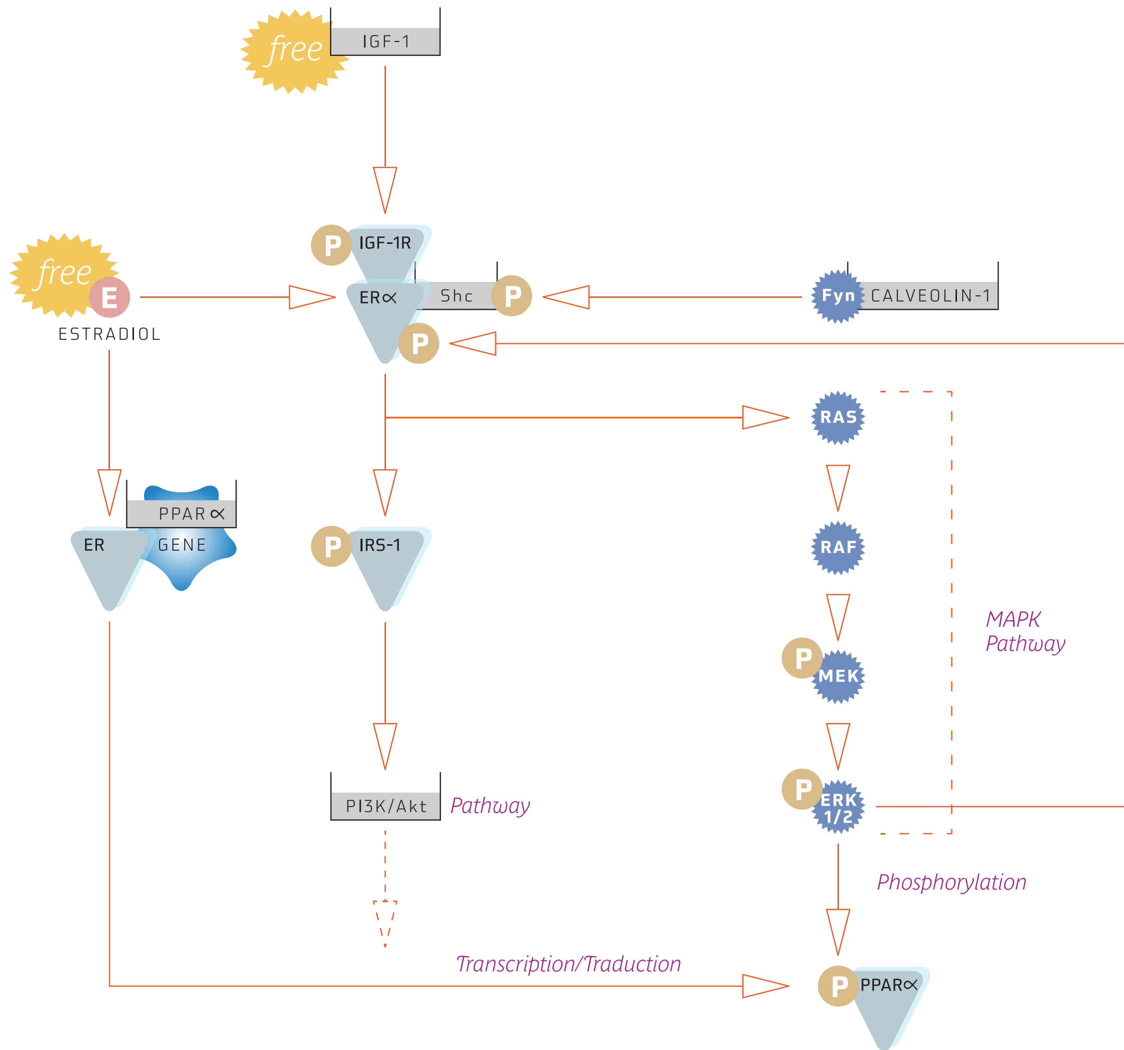

Fig. 2. Estradiol: PPARα transcription and phosphorylation.

