Regulation of Adipose Tissue Biology by Long-Chain Fatty Acids: Metabolic Effects and Molecular Mechanisms

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Long-chain fatty acids (LCFA) modulate metabolic, oxidative, and inflammatory responses, and the physiological effects of LCFA are determined by chain length and the degree of saturation. Adipose tissues comprise multiple cell types, and play a significant role in energy storage and expenditure. Fatty acid uptake and oxidation are the pathways through which fatty acids participate in the regulation of energy homeostasis, and their dysregulation can lead to the development of obesity and chronic obesity-related disorders, including type 2 diabetes, cardiovascular diseases, and certain types of cancer. Numerous studies have reported that many aspects of adipose tissue biology are influenced by the number and position of double bonds in LCFA, and these effects are mediated by various signaling pathways, including those regulating adipocyte differentiation (adipogenesis), thermogenesis, and inflammation in adipose tissue. This review aims to describe the underlying molecular mechanisms by which different types of LCFA influence adipose tissue metabolism, and to further clarify their relevance to metabolic dysregulation associated with obesity. A better understanding of the effects of LCFA on adipose tissue metabolism may lead to improved nutraceutical strategies to address obesity and obesity-associated diseases.

Key words: Dietary fats, Adipogenesis, Thermogenesis, Inflammation, Beige adipocytes, Macrophages

INTRODUCTION

Adipose tissue comprises many cell types, such as adipocytes, adipose precursor cells (including fibroblasts and endothelial cells), and immune cells (including macrophages, dendritic cells, and T cells), and produces various secretory proteins called adipokines, such as leptin and adiponectin. Therefore, in addition to being an energy reservoir, adipose tissue acts as a key control center for energy homeostasis and lipid metabolism. Obesity leads to excessive accumulation of white adipose tissue (WAT) through both hyperplasia (increased cell number) and hypertrophy (increased cell size) of adipocytes. While hyperplasia is considered a healthy expansion of WAT, hypertrophy causes necrosis of adipocytes and inflammation, which leads to various health issues such as type 2 diabetes, cardiovascular disease, and certain types of cancer.

The dietary pattern is one of the most important factors relevant to obesity development. Although dietary fat consumption is critical for absorption of fat-soluble vitamins (vitamin A, D, E, and K) and essential fatty acids, including linoleic acid (LNA; C18:2n-6) and α-linolenic acid (ALA; C18:3n-3), it also contributes to excessive caloric intake causing obesity and obesity-related chronic diseases. The dietary fatty acid profile is an important determinant of obesity risk. It has been reported that after the Industrial Revolution, intake of total fat, trans fatty acids, and n-6 fatty acids increased astronomically; however, intake of n-3 fatty acids from marine or vegetable sources increased only slightly. This change is
thought to partly account for the increased risk of obesity and obesity-related inflammatory diseases in recent times.\(^8\)

Therefore, this review focuses on the molecular mechanisms by which multiple types of long-chain fatty acids (LCFA) with differing numbers of double bonds in various positions influence key parameters of adipose tissue biology, including adipogenesis, thermogenesis, and inflammation in adipose tissue, and on the clinical implications of dietary fatty acid composition in metabolic diseases related to obesity.

**ADIPOSE TISSUE BIOLOGY**

Adipocyte differentiation

Adipocytes are divided into white, beige, and brown adipocytes, and all of these cells arise from multipotent mesenchymal precursor cells that are able to differentiate into not only adipocytes but also myoblasts, fibroblasts, chondrocytes, and osteoblasts.\(^9\) Previous studies have identified various lineage markers of adipose precursor cells, and showed that distinct lineages contribute to specific phases of adipose tissue biology and different adipose tissue depots.\(^1\) For example, α-smooth muscle actin-expressing cells generate adipocytes during the homeostatic or adult phase, whereas platelet-derived growth factor receptor α-expressing cells generate adipocytes during the developmental phase.\(^1,10\) Smooth muscle protein 22-expressing cells generate adipocytes in both subcutaneous and visceral WAT, but paired-related-homeobox-1-expressing cells generate adipocytes in subcutaneous WAT only.\(^1\) Also, brown and beige adipocytes, expressing common thermogenic genes, have different developmental origins.\(^1\) Myogenic factor 5-expressing precursors can become brown adipocytes but not white adipocytes, and beige adipocytes are differentiated from the same lineage as white adipocytes.\(^9\)

