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DOSSIER

Disequilibrium of polyunsaturated fatty acids status and its dual effect in modulating adipose tissue development and functions

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Abstract – White adipocytes are storing energy under the form of triglycerides whereas brown adipocytes dissipate energy from triglycerides by producing heat. In rodents and possibly in humans both types of fat cells participate in the total energy balance. From a quantitative view point, a positive energy balance (energy intake > energy expenditure) is commonly regarded as a major factor contributing to obesity. Recent studies demonstrate that by altering rates of adipocyte differentiation and proliferation, differences in fatty acid composition of dietary fats may also contribute to adipose tissue development, in particular with respect to the relative intake of $\omega 6$ to $\omega 3$ poly-unsaturated fatty acids (PUFAs). The $\omega 6/\omega 3$ ratio determines the availability of $\omega 6$-arachidonic acid (ARA) within adipose tissue and thus the level of various prostaglandins derived from the cyclooxygenase-mediated pathway. We had shown earlier that prostacyclin (Prostaglandin I2) stimulates fat cell differentiation and this effect could be reversed by $\omega 3$-PUFA supplementation. Moreover, we had assessed that under conditions of genome stability a Western-like fat diet rich in $\omega 6$-PUFA was sufficient to induce a gradual fat mass enhancement across generations. Recently, we have characterized a second effect of some ARA metabolites (prostaglandins E2 and F2α) which appear to inhibit the formation of brown adipocytes within white adipose tissue. Altogether, our results demonstrate that, in addition to favoring white adipose tissue formation, dietary excess of $\omega 6$-PUFA prevents the "browning" process to take place in white adipose tissue depots, and strongly suggest a favorable role of $\omega 3$-PUFA supplementation in preventing both processes.

Keywords: White adipocyte / brite/brown adipocyte / arachidonic acid / prostaglandin / obesity

Résumé – Double effet d'un déséquilibre du statut en acides gras polyinsaturés sur le développement et les fonctions du tissu adipeux. Les adipocytes blancs stockent l'énergie sous forme de triglycérides alors que les adipocytes bruns dissipent l'énergie issue de ces triglycérides en produisant de la chaleur. Chez les rongeurs, et certainement chez les humains, ces deux types d'adipocytes participent à l'équilibre énergétique global. D'un point de vue quantitatif, une balance énergétique positive (apports énergétiques > dépenses énergétiques) est généralement considérée comme un facteur important contribuant à l'obésité. Des études récentes démontrent que des différences de composition en acides gras des graisses alimentaires en particulier le ratio entre les acides gras polyinsaturés $\omega 6$ et $\omega 3$, contribuent au développement du tissu adipeux en altérant les niveaux de prolifération et de différenciation des adipocytes. Le ratio $\omega 6/\omega 3$ détermine la disponibilité de l'acide arachidonique $\omega 6$ (ARA) au sein du tissu adipeux et ainsi le niveau des différentes prostaglandines dérivées de la voie métabolique contrôlée par les cyclooxygénases. Nous avons précédemment montré que la prostacycline (Prostaglandin I2) stimule la différenciation des adipocytes et que cet effet pouvait être inversé grâce à une supplémentation en acides gras polyinsaturés $\omega 3$. De plus, nous avons démontré que, dans une situation de stabilité génomique, un régime alimentaire occidental riche en acides gras polyinsaturés $\omega 6$ suffisait à induire une augmentation progressive de la masse grasse d'une génération à l'autre. Récemment, nous avons caractérisé un second effet de certains métabolites de l'acide arachidonique (prostaglandines E2 et F2α) qui est d'inhiber la formation des adipocytes bruns au sein du tissu adipeux blanc. Pris ensemble, ces résultats démontrent que, en plus de favoriser la formation du tissu adipeux blanc, la consommation excessive d'acides gras polyinsaturés $\omega 6$ réduit la mise en place

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du processus de « brunissage » dans les dépôts de tissus adipeux blancs. Enfin, cela suggère fortement un rôle favorable d'une supplémentation en acides gras ω3 pour prévenir les deux processus.

Mots clés : Adipocyte blanc / adipocyte brun/brite / acide arachidonique / prostaglandine / obésité

1 Introduction

The energy unbalance in animals and humans is due largely to substantial reduction in energy expenditure worsened by fat or carbohydrate overconsumption.