(Garcia-Segura *et al.*, 2006; Varea *et al.*, 2010; Park *et al.*, 2014) and in breast cancer cells (Song *et al.*, 2010). The anabolic action of IGF-1 is mediated by the IGF-1 receptor (IGF-1R). When IGF-1 binds to the IGF-1R, it causes a conformational change to the receptor, inducing the auto-phosphorylation of tyrosine residues (Hubbard and Till, 2000). This leads to the recruitment of insulin receptor substrates (IRS-1–4), which in turn phosphorylate the tyrosine residues of the IRSs. Estradiol stimulates the rapid activation of the IGF-1R through phosphorylation *via* ERα, and induces the formation of a ternary protein complex comprising of phosphorylated Shc protein, ERα and IGF-1R (Song *et al.*, 2004). Adapter protein Shc generally acts by activating MAPK and phosphoinositide-3-kinase/Akt signaling pathways (Gu *et al.*, 2000; Vindis *et al.*, 2003). The tyrosine phosphorylation of *Shc* is mediated by the tyrosine kinase Fyn (Src family kinase) associated with caveolin-1 (scaffolding protein). Upon integrin ligation, Fyn is activated and binds to Shc *via* its SH3 domain. Shc is subsequently phosphorylated at tyrosine 317 (Wary *et al.*, 1998). IGF-1R activation stimulates MAPK kinases and consequently phosphorylation of ERK1/2. Activation of ERK1/2 may in turn lead to phosphorylation of ERα (Kato *et al.*, 1995; Russo *et al.*, 2002). This process leads to the activation of two main downstream signaling pathways: phosphoinositide-3-kinase (PI3K)/Akt and MAPK cascades (Zheng *et al.*, 2000). Thus, free estradiol induces MAPK activation (Kahlert *et al.*, 2000) and PPARα phosphorylation. This is also true of ELK-1 (Duan *et al.*, 2001) (Fig. 2).

The activated PPARα function is then regulated by its ligands, initially by binding to RXRα. Each PPARα and RXRα ligand modifies the tertiary structure of each transcription factor, creating a specific PPARα-RXRα heterodimer conformation that modulates binding to the *FADS2* gene. The change in ligand binding domain conformation (AF-2) following ligand binding induces the recruitment of coregulators. In the absence of a ligand or in the presence of an antagonist, PPARα interacts with nuclear receptor corepressors (NCoR1/2), which block coactivators from binding and prevent the formation of the transcriptional complex (Dowell *et al.*, 1999). This repression is reversible. When ligands (all-trans retinoic acid, 9-cis-retinoic acid) (Allenby *et al.*, 1993) are bound by RAR (the retinoic acid receptor), this promotes the dissociation of the PPRE-NCoR complex and the subsequent interaction of

