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Involvement of polyunsaturated fatty acids in the control of energy storage and expenditure☆

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Abstract – Within heterotrophic organisms, fat, sugar and protein are required to bring energy. In humans, energy homeostasis (*i.e.* the balance between energy intake and energy expenditure) is tightly regulated. Obesity, characterized by an excess of white fat mass, is a consequence of dysregulation of this balance in which decreased energy expenditure plays an important role. Among dietary components, fat represents approximately 30% of daily intake. Recent studies have shown that, besides its caloric input, fatty acid composition of fat represents an important qualitative issue. The impact of ω6 and ω3 polyunsaturated fatty acids on weight gain and development has been extensively studied. Interestingly, the role played by these polyunsaturated fatty acids in energy expenditure has been also characterized and will be discussed in relation to the various organs involved, in particular brown adipose tissue.

Keywords: thermogenesis / fever / shivering / PUFA / oxylipins

Résumé – Implication des acides gras polyinsaturés dans le contrôle du stockage et de la dépense énergétique. Au sein des organismes hétérotrophes, les lipides, les sucres et les protéines sont nécessaires à l'apport d'énergie. Chez l'Homme, l'homéostasie énergétique (c'est-à-dire l'équilibre entre l'apport et la dépense d'énergie) est finement régulée. L'obésité, caractérisée par un excès de tissu adipeux blanc, est une conséquence de la dérégulation de cet équilibre dans laquelle une diminution de la dépense énergétique joue un rôle important. Parmi les composants alimentaires, les lipides représentent environ 30 % de l'apport quotidien. Des études récentes ont montré que, outre son apport calorique, la composition qualitative en acides gras des lipides alimentaires représente un problème important. En ce sens, l'impact des acides gras polyinsaturés ω6 et ω3 sur la prise de poids et le développement a fait l'objet de nombreuses études. De plus, il est intéressant de noter que le rôle joué par ces acides gras polyinsaturés dans les dépenses énergétiques a également été caractérisé et sera discuté en relation avec les différents organes impliqués, en particulier le tissu adipeux brun.

Mots clés : thermogénèse / fièvre / frisson / AGPI / oxylipines

1 Obesity, adipose tissue and nutrition

Obesity results from an imbalance between energy input and expenditure. This energy homeostasis is maintained by the activity of metabolic tissues, including white and brown adipose tissue. As adipose tissue is the main peripheral target organ handling fatty acids, any change in lipid intake involves modifications in its development and functions. Importantly, major dietary quantitative and qualitative changes have taken place in the last decades in the Western industrialized world, particularly the overconsumption of ω6 polyunsaturated fatty acids (PUFAs) and the underconsumption of ω3 PUFAs by both humans and domesticated animals, which have been associated to an increase in white fat mass leading to obesity. Over the last years, in addition to the well-known relationship between PUFAs and energy storage, new data have emerged linking PUFA to the different mechanisms of energy expenditure.

In this review, we listed the various effects of ω6 and ω3 PUFA and long-chain PUFAs to explain that inadequate intake

☆ Contribution to the Topical Issue "Lipids and health / Lipides et santé"

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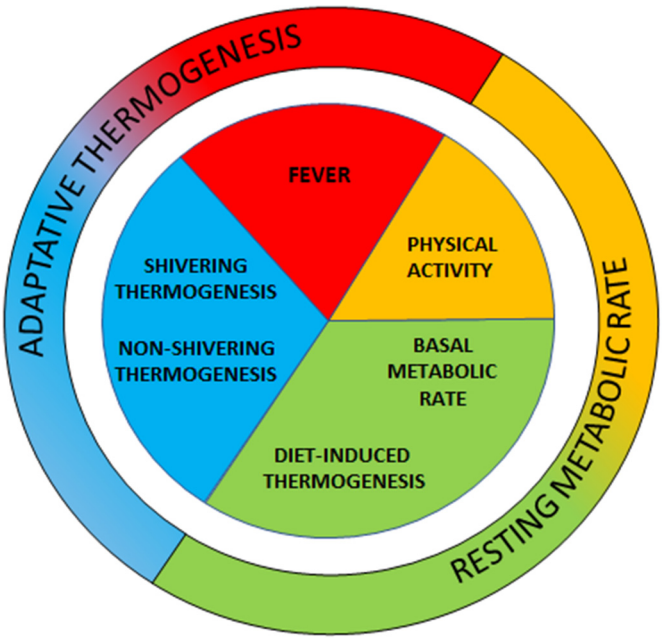

Fig. 1. The different ways of energy expenditure.

of PUFA contributes to energy homeostasis disequilibrium and may represent a risk factor to the occurrence of obesity and metabolic disorders.