So far, high-fat diets are considered to be obesogenic in that they produce a consistent increase in white fat mass that is directly related to the content of the diet and duration of feeding. However, the contribution of dietary fats in front of an excess of energy intake in increasing body weight remains controversial, as no major change in the total amount of ingested fats has occurred in the last two decades (Troiano *et al.*, 2000; Willett *et al.*, 2002), raising the possibility of a qualitative issue. Indeed qualitative changes in the composition of dietary lipids have occurred in Western populations. More specifically the balance of polyunsaturated fatty acids (PUFAs) of n-6 series (linoleic acid, LA: 18:2 n-6) and n-3 series (α-linolenic acid, LNA: 18:3 n-3) and their major metabolites, respectively arachidonic acid (ARA, 20:4 n-6) and EPA (20:5 n-3) and DHA (22:6 n-3), has led to substantial increases in the ω6/ω3 (or n-6/n-3) ratio. Both a high intake of ω6 linoleic acid and a very high ω6/ω3 ratio have been implicated in the promotion of many diseases, including cardiovascular inflammatory and autoimmune diseases and cancer (Okuyama *et al.*, 2007; Hibbeln *et al.*, 2006; Simopoulos, 2003). Regarding fat mass, recent studies have shown that perinatal exposure of mice to a high ω6 PUFA diet results in a progressive accumulation of body fat across generations, in agreement with the fact that in humans, overweight and obesity have steadily increased in the last decades, and emerge earlier in life (Massiera *et al.*, 2010).

More recently another qualitative issue with respect to PUFAs of the ω6 series has been reported, *i.e.* their inhibitory role in the browning process of white fat cells converted into energy-dissipating fat brite (brown-like, see below) cells which are postulated to play a role in controlling energy balance by lowering body weight.

Herein, we summarize from our own data the potential importance of the fatty acid composition of dietary fats as a factor that plays a dual role in adipose tissue development and functions. More specifically will be discussed the role of the well-characterized arachidonic acid metabolites derived from the cyclooxygenase (COX) pathway (Fig. 1), on one hand prostaglandin I2 (prostacyclin, PGI2) and prostaglandin E2 (PGE2) which favor the formation of energy storing white adipocytes and, on the other hand PGE2 and prostaglandin F2α (PGF2α) which prevent the formation of energy-dissipating brown-like adipocytes within white adipose tissue (WAT). Of note arachidonic acid is highly metabolized in this tissue and originates from different sources within adipocytes, *i.e.* directly from the diet or indirectly from LA metabolism in liver as well as from (i) phospholipids of preadipocytes and adipocytes *via* phospholipase activities and (ii) endocannabinoids *via* fatty acid amide hydrolase and monoacylglycerol lipase activities (Fig. 1).

2 Arachidonic acid, prostacyclin, PGE2 and white adipogenesis

Under isolipidic isoenergetic conditions, pups from mice fed a LA-rich diet (ω6/ω3 ratio of 59) were heavier at weaning and fat mass was increased compared with pups where inclusion of LNA in the diet was taking place (ω6/ω3 ratio of 2). In other words, inclusion of LNA in the isoenergetic diet rich in LA prevented the enhancement of fat mass and the difference in body weight was maintained into adulthood (Massiera *et al.*, 2003). Importantly, recent studies have shown that perinatal exposure to a high ω6 PUFA diet results in a progressive accumulation of body fat across generations (Massiera *et al.*, 2010). Importantly also, in the guinea pig, which is considered as the best animal model of human adipose tissue growth, increasing the LA/LNA ratio from 2:1 to 30:1 during the preweaning period also resulted in increased fat mass in adulthood (Pouteau *et al.*, 2010; Castaneda-Gutierrez *et al.*, 2011).