In the committed adipose precursors, expression of transcription factors, including CCAAT/enhancer binding protein (C/EBP) α and peroxisome proliferator-activated receptor (PPAR) γ, are upregulated.\(^11\) These two transcription factors interact significantly and induce adipocyte differentiation. During the differentiation phase, the cells undergo extreme changes in cell shape; consequently, differentiated adipocytes have a spherical shape (Fig. 1). This morphological change is accompanied by an extreme reduction in the expression of actin, tubulin,\(^12\) and fibronectin.\(^13\) At the terminal differentiation stage, C/EBPα and PPARγ target gene expression are greatly increased.\(^13\) The downstream target genes of both C/EBPα and PPARγ are associated with lipid metabolism, including lipogenic enzymes such as acetyl-CoA carboxylase and fatty acid synthase, and fatty acid binding proteins (FABP), and the upregulation of these genes promotes lipid accumulation in adipocytes.\(^14\) In addition, differentiated adipocytes become sensitive to insulin as a result of increased expression of glucose transporter 4 (GLUT4) and the insulin receptor.\(^15\)

During brown/beige adipogenesis, PRD1-BF1-RIZ1 homologous domain containing 16 (PRDM16) plays a significant role.\(^16\) It induces the commitment of precursors to brown adipocytes by binding to and modulating the activity of PPARα, PPARγ, and peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α).\(^16\) This activity increases mitochondrial biogenesis and induces expression of brown-adipocyte-specific genes such as uncoupling protein 1 (UCP1) and cell-death-inducing DFFA-like effector a

![Figure 1. Morphological changes of adipocytes during differentiation. Stromovascular cells, containing adipose precursor cells, were isolated from mouse subcutaneous white adipose tissue, cultured in Dulbecco’s modified eagle’s medium nutrient mixture F-12 Ham supplemented with fetal bovine serum, and differentiated with insulin, dexamethasone, and 3-isobutyl-1-methylxanthine for 9 days after 2 days of confluence.](https://www.jomes.org)
Adipose thermogenesis

Whereas white adipocytes with a single giant lipid droplet (LD) are able to store energy efficiently,20 brown adipocytes contain a number of small LDs and mitochondria that facilitate heat generation through UCP1.21 Beige adipocytes are another type of thermogenic adipocytes found in WAT depots. Under basal conditions, beige adipocytes act like white adipocytes, but in response to certain stimuli, including cold exposure and catecholamine treatment, they become brown-like adipocytes.20 Obesity induces adipogenesis (de novo adipocyte formation) and hypertrophy (adipocyte size increase) of white adipocytes, and also drives whitening of brown and beige adipocytes (Fig. 2).1

Stimulation of β-adrenergic signaling is required for thermogenesis in both classical brown adipocytes and beige adipocytes.22 Among the three β-AR subtypes (β1-AR, β2-AR, and β3-AR), the most relevant to brown adipose tissue (BAT) physiology is β3-AR.22 The receptors couple with the α subunit of stimulatory G protein and activate adenylyl cyclase (AC). Activated AC increases the level of intracellular cyclic adenosine monophosphate (cAMP), which activates protein kinase A (PKA) also known as cAMP-dependent enzyme.23 Activated PKA then phosphorylates and activates p38 mitogen-activated protein kinase (MAPK) and PGC-1α. Activated PGC-1q interacts with PPARα and PPARγ, and induces expression of thermogenic genes, including Ucp1 and Pgc1a.23 Since UCP1 uncouples oxidation of glucose or fatty acids from ATP synthesis, UCP1+ cells generate heat from the stored energy.24 Therefore, promoting UCP1+ cell division enhances thermogenesis, and blocking UCP1+ cell division suppresses thermogenesis in vivo.25

After a single intraperitoneal injection of norepinephrine, a catecholamine activating β-adrenergic signaling, lipolysis is increased and thermogenic genes are upregulated in both WAT and BAT of mice.26 Both prolonged cold exposure and chronic β-adrenergic stimulation have been reported to promote adaptive changes in WAT, leading to the acquisition of a BAT-like phenotype and the appearance of multilocular UCP1-positive adipocytes.27 This transformation is caused by a progressive reduction in the size of LDs due to sustained activation of lipolysis. The number of small or micro-LDs, which appear throughout the cytoplasm after the β-adrenergic stimulation, increases over time under such stimuli. The appearance of micro-LDs is preceded by the breakdown of the pre-existing large LDs; however, recent research data shows that de novo synthesis of LDs also contributes to this change.20

Adipose tissue inflammation

Obesity-induced systemic and low-level chronic inflammation is a significant contributor to the development and the progression of many diseases, such as insulin resistance, cardiovascular diseases, and cancers.28 Several types of leukocytes, including macrophages,
dendritic cells, and T cells, reside in adipose tissue, and obesity stimulates quantitative and qualitative changes within these inflammatory components. These inflammatory changes play a significant role in obesity by chronically elevating levels of inflammatory cytokines and adipokines.\(^\text{28}\)