2 Energy expenditure and thermogenesis

Energy expenditure involves resting and adaptative energy expenditure (Fig. 1). Resting energy expenditure or resting metabolic rate includes physical activity (excluding exercise), diet-induced thermogenesis and all energy expenses required to sustain life functions (named basal metabolic rate and corresponding to breathing, blood circulation, brain and nerve functions). Adaptative energy expenditure is known as a response to specific situations, such as fever with shivering in response to infection and non-shivering thermogenesis in response to cold. Both processes can be modulated/affected by exogenous stimuli which include dietary fatty acids (Himms-Hagen, 2001).

2.1 Non-shivering thermogenesis

Non-shivering thermogenesis is activated in response to a cold environment and corresponds to an increase in metabolic heat production above basal metabolism rate (Cannon and Nedergaard, 2004). Distinct from shivering thermogenesis, it is not exclusively associated with muscle activity. It occurs mainly through metabolism of brown fat and less to that of skeletal muscle, liver, brain, and white fat (Cannon and Nedergaard, 2004; Ouellet *et al.*, 2012).

In contrast to white adipose tissue (WAT) involved in energy storage and release, brown adipose tissue (BAT) is endowed with this thermogenic activity to regulate body temperature by dissipating energy. This process is due to the unique occurrence of the Uncoupling protein 1 (UCP1) localized in BAT mitochondria and is both activated and induced in response to cold *via* β-adrenergic stimulation (Cannon and Nedergaard, 2004). The energy-dissipating properties of UCP1 lead to an increased oxidation of fatty acids and carbohydrates and are important for body weight regulation (Blondin *et al.*, 2017). BAT displays various anatomic localizations in humans where the interscapular localization found only in newborns is replaced by cervical and thoracic localization in adults (Zhang and Hao, 2018). In other mammals, the interscapular localization of BAT is maintained throughout adult life in addition to other sites, but its mass and activity decreases with aging (Graja and Schulz, 2015).

Importantly, an additional population of UCP1-positive adipocytes is present in WAT and is termed brite for "brown in white" or beige adipocytes (Barbatelli *et al.*, 2010). These brown-like adipocytes appear in response to cold exposure or to high-fat diets. These cells which stem from progenitors or by direct conversion of mature white adipocytes have been recently found in adult humans (Rosenwald and Wolfrum, 2014). Induction of brown and brite adipocyte activity appears as a novel strategy to combat obesity by enhancing body energy expenditure, *i.e.* by increasing oxidation of fatty acids within these cells and therefore limiting fat storage in peripheral tissues.

2.2 Diet-induced thermogenesis

In addition to the well-known function of BAT in cold acclimation, several other functions of this tissue have been described. The most intriguing response is its post-prandial activation in response to various diets, *i.e.* diet-induced thermogenesis which takes place concomitantly to the insulin peak which favors energy storage as triglycerides and glycogen (Hibi *et al.*, 2016).

2.3 Physical activity

"Physical activity" includes occupational, sports, conditioning, household, or other activities whereas "Exercise" is a subset of planned and structured physical activity. Importantly, physical activity is mainly performed by rapid skeletal muscles known as glycolytic and thus uses preferentially carbohydrates. Thus, it is likely that the fat composition of diet should have lower impact, if any, on this kind of energy expenditure (Westerterp *et al.*, 1996).

2.4 Shivering thermogenesis

Exposure to cold induces the activation of involuntary muscle contractions leading to shivering thermogenesis. Skeletal muscles are thus involved in cold resistance and are the main contributor of heat in adult humans compared to other mammals in which BAT thermogenesis prevails (Blondin *et al.*, 2017). In humans, both types of thermogenesis seem more exclusive than additive as shivering activity is inversely correlated to the occurrence of BAT (Ouellet *et al.*, 2012). Shivering thermogenesis uses a variety of metabolic fuels, as oxidation of carbohydrates, lipids and proteins. When one fuel source is depleted or reduced, the others compensate in order to maintain shivering intensity and core temperature (Weber and Haman, 2005).