In search of an indirect contribution of LA in enhancing adipose tissue development, female mice fed a LA-rich diet exhibited higher ARA levels in their milk (70%) compared with mice fed the more balanced LA/LNA diet. Moreover, the LA-rich diet decreased ω3 long-chain PUFA in mother's milk, thereby inducing an unbalanced ratio between ARA, EPA and DHA for suckling pups. Consistent with a role of ARA in adipose tissue development, a significant positive association between plasma ARA levels and human infant body weight at 4 months of age was reported, as well as between ARA levels of adipose tissue lipids and BMI in children of Cyprus and Crete (Savva *et al.*, 2004; Jensen *et al.*, 1997). These human data were supporting our *in vitro* studies which had shown earlier that, among long chain fatty acids, ARA was the main adipogenic component of fetal bovine serum required for adipocyte differentiation (termed adipogenesis) of cultured mouse white preadipocytes. We had also shown that ARA was acting through prostacyclin synthesis whereas the ω3 isomer of ARA as well as EPA and DHA not giving rise to prostacyclin were no more potent than saturated and monounsaturated fatty acids in stimulating weakly adipogenesis (Massiera *et al.*, 2003). After secretion from preadipocytes, prostacyclin was found to be active externally *via* the prostacyclin receptor (IP) present at the cell surface of preadipocytes. ARA, acting through the IP/prostacyclin system, triggered cAMP production and activated the pro-adipogenic protein kinase A pathway (Aubert *et al.*, 2000; Vassaux *et al.*, 1992a) (Fig 2). In rodents, both *ex vivo* and *in vivo* exposure of white adipose tissue to carbaprostacyclin, a stable ligand of IP, was able to stimulate the formation of adipocytes (Saint-Marc *et al.*, 2001). Similar results were obtained with human preadipocytes (Jia *et al.*, 2012). Moreover, ARA and some of its metabolites generated through cyclooxygenase activities had been described as activators/ligands of peroxisome proliferator activated receptors (PPARs) which stimulate adipogenesis (Hihi *et al.*, 2002; Jehl-Pietri *et al.*, 2000). Thus ARA was a potent activator