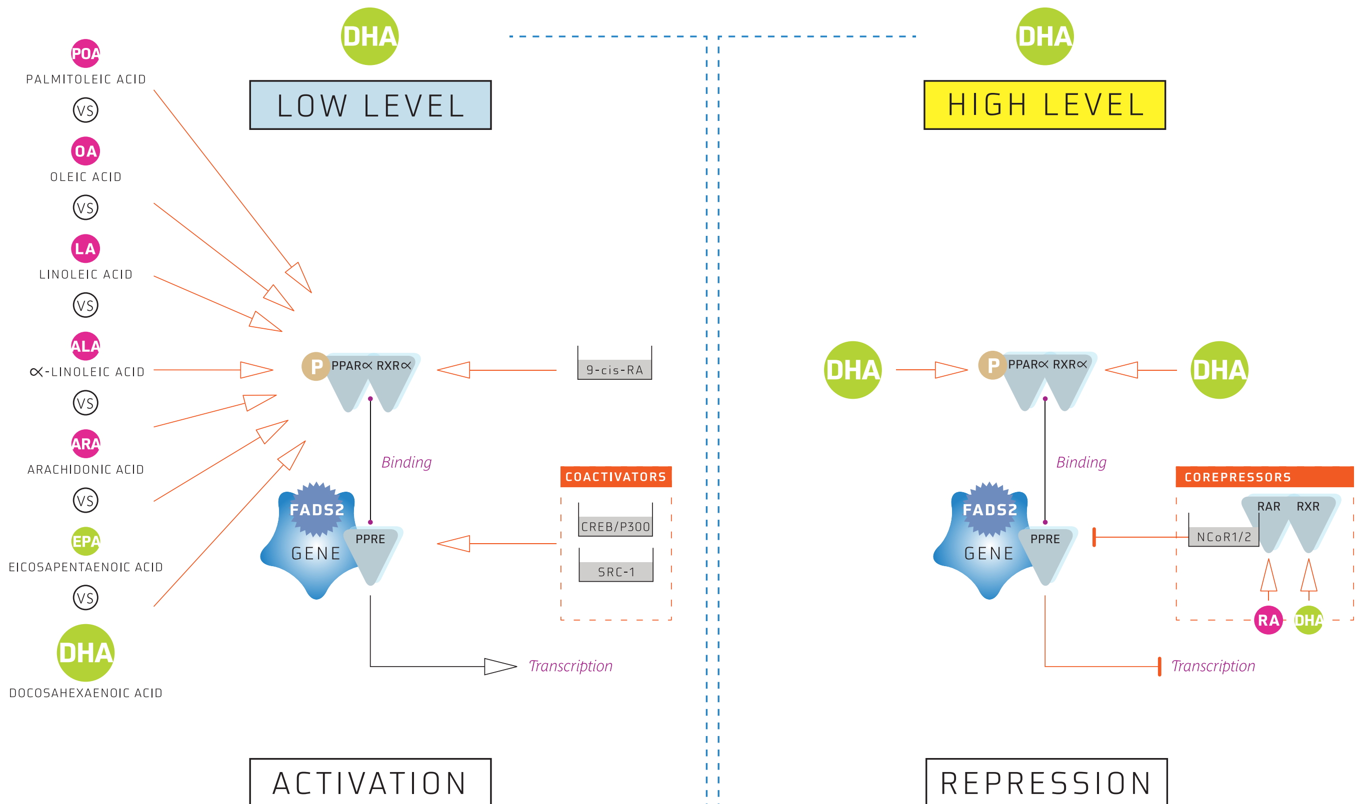

Fig. 3. Putative transcriptional regulation of the *FADS2* gene by PPARa-RXRa.

PPRE with one or more coactivator proteins including the cAMP response element-binding protein (CREB)/p300 (Dowell *et al.*, 1997), and steroid receptor coactivator 1 (SRC-1) (Gocke *et al.*, 2009).

Given that the expression of Δ6-desaturase is retro-inhibited by free intracellular DHA (Matzusaka *et al.*, 2002; Bewicz-Binkowska *et al.*, 2019), we propose the following original hypothesis: when DHA simultaneously binds to phosphorylated PPARαP and RXRα, the DHA-PPARαP-RXRα-DHA heterodimer represses the *FADS2* gene *via* PPRE. Thus, depending on its concentration and binding affinities with PPARα and RXRα, DHA could block other competing ligands from accessing the two transcription factors. Both blockage and inhibition are reversible (Fig. 3). They can be overcome by competition between free DHA not bound to its binding protein called FABP (fatty acid binding protein), which is tissue-dependent (the FABP-bound fraction is not biologically active) and (i) free MUFAs (palmitoleic acid, oleic acid) or PUFAs (LA, ALA, EPA, ARA), not bound to FABP, on PPARα; (ii) free 9-cis-retinoic acid, not bound to its binding protein (retinoic acid-binding protein), on RXRα. Indeed, in the absence of 9-cis-retinoic acid, DHA diminishes *FADS2* gene expression, and, in its presence, DHA upregulates its expression, especially in astrocytes (Dziedzic *et al.*, 2018). At 75µM, DHA represses PPARα transactivation almost completely, in a dose-dependent manner, and acts as an antagonist (Lee and Hwang, 2002); conversely, DHA activates at lower doses (Popeijus *et al.*, 2014).