2.5 Fever

Fever, or pyrexia, is an evolutionarily conserved host thermogenic response to microbial infection. It is defined as an elevated core temperature and is a reflect of an enhanced metabolism characterized by an increase in energy expenditure. Fever is mediated by pyrogenic mediators, such as cytokines (interleukin-1 and −6, IL-1 and IL-6) (Kozak *et al.*, 1998), adipokines (leptin) (Luheshi *et al.*, 1999) or eicosanoids derived from polyunsaturated fatty acids (prostaglandin E2, PGE2) (Engblom *et al.*, 2003) which trigger thermogenic recruitment of peripheral tissues (Evans *et al.*, 2015). This response is counteracted by anti-pyrogenic agents (corticoids, arginin-vasopressin and IL-1 receptor antagonist, IL-1RA) which prevent an harmful increased body temperature (Tatro, 2000). In this respect, the involvement of BAT in fever remains disputed as, on one hand, inflammatory signals allow secretion of norepinephrine by central nervous system, which is considered as a major activator of BAT but, on the other hand, BAT seems excluded from the process which triggers fever in response to endotoxemia (Riley *et al.*, 2016).

3 Energy expenditure in response to PUFAs

Polyunsaturated fatty acids (PUFAs) are defined as a class of fatty acids displaying two or more double bonds. The two major PUFAs are ω6 linoleic acid (LA, 18:2n-6), the precursor of dihomo-γ-linolenic acid (DGLA, 20:3n-6) and arachidonic acid (ARA, 20:4n-6), and ω3 α-linolenic acid (LNA, 18:3n-3), the precursor of ω3 eicosapentaenoic (EPA, 20:5n-3) and docosahexaenoic (DHA, 22:6n-3) acids. These PUFAs (LA and LNA) and long-chain PUFAs (LC-PUFAs) (ARA, DGLA, EPA and DHA) trigger a variety of biological responses and are required for normal development.

In animals, PUFAs are considered as essentials for health owing to their low efficiency (for DHA and to a lower extent for ARA and EPA) or to their inability (for LA, LNA) to synthesize them. Indeed, animals lack the Δ-12-and Δ-15-desaturases able to introduce double bonds in C18 long chain fatty acids. LA can be found at high proportions in most consumed oils (sunflower [75%], safflower [79%], evening primrose seed [72%], corn [57%], peanut [31%] and brassica [19%]). ALA is found in linseed (also named flaxseed) and various oils (linseed [50%], black currant seed [14%] and for a lower extent in rapeseed [9%]). EPA and DHA are present mainly in algae and marine bacteria. PUFAs can be also ingested *via* meat and fish, due to their high consumption of ω6 and ω3 PUFAs. Indeed, ARA is found in high amounts in bovine, porcine, ovine and poultry meats as well as in fish flesh, milk and eggs. Intake of EPA and DHA is less important than ARA intake as only found in wild fishes 'salmon, mackerel and tuna). In order to increase EPA and DHA intake in humans, two strategies are developed using dietary supplements (fish oil, seed oil) or supplementing livestock diet (especially cow, pork, chicken and salmon) with ω3-enriched food like linseed and algae (Weill *et al.*, 2002; Bourre, 2005).

3.1 The critical ω6 and ω3 PUFAs intakes in obesity and chronic diseases

Both ω6 and ω3 PUFAs are transported into the bloodstream and are incorporated as phospholipids in plasma membranes or as triglycerides within adipocyte droplets. PUFAs are released by lipases and then oxidized. ω6 and ω3 PUFAs are known to compete at different enzymatic steps that modulate the availability of their respective metabolic products (Fig. 2). LA and LNA are substrates of the same Δ-5- and Δ-6-desaturases and elongases to generate the LC-PUFAs ARA, DGLA, EPA and DHA. They are also competitors as substrates for the synthesis of oxygenated derivatives or for β-oxidation, ω3 PUFAs being more rapidly oxidized compared to ω6 PUFAs and to mono-unsaturated fatty acids (Cunnane, 2003). Due to these different competition levels, the intake amount of ω6 and ω3 PUFAs is crucial to determine the kind of mediators available and the downstream biological processes which will be ultimately induced (Bibus and Lands, 2015). For a long-time, dietary recommendations were mainly addressed to pregnant women and based on an optimal LA/LNA ratio for a healthy development of fetuses and children (Simopoulos and DiNicolantonio, 2016).