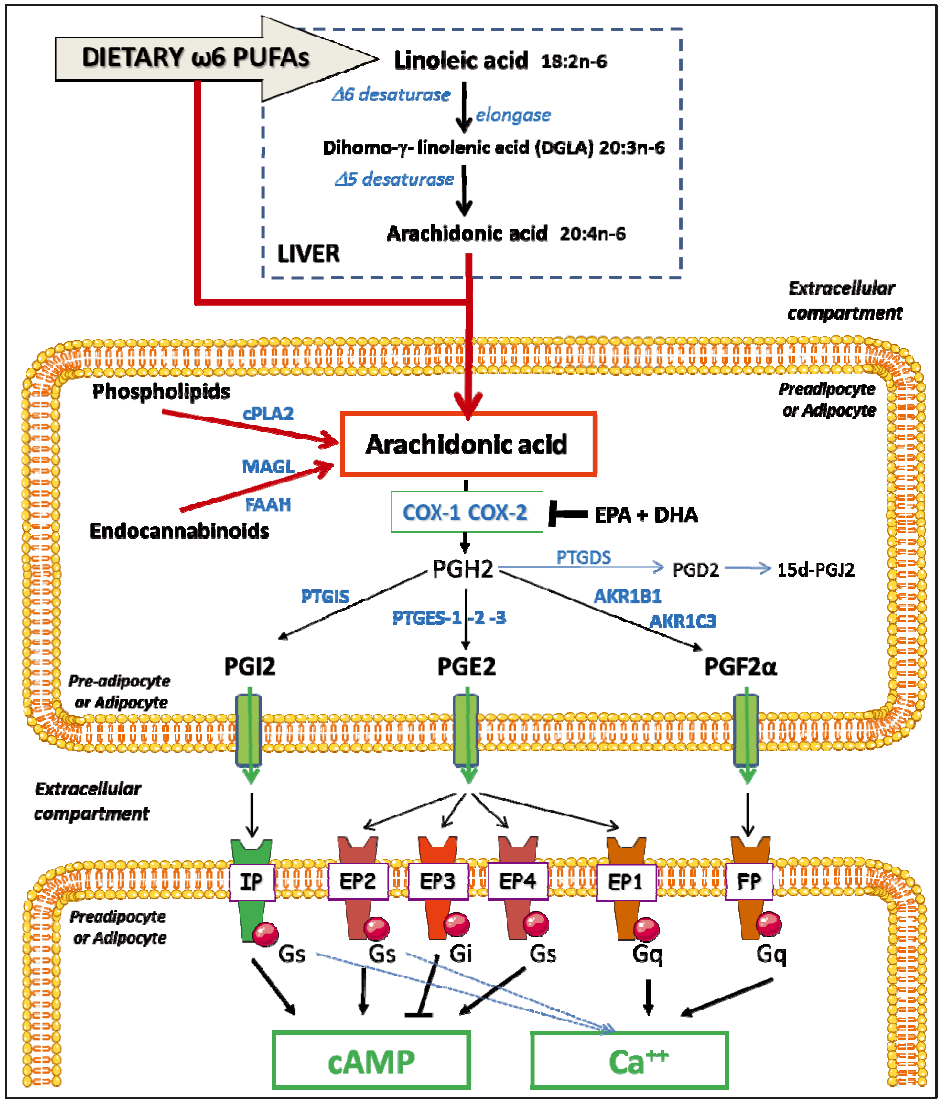

Fig. 1. Arachidonic acid synthesis from linoleic acid in hepatocytes and its metabolism in preadipocytes and adipocytes. Enzymes are shown in blue (cPLA2, cytosolic phospholipase A2; MAGL, monoacylglycerol lipase; FAAH, fatty acid amide hydrolase; COX, cyclooxygenase AKR1, acyl keto reductase 1). Sources of arachidonic acid are indicated with red arrows. Only the prostaglandins discussed in this review are displayed.

of adipogenesis that acts early through both cell-surface IP and later, like other long chainfatty acids, through nuclear PPARs (Fig. 2). To gain further insight into the contribution of prostacyclin signaling pathway in mouse adipose tissue development, wild-type mice and mice invalidated for IP ($ip^{-/-}$) were used. In contrast to wild-type mice, pups from $ip^{-/-}$ mice showed no gain in body weight or in fat mass when fed a LA-rich diet compared to the LA/LNA diet (Massiera *et al.*, 2003). This striking observation demonstrated that the prostacyclin signaling pathway was a key event in increasing fat mass in response to excess of dietary LA. In other words, decreasing the dietary LA/LNA ratio decreased the potency of this pro-adipogenic pathway and thus prevented overweight.

The key question is whether a similar situation applies to humans. Controversial results have been obtained. High $\omega6/\omega3$ ratio determined in umbilical cord blood phospholipids was associated with a high subscapular skin-fold thickness at 3 years of age taken as an index of child adiposity (Donahue *et al.*, 2011). In contrast, supplementation with EPA/DHA and recommendation to lower arachidonic acid intake during pregnancy and lactation did not show any effect on infant fat mass and fat distribution during the first year of life (Hauner *et al.*, 2012). Ongoing time-consuming studies should help to solve this issue.

3 Arachidonic acid, PGF2α and inhibition of the browning process in white adipose tissue

Brown adipose tissue (BAT) dissipates energy from triglycerides as heat (thermogenesis) by uncoupling the mitochondrial electron transport chain activity from ATP synthesis. This is due to the exclusive expression of the uncoupling protein (UCP)-1 in brown adipocyte mitochondria (Nedergaard *et al.*, 2001; Frontini *et al.*, 2010). In addition to the