Under basal conditions, the RARα-RXRα heterodimer represses the transcription of target genes by recruiting corepressor complexes on RARα, such as NCoR1/2 (Farboud *et al.*, 2003). When a ligand binds to RARα, it causes a change to the receptor's conformation. These changes cause a transition from transcriptional repressor activity to an activator state through the loss of corepressors and the recruitment of coactivator complexes, such as CBP/p300 and SRC-1. In the RARα-RXRα heterodimer, RXRα acts as a transcriptionally silent partner to RARα while it is active in the RXRα-RXRα homodimer. This phenomenon is known as the "subordination" of RXRα to RARα (Le Maire *et al.*, 2019): (i) in the RARα-RXRα heterodimer, an RARα agonist alone allows for the transactivation of target genes; (ii) an RXRα agonist (9-cis-RA) alone is unable to dissociate corepressors from the complex, preventing RXRα/coactivator binding; (iii) the binding of retinoic ligands to RARα and RXRα induces a binding synergy with a coactivator. Above a certain concentration, we suggest that DHA would both bind to PPARα and replace 9-cis-RA in binding with RXRα. In such a case, RXRα-DHA would form one heterodimer with PPARα-DHA, and another with RARα-retinoic acids. However, the retinoic acids-RARα-RXRα-DHA heterodimer would not dissociate in the presence of corepressors and would prevent binding with coactivators. Thus, above a certain concentration (Popeijus *et al.*, 2014), DHA retro-inhibits the *FADS2* gene, limits translation into D6D and the synthesis of DHA (Fig. 3).

It is interesting to note that the PPARα-RXRα regulation mechanisms governing the *FADS2* gene are similar to those governing the human *SCD* gene. Stearoyl-CoA desaturase (SCD) is a lipid-metabolic enzyme that catalyses the insertion of a double bond between carbon atoms 9 and 10 in the

saturated fatty acids palmitic acid and stearic acid to generate the mono-unsaturated fatty acids palmitoleic acid and oleic acid respectively (Fig. 1). SCD is a key, rate-limiting enzyme in the cellular synthesis of MUFAs from saturated fatty acids. A functional PPRE has been identified in the promoter of the *SCD* gene (Rakhshandehroo *et al.*, 2010) and its gene expression is regulated by PPARα (Miller and Ntambi, 1996; Hebbachi *et al.*, 2008).

DHA lowers the SCD gene's protein expression and mRNA expression levels (Bellenger *et al.*, 2004; On *et al.*, 2019). All-trans-retinoic acid and 9-cis-retinoic acid increase *SCD* mRNA expression in a dose-dependent manner (Miller *et al.*, 1997; Samuel *et al.*, 2001; Mahesh *et al.*, 2016). All these elements suggest that SCD regulation appears to be mediated by PPARα-RXRα and RARα-RXRα heterodimers with inhibition by DHA and activation by retinoic acids.

Thus, DHA seems to retro-regulate the *FADS2* gene in two ways: (i) directly, by inhibiting the expression of the *FADS2* gene, (ii) indirectly, by inhibiting the *SCD* gene. This repression downregulates SCD and decreases palmitoleic acid and oleic levels; these two MUFAs are PPARα ligands in competition with DHA.