Numerous studies carried out in rodent models and in human cohorts have shown a tight link between increased ω6 PUFA intake, generally associated with a high LA/LNA ratio, and enhanced fat mass. In mice, high fat diet rich in ω6 PUFA favored fat accumulation, in contrast to ω3 PUFA-enriched diet which lowered this accumulation (Javadi *et al.*, 2004). Similar results have been obtained in rats, where ω6 PUFA-enriched diet enhanced fat pad weight compared to saturated FA or ω3 PUFA-enriched diets (Okuno *et al.*, 1997). Interestingly, transgenerational studies developed in rodents have shown that perinatal exposition to high fat diets with high levels of ω6 PUFA induced a progressive accumulation of body fat across generations (Massiera *et al.*, 2010). In the same way, increasing the LA/LNA ratio from 2 to 30 during the preweaning period of guinea pigs led to an increased fat mass at the middle age (Pouteau *et al.*, 2010; Castaneda-Gutierrez *et al.*, 2011). In humans, a high LA/LNA PUFA ratio in maternal milk, independently from mother weight, is positively associated with the adiposity of infants at 6 months, 3 and 4 years of age (Donahue *et al.*, 2011; Moon *et al.*, 2013; Rudolph *et al.*, 2017). In adults, ω6 PUFA intake correlates positively with the body mass index (BMI) and the associated metabolic syndrome (Garaulet *et al.*, 2001; Williams *et al.*, 2007; Inoue *et al.*, 2013).

Moreover, in adults both a high intake of ω6 LA and diets associated with a very high LA/LNA PUFA ratios have been associated with the development of several chronic diseases, including cardiovascular, inflammatory and especially overweight/obesity (Ailhaud and Guesnet, 2004; Hibbeln *et al.*, 2006; Okuyama *et al.*, 2007a, b). Accordingly, new dietary recommendations emphasize higher intake of ω3 PUFAs and lower intake of ω6 PUFAs to improve human health (Ailhaud *et al.*, 2006; Muhlhausler and Ailhaud, 2013; Simopoulos, 2016; Simopoulos and DiNicolantonio, 2016).

In contrast to ω6 PUFA excessive intake, it has been reported that diets enriched with ω3 PUFAs or ω3 LC-PUFAs