Adipose tissue macrophages (ATM), the dominant immune cell type in adipose tissue, from 10% to 15% of the stromal vascular fraction (SVF) of adipose tissue in the lean state, and up to 50% of SVF in the obese state.\(^\text{29}\) In lean subjects, type 2 macrophages (M2) are widely found in WAT, secrete anti-inflammatory markers, such as interleukin (IL)-10 and arginase that block inducible nitric oxide synthase activity,\(^\text{30}\) and activate beige adipocytes by stimulating the \(\beta\)-adrenergic signaling pathway in WAT.\(^\text{31}\) However, overnutrition increases the number of type 1 macrophages (M1), leading to inflammation by secreting IL-6, tumor necrosis factor (TNF)-\(\alpha\) and monocyte chemotactic protein 1 (MCP-1).\(^\text{30}\) Hypertrophic adipocytes induced by overnutrition undergo necrosis due to lack of oxygen and nutrients. The function of MCP-1 is to recruit more M1 macrophages, and the infiltrating M1 macrophages surround dead adipocytes\(^\text{32}\) to form crown-like structures (Fig. 3) that augment pro-inflammatory cytokine secretion and generation of reactive oxygen species.\(^\text{28}\) The release of adipokines into the bloodstream may lead to the extension of adipose tissue inflammation to other tissues involved in meta-inflammation, including the liver, skeletal muscle, and hypothalamus.\(^\text{33}\)

Increased infiltration of pro-inflammatory M1 macrophages activates nuclear factor kappa B (NF-\(\kappa B\)) signaling.\(^\text{30}\) The NF-\(\kappa B\) transcription factor, typically composed of p65 and p50 subunits, is a protein complex that controls the transcription of genes associated with a variety of biologic processes, including cellular stress responses, inflammation, innate and adaptive immunity, proliferation, and cell survival.\(^\text{34}\) In obesity, activation of NF-\(\kappa B\) signaling can induce insulin resistance by inducing phosphorylation of insulin receptor substrate 1 at serine/threonine residues (rather than at tyrosine residues) or by inducing adipocyte dedifferentiation.\(^\text{35}\) The pro-inflammatory cytokines that are the target genes of NF-\(\kappa B\) suppress adipogenesis in human\(^\text{36}\) and murine adipocytes.\(^\text{37}\) Culturing human adipocytes in macrophage-conditioned media or in activated-macrophage-conditioned media activates NF-\(\kappa B\) signaling in adipocytes by increasing phosphorylation of the NF-\(\kappa B\) p65 subunit and degradation of the IkB subunit, which results in the downregulation of the expression of adipogenic genes, including \(Pparg, Cebpa, Fabp4\), and \(Fasn\).\(^\text{38}\) Since these adipocytes are not insulin-sensitive, they cannot take up glucose for triacylglycerol synthesis, leading to ectopic lipid storage, as seen in fatty liver.\(^\text{36}\)

**MECHANISMS OF THE METABOLIC EFFECTS OF LONG-CHAIN FATTY ACIDS ON ADIPOSE TISSUE BIOLOGY**

**PPAR activation**

PPAR proteins, which belong to the nuclear receptor family, are ligand-activated transcription factors\(^\text{39}\) and control the process of adipocyte differentiation.\(^\text{40}\) Two PPAR isoforms, in addition to PPAR\(\alpha\), are important for adipose tissue biology: PPAR\(\delta\), expressed in the initial stages of adipocyte differentiation, is thought to modu-
late clonal expansion of adipocytes leading to increased cell proliferation, while PPARγ target genes induce lipid accumulation at the terminal stage of adipocyte differentiation. Ppard deletion in adipose progenitor cells severely disrupts WAT development or maintenance, and PPARγ ligands induce differentiation of fibroblasts and myoblasts into adipocytes in vitro.

LCFA act as natural ligands for PPAR, and the effects of PPARγ binding is determined by the type of ligand activating the receptor. Fatty acids, containing 16–20 carbons, are reported to have the highest binding affinity for PPAR isoforms, and polyunsaturated fatty acids (PUFA) are more effective ligands than monounsaturated fatty acids (MUFA) or saturated fatty acids (SFA). While high-fat feeding usually induces both hypertrophy and hyperplasia, PUFA are generally able to limit both hyperplasia and hypertrophy in animals fed high-fat diets (HFD). In particular, omega-3 (n-3) fatty acids such as eicosapentaenoic acid (EPA; C20:5n-3) and docosahexaenoic acid (DHA; C22:6n-3), plays key roles in the development of adipose tissue. EPA and DHA are reported to increase the differentiation of subcutaneous white adipocytes, increase mitochondrial content, and induce the expression of key thermogenic genes, such as UCP1 and PGC-1α. EPA (100 μM, 7 days) or DHA (10 μM, 3 days) upregulated UCP1 and PGC-1α at the mRNA level to a greater extent than stearic acid (C18:0).