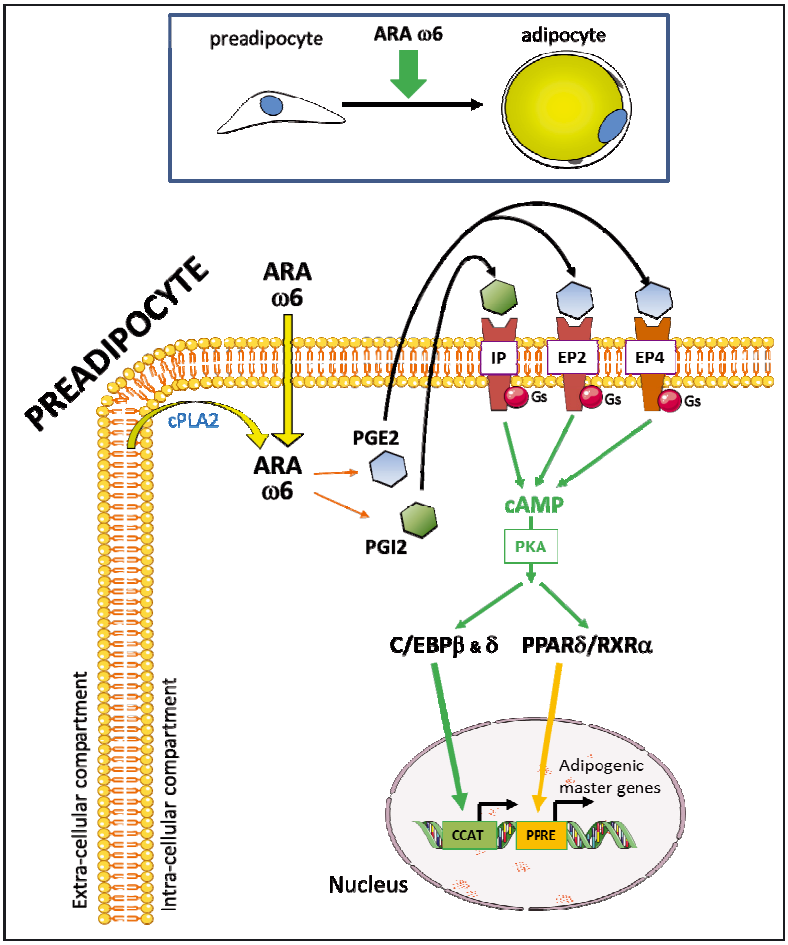

Fig. 2. Pathways involved in white adipocyte formation. (cPLA2, cytosolic phospholipase A2; PKA, protein kinase A; PPRE, PPAR response element; CEBP, CCAT/enhancer-binding protein; RXR, retinoid X receptor).

thermogenic adipocytes located in BAT – containing brown adipocytes – WAT contains inducible brown-like fat cells – called "brown-in-white" ("brite") or "beige" adipocytes – which are able to burn fat and carbohydrates *via* non-shivering thermogenesis (Petrovic *et al.*, 2010; Ricquier *et al.*, 2000; Barbatelli *et al.*, 2010; Shabalina *et al.*, 2013). Brite adipocytes appear to arise to a large part from the direct conversion of mature white adipocytes, and this mechanism is reversible (Barbatelli *et al.*, 2010; Lee *et al.*, 2014; Rosenwald *et al.*, 2013). During the last decade, various laboratories have shown that healthy adult humans display islets of energy-dissipating thermogenic adipocytes of metabolic significance. Their activity, measured by 18F-fluorodeoxyglucose uptake, appears inversely proportional to WAT mass (Cypess *et al.*, 2009; Nedergaard *et al.*, 2007; Saito *et al.*, 2009; van Marken Lichtenbelt *et al.*, 2009; Virtanen *et al.*, 2009), and these observations are in line with recent data which indicate that a lack of thermogenic adipocytes may be sufficient to cause obesity in mice and humans (Feldmann *et al.*, 2009; van Marken Lichtenbelt *et al.*, 2009). In addition, cold exposure led, in humans, to a decrease in body fat while recruiting brown adipocytes (Blondin *et al.*, 2014; van der Lans *et al.*, 2013; Yoneshiro *et al.*, 2013). Altogether, these data explore new avenues and emphasize the occurrence of thermogenic adipocytes as novel important candidates in controlling body weight and the metabolism of lipids and carbohydrates through modulation of energy expenditure (Schottl *et al.*, 2013). Importantly, brown adipocytes found in adult humans display a different molecular signature that the "true" brown adipocytes found in newborns but are rather reminiscent of the brite adipocytes described in rodents (Lidell *et al.*, 2013). Therefore, investigations on the regulation of brite adipocyte recruitment and activation in humans are in demand from a nutritional view point, in particular to assess the possible impact of dietary ω6 PUFA and their metabolites.

Recently, we have demonstrated that among ω6 PUFAs, ARA inhibits late steps of brite adipocyte differentiation and maintains a white phenotype (Pisani *et al.*, 2014). This observation has been described *in vitro* using a human cell model of white to brite adipocyte conversion (hMADS cells) and in mice using a nutritional approach. In the process of brite adipocyte formation from white hMADS adipocytes, ARA inhibited the expression of UCP1 and led to a decrease in their thermogenic capacity characterized by lower mitochondrial activity and basal oxygen consumption. The effect of ARA was mediated *via* cyclooxygenase activities leading to increased synthesis and release of PGE2 and PGF2α. Thorough analysis of the role of PGE2 and PGF2α demonstrated that an oscillatory calcium