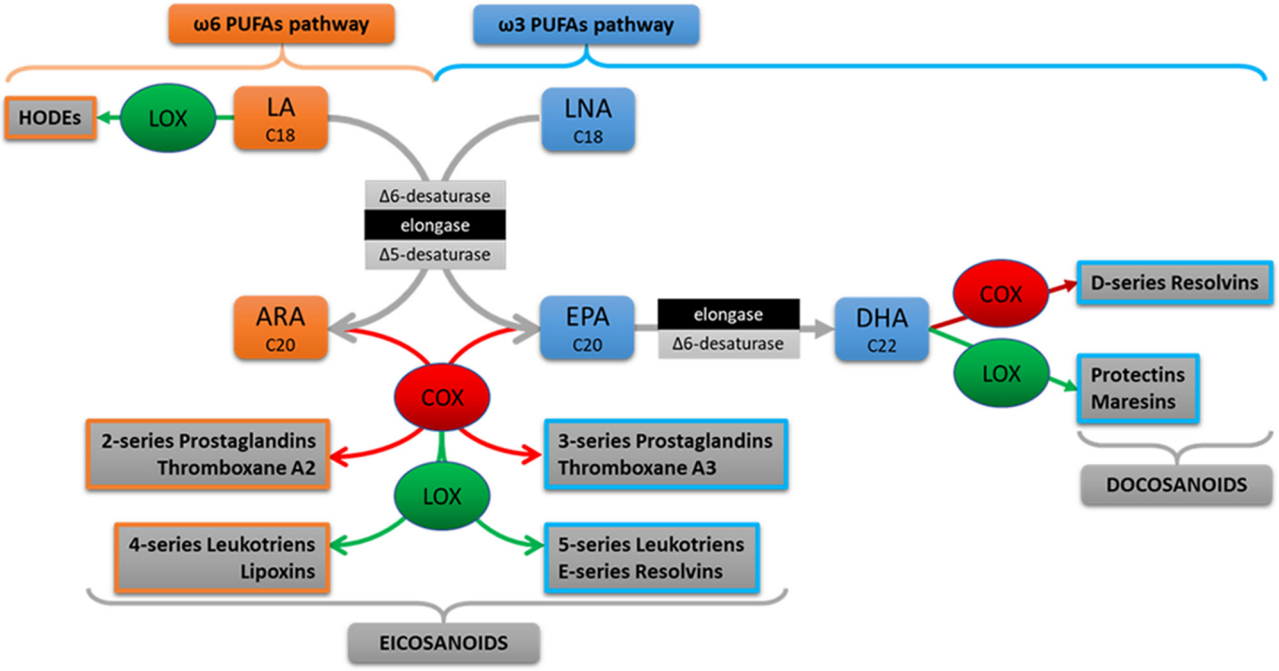

Fig. 2. Major pathways of PUFA metabolization, from dietary fatty acids to major members of the oxylipin family, including the commons enzymatic hubs of metabolization between ω6 and ω3 PUFAs. COX: cyclooxygenase; LOX: lipoxygenase; HODEs: hydroxyoctadecadienoic acids; LA: linoleic acid; LNA: alpha-linolenic acid; ARA: arachidonic acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid. The number of carbon atoms is indicated.

lead to beneficial effects and contribute to improve of human health. Cohort analyses have shown normalization of inflammation, lowering plasma triglycerides and amelioration of the cardiovascular metabolic status (Duda *et al.*, 2009; Innes and Calder, 2018). In rodents, inclusion of LNA in LA- rich high fat diet prevents the enhancement of fat mass (Massiera *et al.*, 2003). A similar favorable effect is observed for body weight in humans whereas inclusion of EPA and DHA leads to lower cardiovascular disease risk and ameliorates metabolic markers (Simopoulos and DiNicolantonio, 2016; Jayarathne *et al.*, 2017).

3.2 Active metabolites of PUFAs

Most biological functions are not attributed directly to PUFAs but rather mediated through some of their oxygenated metabolites. These metabolites, termed oxylipins, are synthesized in a highly regulated manner, mainly by cyclooxygenases (COX-1 and COX-2) and lipoxygenases (3-, 5-, 12- and 15-LOX) activities (Fig. 2), displaying both a high biological potency and a short half-life (Funk, 2001, Perez-Chacon *et al.*, 2009). After synthesis, these oxygenated derivatives can:

- undergo new enzymatic modifications;
- activate soluble intracellular receptors;
- diffuse out of the cell through the plasma membrane and signal through membrane receptors in a paracrine or autocrine manner;
- stored as esterified fatty acids included within cell membranes.

In turn, these esterified oxylipins can be hydrolyzed from the membrane under specific stimuli to actively participate into various biological responses (Hammond and O'Donnell, 2012).

Synthesis of oxylipins takes place from developmental stages to adult life. In mammals, oxylipins can be divided into two main categories (Fig. 2), the eicosanoids (synthesized from C20 PUFAs, *i.e.* ARA, EPA and dihomo-γ-linolenic acid, DGLA) and the docosanoids (synthesized from C22 PUFAs, i.e. DHA) (Massey and Nicolaou, 2013). A third class of metabolites are derived directly from linoleic acid and composed of two members, 9- and 13-HODEs (hydroxyoctadecadienoic acid). Oxylipins, which differ by their length and double bond configuration, are synthesized by several alternative and consecutive reactions and display crucial signaling functions. Among ARA metabolites, prostacyclin (PGI2) has been shown in mice to trigger *in vitro* adipose cell differentiation (Negrel *et al.*, 1989) and *in vivo* adipose tissue formation (Massiera *et al.*, 2003).

There is a direct link between PUFA dietary intake and synthetized oxylipins in plasma and tissues. In rodents, increasing ARA or LA intake increases ω6 PUFA-derived oxylipins (Pisani *et al.*, 2014; Pisani *et al.*, 2015; Ghandour *et al.*, 2018), a profile reversed by addition of LNA (Ghandour *et al.*, 2018; Colson *et al.*, 2019). In humans, studies have been mainly focused on ω3-diet supplementation which leads to an increase of ω3-derived metabolites; however the oxylipin levels return to almost normal levels when the ω3-diet supplementation was discontinued (Fischer *et al.*, 2014). Moreover, in a cohort of hyperlipidemic patients, a 3-month diet supplemented in ω3 PUFAs leads to an increase in ω3-derived metabolites in red blood cell membranes, almost attaining the proportion observed in healthy patients (Harris

and Von Schacky, 2004; Schmocker *et al.*, 2018). This increase in oxylipin synthesis can be acute, as demonstrated recently where both EPA- and DHA-enriched meals induce within 4 hours a potent increase of ω3-derived metabolites in plasma (McManus *et al.*, 2016).