In murine primary adipocytes, PUFAs, including LNA (C18:2n-6), ALA (C18:3n-3), γ-linolenic acid (GLA; C18:3n-6,Δ6,9,12), and PLA (C18:3n-6,Δ5,9,12), were shown to upregulate Ucp1 and Pgc1a at the mRNA level to a greater extent than stearic acid (C18:0) and oleic acid (OLA; C18:1n-9). Fish oil, rich in n-3 fatty acids such as eicosapentaenoic acid (EPA; C20:5n-3) and docosahexaenoic acid (DHA; C22:6n-3), stimulates thermogenic activity both in BAT and in subcutaneous WAT. Fish oil supplementation was also shown to suppress HFD-induced weight gain and fat accumulation in mice, and improves glucose tolerance and dyslipidemia by enhancing expression of thermogenic genes, including Ucp1, Pgc1a, and Adrb3 (β3-AR encoding gene). In addition, incubation of human and mouse inguinal subcutaneous adipocytes with EPA upregulates mitochondrial and thermogenic gene expression.

### Table 1. In vitro effects of long-chain fatty acids on adipocyte thermogenesis

| Study                        | Experimental model                                      | Treatment (concentration, duration) | Outcome                                                                 |
|------------------------------|---------------------------------------------------------|-------------------------------------|--------------------------------------------------------------------------|
| Laiglesia et al.⁵⁵            | Human subcutaneous white adipocytes                     | EPA (100–200 μM, 24 hr)            | ↑ Sirt1, Tiam, and Cox4 mRNA expression                                  |
|                              |                                                         |                                     | ↑ SIRT1 activity                                                         |
|                              |                                                         |                                     | ↑ p-AMPK/AMPK ratio                                                     |
|                              |                                                         |                                     | ↑ PGC-1α acetylation                                                    |
|                              |                                                         |                                     | ↑ Ucp1, Pgc1a, and Cidea mRNA expression                               |
| Pisani et al.⁵²              | Human multipotent adipose-derived stem cells            | ARA (10 μM, 3 day)                  | ↑ Ucp1 and Fgf21 mRNA expression                                        |
|                              |                                                         |                                     | ↑ UCP1 protein expression                                               |
|                              |                                                         |                                     | ↑ Basal oxygen consumption rate                                         |
|                              |                                                         |                                     | ↑ Cytochrome c oxidase activity                                         |
| Shin and Ajuwon⁵⁶            | Murine subcutaneous white adipocytes                    | LNA, ALA, GLA, or PLA (50 μM, 24 hr) | ↑ Ucp1 and Pgc1a mRNA expression                                        |
|                              |                                                         | PLA (50 μM, 24 hr)                  | ↑ Nonopinephrine-induced Ucp1 mRNA expression                           |
| Zhao and Chen⁵⁶              | Murine subcutaneous white adipocytes                    | EPA (200 μM, 8 day)                 | ↑ Ucp1, Ucp2, Ucp3, Cidea, Vegfa, and Glut4 mRNA expression             |
|                              |                                                         |                                     | ↑ Mitochondrial DNA content                                             |
|                              |                                                         |                                     | ↑ p-AMPK/AMPK ratio                                                     |
|                              |                                                         |                                     | ↑ Ucp1, Pgc1a, and Cox4 mRNA expression                               |
|                              |                                                         |                                     | ↑ Mitochondrial DNA content                                             |
| Kim et al.⁷                  | Murine brown adipocyte precursor cells                  | EPA (100 μM, 7 day)                 | ↑ Ucp1, Cidea, Glut4, Pmdn18, Ppar, and Elovl3 mRNA expression        |
|                              |                                                         |                                     | ↑ UCP1, PPARY, AP2, and PPARα2 mRNA expression                         |
|                              |                                                         |                                     | ↑ Oxygen consumption rate (basal, uncoupling, and maximal)              |

↑, increase; ↓, decrease; EPA, eicosapentaenoic acid (C20:5n-3); p-AMPK, phospho-AMP-activated protein kinase; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator 1α; ARA, arachidonic acid; UCP1, uncoupling protein 1; LNA, linoleic acid (C18:2n-6); ALA, α-linolenic acid (C18:3n-3); GLA, γ-linolenic acid (C18:3n-6,Δ6,9,12); PLA, pinolenic acid (C18:3n-6,Δ5,9,12); PPAR, peroxisome proliferator-activated receptor; AP2, adipocyte protein 2.
Both PPARα and PPARγ, suppressing NF-κB activity and expression of NF-κB target genes, alleviate inflammation in many inflammatory conditions such as obesity, type 2 diabetes, and cardiovascular diseases. 