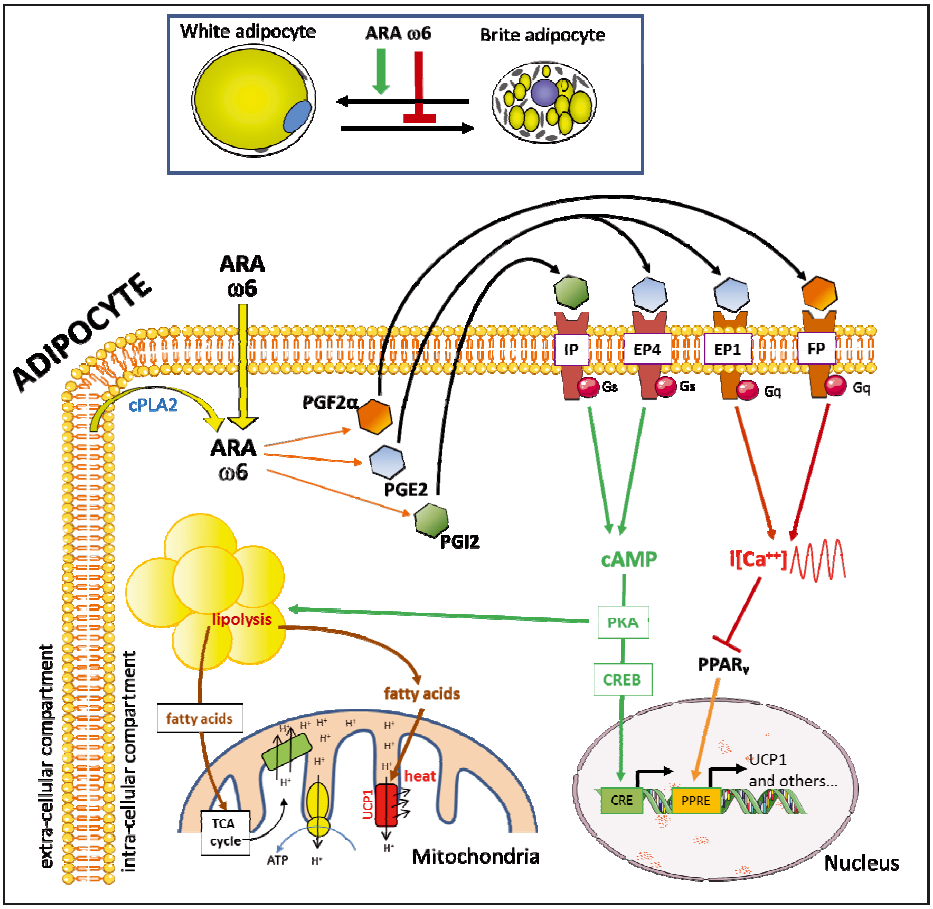

Fig. 3. Dual role of arachidonic acid in adipose tissue and the pathways involved in the white to brite adipocyte conversion (cPLA2, cytosolic phospholipase A2; PKA, protein kinase A; PPRE, PPAR response element; CRE, C-AMP Response Element; CREB, CRE-binding protein; TCA, tricarboxylic acid).

pathway, due respectively to EP1 and FP receptor activation, was responsible of impairing the browning process. The sustained i[Ca^{++}] oscillations led in turn to the inhibition of the expression of PPARγ target genes, including UCP1 gene and suggest a broader inhibitory effect of prostaglandin-mediated pathway *via* the modulation of PPARγ activity (Fig. 3).

As ARA is the precursor of numerous metabolites which trigger distinct signaling pathways, regulation of prostaglandin synthases should be crucial in inducing a given pathway. In this respect, it is worth noticing that ARA specifically inhibits expression of PTGIS (the enzyme responsible for prostacyclin synthesis) in hMADS adipocytes, thus favoring PGF2α and PGE2 effects in hMADS cells at the expense of prostacyclin during the conversion of white to brite adipocyte.