Some studies suggest that D6D expression is dually regulated by SREBP-1c and PPARα (Matsuzaka *et al.*, 2002). However, SREBP-1c's mechanism of action remains under debate. The transcription factor, sterol regulatory element-binding protein (SREBP)-1c, controls lipogenesis in the liver (Shimano *et al.*, 1999), but also in astrocytes (Tabernero *et al.*, 2002) among other tissues. It regulates the expression of several genes that encode enzymes involved in fatty acid synthesis, in particular stearoyl-CoA desaturase (SCD)-1. SCD-1 catalyzes the rate-limiting step in biosynthesis (Kim *et al.*, 2002). SCD-1 has a specific affinity for palmitic and stearic acid. Palmitoleic acid is synthesized from palmitic acid (Fig. 1) directly by desaturation (SCD-1) (likewise, oleic acid is synthesized from stearic acid). Palmitoleic acid is regarded as a lipid-controlling hormone, or "lipokine", because it modulates lipid metabolism. This characteristic (regulatory signal) distinguishes palmitoleic acid from oleic acid (Cao *et al.*, 2008). Otherwise, palmitoleic acid functions as a ligand for PPARα and increases its transactivation (Popeijus *et al.*, 2014). Thus, we can assume that the regulation of D6D expression by SREBP-1c is carried out indirectly *via* SCD-1 and the synthesis of palmitoleic acid. This regulation would be upstream of PPARα and complementary to this transcription factor (Fig. 4).

SREBP-1c is bound to two other proteins: SCAP (SREBP-cleavage-activating protein), a polytopic membrane protein that serves as an escort for both SREBPs (Sakai *et al.*, 1997) and Insig-1 (insulin-induced gene 1). The dissociation of Insig-1 from the SREBP-SCAP complex allows the complex to migrate from the endoplasmic reticulum to the Golgi apparatus, where SREBP is cleaved by S1P and S2P (site-1 and −2 protease) – two enzymes that are activated by SCAP. The cleaved SREBP-1c then migrates to the nucleus and acts as a transcription factor to bind to the sterol regulatory element (SRE). The retention of the SREBP-SCAP complex in the endoplasmic reticulum depends on whether it binds to the endoplasmic reticulum resident proteins, Insig-1. By binding with SREBP-1c, Insig-1 inhibits these proteins depending on the level of Insig-1. Insig-1 is a critical regulator of SREBPs (Yang *et al.*, 2002; Yabe *et al.*, 2002) (Fig. 4).

It should be noted that DHA has been known to negatively regulate SREBP-1c (Song *et al.*, 2014). Otherwise, the PPARγ-RXRα heterodimer, activated by DHA (Song *et al.*, 2017), transactivates the Insig-1 promoter (Kast-Woelbern *et al.*, 2004). Proteolytic processing of SREBP-1c is inhibited (Hannah *et al.*, 2001). Thus, by intervening on the synthesis of Insig-1, DHA slows the maturation of SREBP-1c and reduces its lipogenic action through the synthesis of D6D (Fig. 4).

4 Promoter polymorphisms of the *FADS2* gene and their consequences

Several significant associations between *FADS* genotypes and long-chain polyunsaturated fatty acids have been confirmed in diverse types of human tissue (erythrocytes, plasma, skin, breast milk, etc.), demonstrating that *FADS2* gene cluster polymorphisms are major regulators of the synthesis of this type of fatty acid. One study (Ameur *et al.*, 2012) examined the genotyping of the *FADS* cluster in five European cohorts, as well as the genomic data available from human populations, archaic hominids and more distant primates. The results show that modern humans have two haplotypes (groups of alleles at different loci on the same chromosome) for the *FADS* cluster: A and D, defined by 28 SNPs. These two haplotypes differ considerably in their capacity to synthesize long-chain fatty acids. In the two families of fatty acids – omega-3 and omega-6 – haplotype D is strongly associated with lower levels of precursors to the synthesis of fatty acids (α-linolenic acid, linoleic acid) and higher levels of EPA, DHA and arachidonic acid. This indicates that this haplotype is more effective at converting precursors. People who are homozygous for haplotype D have 24% more DHA and 43% higher levels of arachidonic acid than homozygotes for haplotype A. Several studies have shown a close correlation between several single nucleotide polymorphisms (SNPs) in the *FADS1* and *FADS2* genes and the concentrations of omega-3 and -6 fatty acids (Schaeffer *et al.*, 2006; Xie and Innis, 2008; Rzehak *et al.*, 2009; Glaser *et al.*, 2011). Homozygous carriers of different minor alleles have higher levels of desaturase substrates (α-linolenic acid, linoleic acid) and lower levels of desaturation products (DHA, EPA, arachidonic acid) (Glaser *et al.*, 2011). This suggests the reduced expression of desaturases in these polymorphisms (Moltó-Puigmarti *et al.*, 2010). Conversely, several studies suggest that some alleles of several SNPs in the *FADS2* gene cluster are associated with higher D6D activity (homozygous carriers of the minor allele of rs1535) (Harsløf *et al.*, 2013).