PPARα and PPARγ agonists inhibit the NF-κB signaling pathway by directly interacting with the NF-κB complex or through competition with NF-κB for binding to transcriptional co-activators. 

PPARγ has been reported to suppress inflammatory pathways by reducing activation of NF-κB signaling in macrophages and aortic smooth muscle cells, and PPARγ also downregulates inflammatory pathways in a wide range of cell types, including adipocytes and macrophages. 

PPARγ upregulates several genes associated with anti-inflammatory activity, and downregulates chemokines and chemokine receptor expression in adipocytes and macrophages, respectively. 

PPARγ depletion activates inflammatory responses in mature TNF-α-stimulated 3T3-L1 adipocytes, and constitutive activation of inflammatory signaling promotes the occurrence and development of several inflammatory diseases. 

Through their interactions with PPARα and PPARγ, both EPA and DHA control expression of genes involved in inflammatory responses, in addition to genes involved in lipid metabolism. 

These data suggest that LCFA, as natural PPAR ligands, participate in the control of adipocyte differentiation, thermogenesis, and inflammation.

Free fatty acid receptor 4 or transient receptor potential vanilloid 1 activation

In addition to PPAR activation, n-3 PUFA promote thermogenesis through other mechanisms, such as activation of free fatty acid receptor 4 (FFAR4) or transient receptor potential vanilloid 1 (TRPV1). 

FFAR4, also called G-coupled protein receptor 120, is a functional receptor for n-3 PUFA and is upregulated by n-3 PUFA treatment. In murine brown progenitor cells, EPA (C20: 5n-3) upregulates Ucp1 and Cidea mRNA expression; however, when FFAR4 is genetically knocked down, EPA-induced brown-fat-specific gene upregulation is reversed. 

Knocking out FFAR4 in mice reduced oxygen consumption in response to β-adrenergic stimulation. 

There is evidence that certain microRNA (miRNA or miR), single-stranded non-coding RNA composed of 19 to 22 nucleotides, may be act as mediators of FFAR4 activation in response to PUFA. Notably, miR-30b and miR-378 induce thermogenesis as downstream targets of cAMP signaling. 

Fish oil enrichment resulted in higher core body temperatures in HFD-fed mice compared to mice fed HFD supplemented with palmitic acid (C16:0)-rich palm oil or OLA (C18:1n-9)-rich olive oil, and this effect was associated with the increased expression of miR-30b and miR-378 in BAT. 

These data indicate that n-3 PUFAs are able to mediate thermogenesis through activation of FFAR4 and upregulation of miR-30b and miR-378.

TRPV1 is a non-selective cation channel expressed in peripheral

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Table 2. In vivo effects of long-chain fatty acids on adipose thermogenesis

| Study | Experimental model | Treatment (dose, duration) | Outcome |
|-------|-------------------|---------------------------|---------|
| Kim et al. | C57BL/6 mice | Fish oil* (15% of energy, 12 wk) | ↑ Ucp1, Cidea, Pdmd16, Pgk1, and Ppargc1a mRNA expression in BAT, ↑ miR-30b, miR-193b, miR-196a, miR-385, and miR-378 expression in BAT |
| Kim et al. | C57BL/6 mice | Fish oil* (1.2%-2.4% w/w, 10 wk) | ↑ Oxygen consumption, ↑ Rectal temperature, ↑ Ucp1, Ppargc1a, Cidea, and Tbx1 mRNA expression in sWAT, ↑ Ucp1, Ppargc1a, and Pdmd16 mRNA expression in BAT, ↑ UCP1 expression in sWAT and BAT |
| Flachs et al. | C57BL/6 mice | LC n-3 PUFA concentrate’ (15% of lipid, 16 wk) | ↓ Ppargc1a mRNA expression in BAT |
| Shin and Ajuwon | C57BL/6 mice | Shea butter‘ (20% of energy, 12 wk) | ↓ Ucp1 and Ppargc1a mRNA expression in sWAT, ↓ Oxygen consumption (indirect calorimetry) |
| Shin and Ajuwon | C57BL/6 mice | Olive oil (20% of energy, 12 wk) | ↓ Oxygen consumption (indirect calorimetry) |
| Shin and Ajuwon | C57BL/6 mice | Safflower oil‘ (20% of energy, 12 wk) | ↓ Oxygen consumption (indirect calorimetry) |
| Sharma and Agnihotri | Wistar rats | Fish oil* (10% of energy, 12 wk) | ↑ UCP1 and PGC-1α protein expression in sWAT |
| Oudart et al. | Wistar rats | EPA and DHA (27% of lipid, 4 wk) | ↑ Mitochondrial cytochrome c oxidase activity in BAT |

†, increase; ↓, decrease; BAT, brown adipose tissue; UCP1, uncoupling protein 1; sWAT, subcutaneous white adipose tissue; LC, long-chain; PUFA, polyunsaturated fatty acids; eWAT, epididymal WAT; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator 1α; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

* n-3 polyunsaturated-fatty-acid-rich oil; † 46% wt/wt DHA, 14% wt/wt EPA; § 70% wt/wt LC n-3 fatty acids, increase; ‡ 46% wt/wt EPA, 34% wt/wt DHA.