3.3 PUFA supplementation and energy expenditure

Few data are available regarding the impact of PUFA and LC-PUFA supplementation on the resting metabolic rate which should be poorly modulated as it is critical for life. In contrast, several studies have analyzed the impact of the different PUFA classes on adaptive thermogenesis and physical activities.

3.3.1 PUFAs and non-shivering thermogenesis

Some studies have been carried out regarding the involvement of PUFA and their metabolites in the activation of BAT and in the conversion of white into brite adipocytes, both *in vivo* and *in vitro* (Kuda *et al.*, 2018). Recently, our group (Pisani *et al.*, 2014; Pisani *et al.*, 2015; Ghandour *et al.*, 2018; Colson *et al.*, 2019) has shown the importance of the ω6 and ω3 PUFAs and LC-PUFAs dietary intake on adipose tissue development and function. ARA enriched diets, known to favor white adipose tissue formation, prevent the "browning" process to take place in white adipose tissue depots (Pisani *et al.*, 2014), suggesting a favorable role of ω3-PUFA supplementation in preventing both processes. Indeed, ω3 PUFA and LC-PUFAs supplementation has beneficial effect on the thermogenic function of adipocytes. A low dietary LA/LNA ratio (4 compared to 25) improved the thermogenic response of BAT and WAT under β3-adrenergic stimulation (Ghandour *et al.*, 2018). The eicosanoid PGF2α appears responsible of these effects, the level of which is influenced by the availability of ω6 and ω3 PUFAs competing at the level of their metabolization.

Few studies showed a direct relationship between ω3 PUFAs enriched diet and induction of brown adipocyte thermogenesis (Adkins *et al.*, 2017, Kuda *et al.*, 2018). However, it also has been shown that ω3 PUFAs favored the formation of the so-called "healthy adipocytes" with high number of mitochondria but not expressing UCP1 (Kuda *et al.*, 2018). Moreover, other studies have shown the beneficial effect of ω3 PUFA supplementation on glucose metabolism (glucose tolerance, insulin sensitivity) and on BAT activation and/or brite adipocyte formation (Kim and Goto, 2015; Pahlavani *et al.*, 2017). *In vivo* studies have shown a global increase in thermogenesis in mice fed fish oil ω3-enriched food, *i.e.* an increased rectal temperature associated with an increase of brown adipocyte markers in BAT (Kim *et al.*, 2016). Furthermore, mice fed fish oil (enriched with EPA or DHA) diets also display a strong increase in UCP1 expression in inguinal WAT (Kim and Goto, 2015). In this study, was examined the pathway by which ω3 PUFAs could exert their effect using β-adreno-receptor blockers. Indeed, 4 hours of fish oil diet are enough to induce UCP1 in BAT and this effect was abolished when the mice received propranolol as a β-adrenergic receptor blocker (Kim and Goto, 2015). In another study, mice fed control diet supplemented with EPA (36 g/kg for 11 weeks) display an increased expression of UCP1 in BAT whereas no effect is observed in WAT (Pahlavani *et al.*, 2017). Although EPA appears important for BAT activity, it cannot be excluded that others ω3 PUFAs present in fish oil are important for this activity.

In addition to their role in brown and brite adipocytes differentiation and function, oxylipins are well-known modulator of white adipocyte development and function. For example, prostacyclin (PGI2) synthesized from ARA can promote adipogenesis. Indeed, secreted prostacyclin from preadipocyte binds to its receptor IP in an autocrine/paracrine way and leads to cAMP pathway activation. This enhances the differentiation of preadipocytes *via* the expression of C/EBPβ and C/EBPδ (C/Enhancer Binding Proteins) (Vassaux *et al.*, 1992; Massiera *et al.*, 2003), both of which being critical for the progression of early phase of adipogenesis and the activation of PPARs (peroxisome proliferator-activated receptors) (Brun *et al.*, 1996). In addition to activating plasma membrane receptors, PGI2 can also signal directly through PPARs activation to promote adipogenesis (Forman *et al.*, 1995). This dual signalling is allowed by the localization of the prostacyclin synthase PGIS at the plasma or at the nuclear membrane (Lim and Dey, 2002). The involvement of PGI2 in adipogenesis have been confirmed *in vivo* in mice invalidated for its receptor IP. Indeed, these mice displayed less body weight and fat mass compared to wild type mice when fed with a LA-rich diet (Massiera *et al.*, 2003). In addition to PGI2, some others ARA metabolites generated through cyclooxygenase activities, as PGD2 and 15d-PGJ2, had been described to stimulate adipogenesis (Forman *et al.*, 1995).