Nwankwo *et al.* (2003) demonstrated that the insertion of a nucleotide in the transcriptional regulatory region of the human *FADS2* gene resulted in D6D deficiency and decreased *FADS2* transcription (minor allele rs968567). Promoter-reporter assays demonstrated a 6-fold decrease in promoter activity in the regulatory region of the polymorphic *FADS2* variant compared with the normal gene, confirming the functional relevance of the insertion mutation to diminished expression of the gene. Lattka *et al.* (2010) showed that the *FADS2* promoter region surrounding SNP rs968567 exhibits promoter activity, which increases when the major C allele of SNP rs968567 is replaced by the minor T allele. This effect could be caused by the allele-specific differential binding affinity of transcription factors.

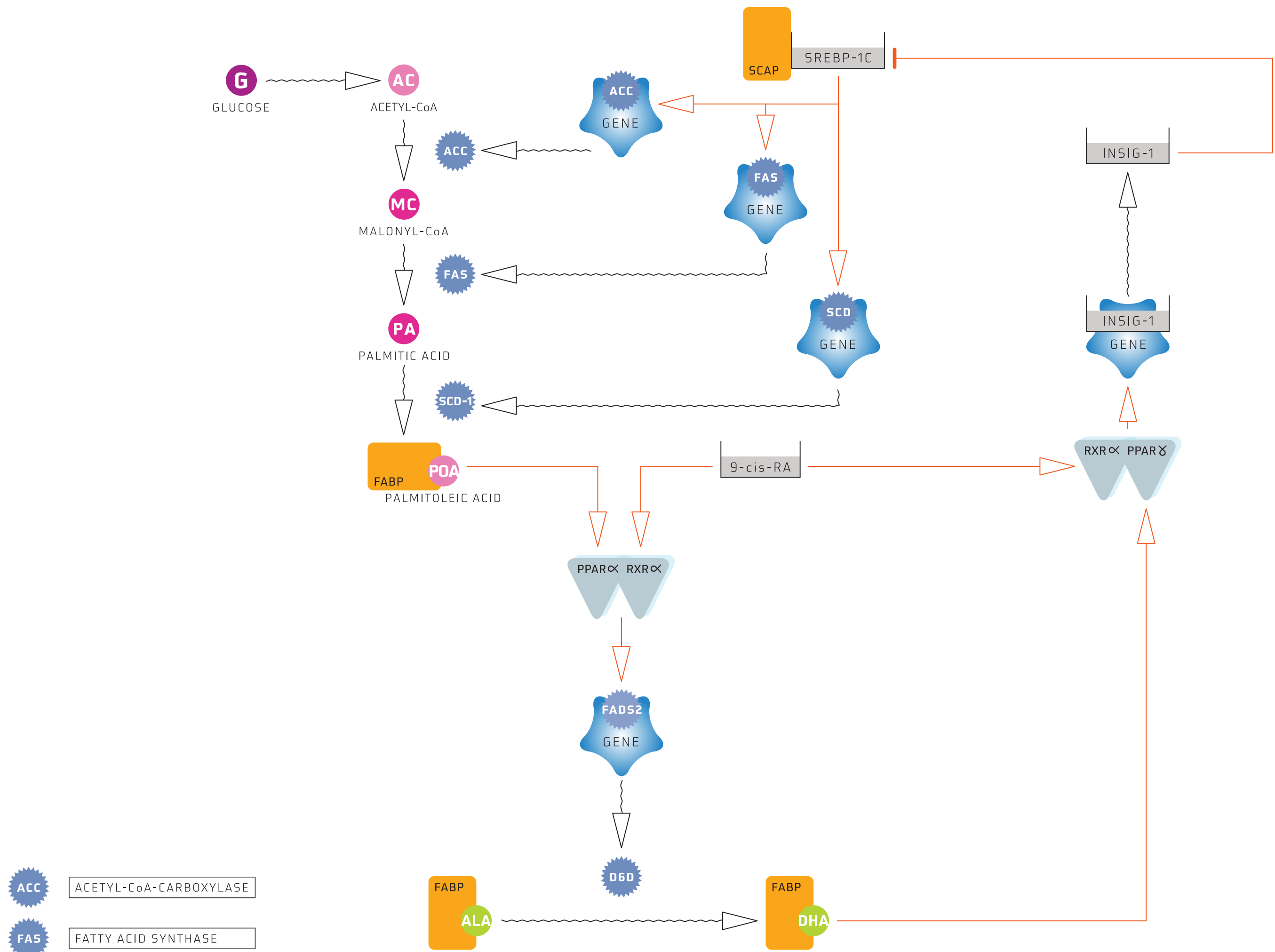

Fig. 4. Expression de D6D – Putative action of SREBP-1c.

Given the hypothesis that the DHA-PPARαP-RXRα-DHA heterodimer represses the *FADS2* gene *via* its PPRE and the results of these studies, we speculate that SNPs, especially those on PPRE, modulate the binding affinity of DHA-PPARαP-RXRα-DHA heterodimer on PPRE. If this affinity is increased, it will take less DHA to bind to PPARα and inhibit the transcription of *FADS2* gene, and vice versa with decreased affinity. Lower production of D6D and DHA result from greater DHA-PPARαP-RXRα-DHA heterodimer affinity for PPRE (Lattka *et al.*, 2010). *FADS2* promoter polymorphism would enhance competition between DHA and other ligands, depending on their concentrations and affinities (dissociation constants Kd).

5 Conclusion