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1. Increase; 2, decrease; BAT, brown adipose tissue; UCP1, uncoupling protein 1; sWAT, subcutaneous white adipose tissue; LC, long-chain; PUFA, polyunsaturated fatty acids; eWAT, epididymal WAT; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator 1α; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

2. n-3 polyunsaturated-fatty-acid-rich oil; 3 46% wt/wt DHA, 14% wt/wt EPA; 4 Saturated-fatty-acid-rich fat; 5 Mono-unsaturated-fatty-acid-rich oil; 6 n-6 polyunsaturated-fatty-acid-rich oil.
sensory neurons. Since TRPV1 activates β-adrenergic signaling and the sympathetic nervous system (SNS), deletion of TRPV1 abolishes SNS-mediated energy expenditure. In addition to capsaicin and capsinoids, n-3 fatty acids are TRPV1 ligands. Fish oil, rich in EPA (C20:5n-3) and DHA (C22:6n-3), has been reported to increase body temperature and oxygen consumption by inducing browning of WAT by stimulating TRPV1. In addition, fish oil induces thermogenesis by elevating cAMP concentration and β-blocker propranolol prevents the thermogenic effect of fish oil. These data confirm that n-3 fatty acids stimulate β-AR through TRPV1 activation. Thus, dietary content of n-3 fatty acids is an important factor in regulating adipocyte browning through activation of the TRPV1 receptor (Tables 1 and 2).

Pattern recognition receptors activation

Pattern recognition receptors (PRR), also known as innate immune system receptors, recognize pathogen-associated molecular patterns (PAMP), which induces expression of pro-inflammatory cytokines, synthesis of reactive oxygen or nitrogen species, and activation of adaptive immune responses. Toll-like receptors (TLR), representative members of the PRR family, control inflammation and immune responses by recognizing a variety of PAMP derived from viruses, bacteria, or fungi. Among multiple types of TLR, TLR4 was the first identified in humans, and lipopolysaccharide (LPS), a structural component of Gram-negative bacteria and composed of polysaccharide and lipid A, acts as an agonist of TLR4.

LPS binds to LPS-binding protein, which promotes LPS binding to cluster of differentiation 14 (CD14), after which CD14 leads LPS along the cell surface and helps LPS bind to TLR4. This binding recruits MyD88 and IL-1 receptor-associated kinase, promoting association of TRAF6 that activates MAPK. Through MAPK, TRAF6 activates IκB kinase, inducing phosphorylation and degradation of IκB. Free NF-κB translocates into the nucleus and upregulates pro-inflammatory cytokines. In mice, LPS challenge induces peripheral inflammation in WAT and other metabolic organs, reduces adipose thermogenesis and fatty acid oxidation, and increases the risk of systemic insulin resistance.

SFA, such as lauric acid (C12:0), stimulate inflammatory responses through TLR4, whereas MUFA and PUFA are not able to activate TLR4 signal transduction because the lipid A component of LPS has 6 SFA molecules with 12 to 16 carbons. When these fatty acids were replaced with MUFA or PUFA, the pro-inflammatory effects of LPS were strongly suppressed. SFA also activate TLR2 and NF-κB signaling, whereas DHA (C22:6n-3) inhibits TLR2 expression and NF-κB signaling and improves insulin sensitivity in both skeletal muscle and WAT of mice fed HFD. In addition, EPA (C20:5n-3) and DHA were shown to suppress recruitment of TLR4 for lipid rafts. Increased consumption of SFA in obesity is linked to increased TLR4 activation and increased inflammation; conversely, consumption of EPA and DHA is associated with reduced activation of NF-κB and inflammation (Table 3).