In search for a direct involvement of ARA *in vivo*, female C57BL/6 mice were fed a standard diet (containing 5% lipids) supplemented with 1.1% of arachidonic acid for 4 weeks. Mice were then treated with a β3-adrenergic receptor agonist (CL316,243, 1mg/kg/day, daily injection for 1 week), known to mimic cold exposure and thus to increase in adipocytes UCP1 expression. Under isoenergetic isolipidic conditions, inclusion of ARA in the diet impaired brite adipocyte recruitment in the sub-cutaneous WAT compared to mice fed a standard diet, demonstrating the direct inhibitory effect of ARA (Pisani *et al.*, 2014). As expected, ARA supplementation increased prostaglandins and prostacyclin levels within the tissue. Of interest, the chronic stimulation of the β3-adrenergic pathway in mice fed a standard or an ARA enriched diet induced a significant decrease in the levels of prostaglandins and prostacyclin but not that of PGF2α which is maintained in ARA-supplemented fed mice, supporting the involvement of this prostaglandin in the ARA-mediated inhibitory effect on UCP1 gene expression.

Interestingly, *in vivo*, COX pathway has been shown to be crucial for the induction of brite adipocytes in 129Sv mice (a strain resistant to obesity due to a high content of brown and brite adipocytes) (Madsen *et al.*, 2010; Vegiopoulos *et al.*, 2010), but an opposite role of the same pathway has been recently described in C57BL/6 mice (a strain sensitive to high fat diets) (Fjaere *et al.*, 2014). In this latter case, when mice were fed a high fat diet the inhibition of cyclooxygenase activities with indomethacin prevented weight gain, partly due to enhanced recruitment of brite adipocytes in the sub-cutaneous WAT. Our data obtained with C57BL/6 mice fed an ARA-supplemented diet in the absence of COX inhibitors are in agreement with this observation regarding the down-regulation of the browning process in WAT by ω6 poly-unsaturated fatty acids.

4 Dual role of PGE2 in adipocyte biology

Extracellular PGE2 is known to bind to its well-characterized cognate receptors EP1, EP2, EP3 and EP4 with different affinities (Kringelholt *et al.*, 2013) and was shown to trigger various signaling pathways as a function of the differentiation step (Fig. 1). EP2 and EP4 promote cAMP signaling, whereas, in an opposite way, EP3 is coupled to Gi protein able to inhibit adenylate cyclase activity. Last but not least, EP1 is a Gq coupled receptor allowing Ca^{++}-mediated pathway.

In preadipocytes, PGE2 promoted cAMP signaling and triggered early adipogenesis *via* EP2 and EP4 (Vassaux *et al.*, 1992b). In differentiated adipocytes, 16,16-dm-PGE2, a stable analog of PGE2, induced a dose-dependent inhibitory effect on UCP1 mRNA expression (Pisani *et al.*, 2014). A maximal effect of 16,16-dm-PGE2 was found at a high concentration (5 μM). Under these conditions, ARA-derived PGE2 bound to the low-affinity receptor EP1 and induced i[Ca^{++}] oscillations. Conversely, PGE2 was able to promote the white to brown/brite conversion at lower concentrations *via* the high-affinity EP4 coupled to the cAMP signaling pathway (Fig. 3).

5 The ω6/ω3 ratio as a critical factor to limit adverse effects

Among lipid dietary factors, profound quantitative and qualitative changes have taken place in the last four decades in the Western industrialized world, particularly the rising intake of ω6 and the declining intake of ω3 PUFA by both humans and domesticated animals. As adipose tissue is the main peripheral target organ handling fatty acids several aspects of disequilibrated PUFA metabolism appear to conspire in stimulating white fat cell formation (↗ energy storage) and in inhibiting the brite adipocyte recruitment (↘ energy expenditure). The increased LA and ARA content of solid foods has been accompanied by a significant increase in the ARA/(DHA+EPA) ratio within adipose tissue, leading in turn to an increase in ARA metabolites, *i.e.* a stimulatory role of prostacyclin favoring white adipogenesis and an inhibitory role of PGF2α preventing the browning process. Along with an increase in fat consumption and sedentarity, we propose that such disequilibration may represent an emerging risk factor which contributes to overweight and obesity as well as associated diseases in addition to the well-established positive energy balance. In other words, a decrease in LA or an increase in LNA/EPA+DHA intakes will allow a lower ω6ω3 PUFA ratio and decreased the potency of this pro-adipogenic pathway and thus prevented overweight.

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