The DHA concentration level is highly dependent on the catalytic capacity of D6D, a key enzyme in DHA synthesis. The regulation of the *FADS2* gene by PPARα-RXRα and their ligands is compatible with the recruitment of coactivators and corepressors. DHA causes dose-dependent genetic feedback inhibition of the *FADS2* promoter.

Mutations in the *FADS2* gene can have positive or negative effects on D6D levels. The polymorphism of this gene appears to have been essential in allowing the *Homo* genus to adapt to its diet and evolve (Majou, 2018). The geographic distribution of *FADS2* genetic variants now differs dramatically between continents. These differences in the capacity to synthesize DHA might contribute to health disparities. For example, over the past 10 years or so, studies have increasingly highlighted the relationship between DHA deficiency and certain pediatric neuropathologies, such as hyperactivity, learning difficulties (Milte *et al.*, 2012), mental retardation (Neggers *et al.*, 2009), epilepsy (Emory University Health Sciences Center, 2004) and autism (Bent *et al.*, 2009). In the elderly, DHA depletion is an aggravating factor in the etiology of Alzheimer's disease (Majou, 2015).

It is essential to understand the regulation modalities of this gene, particularly in relation to its various alleles. Some SNPs in the *FADS2* gene are considered an aggravating factor in DHA deficiency. The dose-dependent feedback inhibition caused by DHA in the DHA-PPARα-RXRα-DHA heterodimer could be a key factor for people with a genetic DHA deficiency. DHA depletion caused by *FADS* gene polymorphisms should be compensated entirely or partially by dietary DHA intake.

Conflicts of interest. The author declares that he has no conflicts of interest in relation to this article.

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