Eicosanoid formation

Eicosanoids are signaling molecules that mediate multiple cellular pathways, and include prostaglandins (PG), prostacyclins (PGI), leukotrienes (LT), and thromboxanes (TX). Upon binding of an agonist with G protein-coupled receptors, phospholipase C is activated and hydrolyzes membrane-bound phosphatidylinositol 4,5-bisphosphate into 1,2-diaclylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). In one downstream pathway, DAG activates protein kinase C, which activates MAPK and extracellular signal-related kinase, and MAPK phosphorylates and activates cytosolic phospholipase A2 (cPLA2). In the other pathway, IP3 opens calcium channels located on the endoplasmic membrane and causes the release of calcium into the cytosol. The increased intracellular Ca2+ concentration induces p-cPLA2 translocation from the cytosol to the membrane, which contains phospholipids composed of arachidonic acid (ARA; C20:4n-6) or EPA (C20:5n-3). The p-cPLA2 then cleaves ARA or EPA esterified at the sn-2 position of membrane phospholipids. The cyclooxygenase (COX), lipooxygenase (LO), and cytochrome p450 (CYP) pathways convert the ARA or EPA to one or more eicosanoid products by oxygenation: COX converts ARA or EPA into PG and TX, and LO converts ARA or EPA into hydroperoxyeicosatetraenoic acid and generates LT. Eicosanoids derived from n-6 and n-3 fatty acids have divergent effects on adipose tissue metabolism. ARA-derived PGI stimulates white adipocyte formation, and carbaprostacyclin, a stable analog of PGI, induces lipid accumulation through the prostacyclin receptor (IP) that is expressed on the surface of adipose precursor cells.
In response to IP deletion, body fat accumulation is suppressed, indicating that PGI signaling plays a key role in adipogenesis. In addition, COX metabolites, including prostaglandin E2 (PGE2) and PGF2α, inhibit thermogenic gene expression by modulating PPARy activity, and COX inhibition induced by indomethacin increases the number of beige adipocytes in subcutaneous WAT. Chronic β-adrenergic stimulation reduces PG and PGI expression, and ARA supplementation impairs the acquisition of a brown-like phenotype by WAT induced by CL316,243 (a specific β3-AR agonist). In contrast, EPA (C20:5n-3) and DHA (C22:6n-3) have been shown to block the effects of ARA-derived eicosanoids, which results in the upregulation of thermogenesis and fatty acid oxidation, and the reduction of body fat mass.

Given LNA (C18:2n-6) can be elongated to ARA (C20:4n-6), the composition of LNA can significantly affect adipocyte differentiation and thermogenesis through conversion of ARA and regulation of COX pathway. In fact, the large increase in the prevalence of overweight and obesity over the past 30 years parallels the increase in the dietary n-6/n-3 ratio, and ARA concentrations in plasma or adipose tissue are positively correlated with body weight or body mass index in humans. In both animal models and human subjects, diets with a high n-6/n-3 ratio, including those containing relatively little ALA (C18:3n-3) or more ARA, increase body fat accumulation and impair leptin signaling and energy homeostasis. In mice, supplementation of safflower oil, containing high LNA (C18:2n-6) and low ALA (C18:3n-3), was shown to reduce thermogenic gene expression and oxygen consumption compared with other dietary oils with low n-6/n-3 ratios.

In addition, n-6 and n-3 eicosanoids exert different effects on the intensity of inflammation. Compared to even-series eicosanoids derived from n-6 fatty acids, including PGE2 and LTB4, odd-series eicosanoids derived from n-3 fatty acids, including EPA and LTB5, tend to be less active in promoting platelet aggregation, inflammation, and vascular muscle contraction. Since n-3 fatty acids, including EPA, compete with ARA for incorporation into membrane phospholipids and metabolism by COX, LO, and CYP, dietary consumption of n-3 fatty acids could prevent excessive production of n-6-fatty-acid-derived eicosanoids by reducing the availability of ARA in the phospholipid membrane and the metabolism of ARA. In many studies, EPA and DHA inhibited expression of pro-inflammatory genes by mitigating NF-κB signaling and a meta-analysis of randomized double-blinded placebo-controlled

Table 3. Effects of long-chain fatty acids on adipose inflammation

| Study          | Experimental model | Treatment (dose, duration) | Outcome                                      |
|---------------|--------------------|---------------------------|----------------------------------------------|
| Lee et al.76  | RAW 264.7 macrophages | LA (1–100 μM, 11 hr)     | ↑ COX-2, INOS, and IL-1α protein expression |
| Lee et al.77  | RAW 264.7 macrophages | EPA and DHA (1–20 μM, 3 hr) | ↓ NF-κB activation, ↓ COX-2 expression, ↑ PGE2 secretion |
| Human peripheral blood monocytes | Fish oil* (6–15 g/day, 4 wk) |                         |                                               |
| Mullen et al.83| THP-1-derived macrophages | EPA and DHA (25 μM, 48 hr) | ↓ LPS-induced IL-1b, IL-6, and TNFα mRNA expression, ↓ LPS-induced NF-κB activation |
| Oliver et al.85| J774.2 macrophages | EPA and DHA (50 μM, 5 hr) | ↓ LPS-induced IL-6 and TNFα mRNA expression, ↓ LPS-induced NF-κB activation, ↑ M2 anti-inflammatory phenotype polarization |
| 3T3-L1 adipocytes | Conditioned medium from EPA- or DHA-treated macrophages (50 μM, 5 hr) |                         | ↑ Basal and LPS-induced NF-κB activation |
| Alvheim et al.86| C57BL/6 mice | ARA (8% of energy, 16 wk) | ↑ Hepatic AEA and 2-AG levels, ↑ Macrophage infiltration in sWAT and eWAT |
| Kuda et al.87| C57BL/6 mice | LC n-3 PUFA concentrate† (15% of lipid, 16 wk) | ↓ 2-AG level in eWAT and isolated adipocytes, ↓ Anamide level in eWAT, ↑ M2 anti-inflammatory phenotype polarization of isolated adipose tissue macrophages |
| Flachs et al.88| C57BL/6 mice | LC n-3 PUFA concentrate† (15% of lipid, 16 wk) | ↓ Macrophage infiltration in eWAT, ↓ Plasma IL-6 level |