3.3.2 PUFAs and fever

Infection and inflammation result in a negative energy balance with an increased thermogenesis (also named fever, pyrexia or febrile state) and decreases food intake. As fever is mediated mainly by leptin, IL-1β, IL-6 and PGE2, all factors modulating production/secretion of these mediators should be able to mediate fever.

IL-1β and IL-6 are two pro-inflammatory cytokines released by immune cells and crucial to the regulation/induction of fever by the brain (Kozak *et al.*, 1998). It is well accepted that ω6 PUFAs leads to the synthesis of inflammatory eicosanoids (including PGE2) and that ω3 PUFAs display anti-inflammatory properties, mainly by the production of anti-inflammatory eicosanoids and docosanoids, but also by the modulation of inflammatory cytokine expression (Calder, 2006). Mice feeding diet enriched with fish or rapeseed oil (ω3-enriched oils) displayed a decreased IL-1β and/or IL-6 levels in blood (Sadeghi *et al.*, 1999) as well as in brain (Delpech *et al.*, 2015) under endotoxemia conditions. This effect of ω3 PUFAs is still under debate as it was not already found under healthy conditions (Colson *et al.*, 2019) but mainly under pathological or inflammatory conditions.

PGE2 is an indispensable brain mediator of fever as demonstrated in studies with targeted disruption of genes encoding either PGE2-synthesizing enzymes (Engblom *et al.*, 2003) or PGE2 receptors (Ushikubi *et al.*, 1998), or using pharmaceutic compounds such as aspirin, salicylate, indomethacin or celecoxib (Romanovsky, 2005). In addition, other prostaglandin and non-prostaglandin metabolites

derived from arachidonic acid have been involved in the central control of fever in response to inflammation (Kozak and Fraifeld, 2004). Due to the tight regulation of oxylipin synthesis in face of the quantity and quality of dietary PUFAs, a direct correlation exists between ω6/ω3 PUFAs and LC-PUFAs ratio and the various pathways involving oxylipins in fever.

Leptin has been characterized in murine models as a fever mediator of body temperature (Luheshi *et al.*, 1999). Little is known about the detailed mechanism linking leptin and pyrexia. Leptin acts at the level of hypothalamus, may be by modulation of IL-1β expression and IL-6 (Pohl *et al.*, 2014), which induces a decrease in heat loss and thus an increase in body temperature (Fischer *et al.*, 2016; Kaiyala *et al.*, 2016). As PUFA intake modulated fat mass development which is directly correlated to leptin secretion (Garaulet *et al.*, 2001; Williams *et al.*, 2007; Inoue *et al.*, 2013), we assume that regulation of fat mass by dietary PUFAs indirectly modulated fever and thus energy expense during inflammation/infection. Interestingly, DHA has been characterized as a determinant of leptin gene expression (Shen *et al.*, 2014), but human studies failed to clearly correlate ω3 PUFA intake to leptin circulating level in diabetic and healthy populations (Kratz *et al.*, 2002; Stirban *et al.*, 2014).

3.3.3 PUFAs and muscle function

Physical activity increases with body weight as body mass to move is increased. Indeed, even if amplitude and velocity are lowered in obese and overweight subjects, the whole strength developed is similar to lean people (Lazzer *et al.*, 2003). Obesity is still associated (as a cause or as a consequence) with a sedentary lifestyle. This behavior, involving as a chronic decrease of physical activity frequency, drives *de facto* a decrease in energy expenditure associated to limited daily life activities (Carneiro *et al.*, 2016). Therefore, as PUFAs intake has been related to fat mass development, if causality between decreased activities and PUFAs intake exists; it should be rather indirect.

Nevertheless, several studies have described a relationship between dietary PUFAs and muscle mass and function, independent of body weight change (Jeromson *et al.*, 2015; Gammone *et al.*, 2018). Firstly, PUFAs seem to affect muscle anabolism, including muscle growth and regeneration (Tachtsis *et al.*, 2018). Other studies have shown an increased muscle protein synthesis in both young and older subjects undergoing a daily administration of ω3 PUFAs for eight weeks (Smith and Atherton, 2011). A similar result on muscle mass is obtained after six months of ω3 PUFAs supplementation in older people with an additional increase in muscle strength (Smith *et al.*, 2015). Secondly, ω3 PUFA intake ameliorates muscle metabolism and function. In mice submitted to a high fat diet, a four-week daily supplementation with ω3 PUFAs reversed lipid accretion and increased oxidative metabolism in muscle. Interestingly, in this study, the authors describe an increase in BAT mass which can be relied to the positive effect of ω3 PUFA intake (Philp *et al.*, 2015).

Overall, even if ω6 and ω3 PUFA intakes do not modulate physical activities *per se*, they have an impact on skeletal muscle capacity and can influence indirectly energy expenditure during exercise.

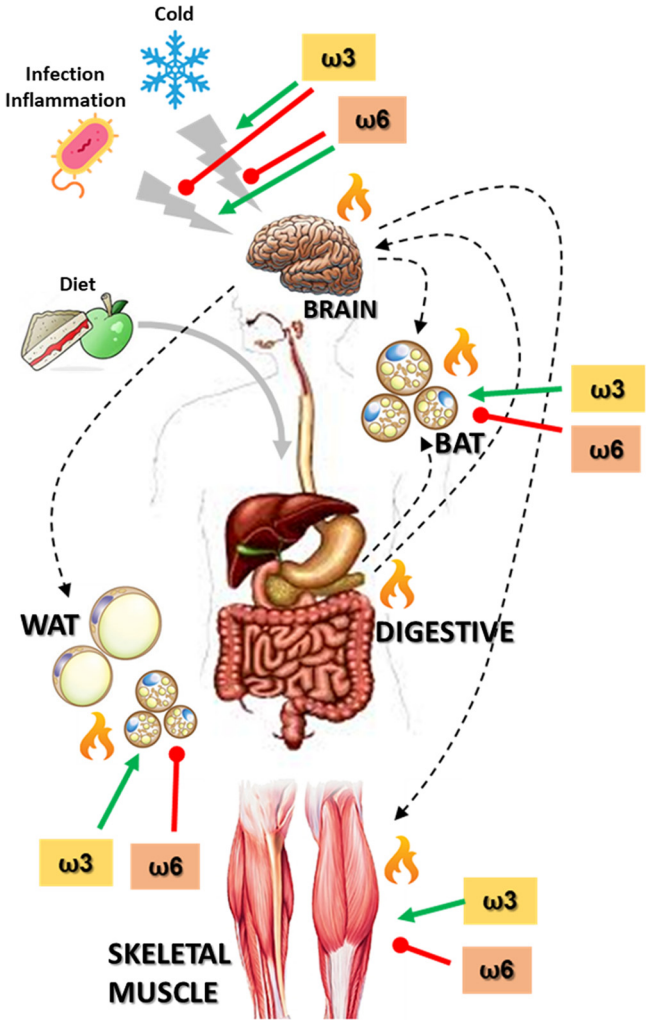

Fig. 3. Major thermogenic tissues, interrelationships and modulation by ω6 and ω3 PUFAs and LC-PUFAs. Red rounded-head arrow: negative action. Green arrow: positive action. Black arrow: modulatory pathways between organs. Grey arrow: environmental effectors. Flame: heat production.

4 Conclusions

ω6 and ω3 PUFAs and LC-PUFAs can be considered as two important actors regulating energy expenditure. Neither exclusive positive nor unfavorable involvement of the different PUFAs is observed, as each of them can promote or inhibit different kinds of energy expenditure (Fig. 3). Nevertheless, excessive dietary intake of ω6 PUFAs can overall be considered as negative regulators and adequate intake of ω3 PUFAs as positive counter-regulators of various metabolic events. Indeed, excess of ω6 PUFAs or insufficient ω3 PUFAs intake favor fat mass development which can be relied to a decrease in both non-shivering thermogenesis and physical activity due to sedentary lifestyle. Conversely, ω3 PUFAs supplementation is limiting fat mass increase as well as promoting thermogenesis and physical activity. Of note, as both ω6 and ω3 PUFAs are essential and metabolically related to each other (Fig. 2), it is difficult to bring unequivocal and

direct effect of ω6 PUFAs distinct from ω3 PUFAs on the different types of energy expenditure (Fig. 3). Another critical issue of the reported studies has been the use of high ω6 PUFAs intake and/or various ω3 PUFAs supplementation which appear widely different from nutritional recommendations. Overall, in 2010, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) recommended an intake of 4% of LA, 1% of LNA and 250 mg of both EPA and DHA for an adult consuming 2000 kCal/day (https://www.anses.fr/en/content/fats), this nutritional recommendation appearing adequate to regulate an optimal impact on energy storage and expenditure.

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