* n-3 polysaturated fatty acid-rich oil; † 46% wt/wt DHA, 14% wt/wt EPA.
† increase, ↓ decrease; LA, lauric acid; COX, cyclooxygenase; INOS, inducible nitric oxide synthase; IL, interleukin; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; NF-κB, nuclear factor kappa B; PGE2, prostaglandin E2; LPS, lipopolysaccharide; TNF, tumor necrosis factor; M2, type 2 macrophages; ARA, arachidonic acid; AEA, arachidonoyl-ethanolamide; AG, arachidonoylglycerol; sWAT, subcutaneous white adipose tissue; eWAT, epididymal WAT; LC, long-chain; PUFA, polyunsaturated fatty acids.
trials reported that high-dose n-3 fatty acid supplementation provided significant protection against cardiac death in patients with a history of cardiovascular disease.100

Endocannabinoid system

Endocannabinoids are bioactive lipid mediators that control both innate and adaptive immune responses.101 In addition to endogenous cannabinoid receptor type 1 and 2, endocannabinoids activate other molecular targets, including TRP channels and PPAR isoforms.102 The endocannabinoid system, which consists of endocannabinoids, their enzymes, and receptors, is dysregulated in many chronic diseases, such as metabolic103 and cardiovascular disorders104 and specific types of cancers.105 Modulation of the system attenuates inflammatory responses by reducing cytokine release, leukocyte infiltration, and reactive oxygen and nitrogen species production.104

The most studied endocannabinoids, anandamide (or N-arachidonylethanolamide; AEA) and 2-arachidonoylglycerol (2-AG), are derived from ARA (C20:4n-6), and dietary intake of n-6 and n-3 fatty acids determine their concentrations. An LNA (C18:2n-6)-rich diet has been shown to elevate AEA and 2-AG levels, and to induce an increase in the size of adipocytes and more infiltration of macrophages in mice.98 However, in white adipocytes derived from epididymal WAT, incubation with n-3 fatty acids (a mixture of EPA and DHA) reduced AEA and 2-AG concentrations,99 and mice fed an n-3-sufficient diet had lower 2-AG levels in brain compared to those fed an n-3 deficient diet.100 Concentrations of other anti-inflammatory endocannabinoids, including N-eicosapentaenoyl ethanolamine and N-docosahexaenoyl ethanolamine, increase with n-3 PUFA consumption in both obese mice and humans, and are negatively correlated with insulin resistance.99 Dietary n-3 fatty acids have also been reported to stimulate polarization of ATMs toward an anti-inflammatory M2 state, decrease macrophage infiltration, and improve insulin sensitivity in mice.99 Thus, the endocannabinoid system may be important in the regulation of adipocyte metabolism, differentiation, and browning by dietary fatty acids (Table 3).

CONCLUSION

As natural ligands for PPARs, LCFA play a major role in the regulation of hyperplasia and hypertrophy of white adipocytes, and thermogenesis in brown and beige adipocytes by promoting interaction between PPAR and PGC-1α. In addition, LCFA-induced FFAR or TRPV1 activation stimulates adipose thermogenesis, and LCFA with different numbers and positions of double bonds induce a variety of inflammatory responses through PRR activation and production of eicosanoids or endocannabinoids, which suppresses thermogenesis. Together these effects indicate that LCFA are able to effectively modulate the development of metabolic disorders by serving as critical regulators of WAT expansion or thermogenic adipocyte activation. In order to include LCFA in nutraceutical strategies to treat obesity and obesity-associated metabolic disorders, clinical trials evaluating the effects of dietary fatty acid composition on the regulation of metabolic phenotype related to adipose tissue metabolism in humans are needed.

CONFLICTS OF INTEREST

The author declares no conflict of interest.

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