Fatty Acid Metabolites as Novel Regulators of Non-shivering Thermogenesis

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Abstract

Fatty acids are essential contributors to adipocyte-based non-shivering thermogenesis by acting as activators of uncoupling protein 1 and serving as fuel for mitochondrial heat production. Novel evidence suggests a contribution to this thermogenic mechanism by their conversion to bioactive compounds. Mammalian cells produce a plethora of oxylipins and endocannabinoids, some of which have been identified to affect the abundance or thermogenic activity of brown and brite adipocytes. These effectors are produced locally or at distant sites and signal toward thermogenic adipocytes via a direct interaction with these cells or indirectly via secondary mechanisms. These interactions are evoked by the activation of receptor-mediated pathways. The endogenous production of these compounds is prone to modulation by the dietary intake of the respective precursor fatty acids. The effect of nutritional interventions on uncoupling protein 1-derived thermogenesis may thus at least in part be conferred by the production of a supportive oxylipin and endocannabinoid profile. The manipulation of this system in future studies will help to elucidate the physiological potential of these compounds as novel, endogenous regulators of non-shivering thermogenesis.

Keywords

Brite adipocytes · Brown adipocytes · Endocannabinoids · Oxylipins · PUFAs · Thermogenesis · Ucp1 · ω-3 · ω-6

1 Introduction

The storage of dietary lipids is a hallmark common to brown (BAT) and white adipose tissue (WAT). Based on the primary functions of these tissues, deposited lipids are predominantly released as fatty acids from triglycerides via lipolytic pathways to fuel energy-consuming processes in place or throughout the body. Besides their function as potent energy source, fatty acids are stored as structural components within biological membranes and act as metabolic regulators. The latter quality is significantly influenced by their conversion into bioactive metabolites within manifold cell types and tissues. Oxylipins and endocannabinoids represent two major metabolite classes. Both classes encompass compounds derived from polyunsaturated fatty acids (PUFAs) via designated pathways following their release from membrane phospholipids. Altogether, these metabolites are well-known for a long time to affect countless physiological processes including various adipocyte-related functions. Evidence pointing toward a novel role of these metabolites in mammalian brown/brite adipogenesis and thermogenic adipocyte function has only recently accumulated. Facing the global burden of obesity, an increase in the abundance or activity of thermogenic cells is considered a possibility to increase energy expenditure, thus reducing fat deposition and related metabolic impairment [for a recent review, see Betz and Enerback (2018)]. The potential of novel effectors and pathways targeting brown or brite adipocyte-based thermogenesis therefore

seems highly valuable to explore and is currently one focus of research related to energy balance regulation (Giordano et al. 2016; Vargas-Castillo et al. 2017; Pradhan et al. 2017).

We here provide a concise summary of the potential of individual fatty acid-derived candidate compounds to affect the abundance or activity of murine and human thermogenic adipocytes, give an overview of their biosynthesis pathways and mechanisms of action, describe state-of-the-art methods for their extraction from adipose tissues and subsequent quantification, and discuss the potency of nutritional intervention studies to modulate their abundance and consequently the capacity for non-shivering thermogenesis.

2 Origin and Formation of Oxylipins and Cannabinoids

2.1 Oxylipins

Oxylipins are oxygenated metabolites primarily derived from the enzymatic oxidation of ω-3 and ω-6 PUFAs, but they can also be generated through nonenzymatic pathways such as autoxidation. Fatty acids serving as oxylipin progenitors include the ω-3 PUFAs eicosapentaenoic acid (C20:5, EPA), docosahexaenoic acid (C22:6, DHA), and α-linolenic acid (C18:3, ALA) as well as the ω-6 PUFAs arachidonic acid (C20:4, ARA) and linoleic acid (18:2, LA) (Fig. 1). The 18-carbon molecules LA and ALA are essential fatty acids, as mammals in contrast to plants lack the enzyme ω-3-desaturase and are therefore unable to endogenously produce these PUFAs. Consequently, plant oils constitute rich sources for LA and ALA. Long-chained PUFAs such as ARA, EPA, and DHA can be produced by mammalian cells through elongation and desaturation of either LA or ALA, respectively. However, as both LA and ALA compete for the same desaturase enzymes, endogenous production of DHA, EPA, and ARA is limited (Simopoulos 2016). Consequently, their individual production may be insufficient to cover needs, which makes their nutritional uptake essential (Plourde and Cunnane 2007). The composition of PUFAs in tissues and the production of their bioactive oxylipin-derivatives can be altered by dietary lipid composition and targeted supplementation of certain lipids such as ω-3 PUFAs (Balvers et al. 2012; Ostermann and Schebb 2017; Schebb et al. 2014). Accordingly, diet is a major factor influencing oxylipin levels in the body. This is important as dietary patterns have changed toward an increased uptake of ω-6 PUFAs at the expense of ω-3 PUFAs, resulting in a dietary ω-6/ω-3 ratio of 20:1 in modern days compared to a ratio of 1:1 during the Paleolithic period (Simopoulos 2001). Furthermore, both a high ω-6 PUFA intake and a high ω-6/ω-3 ratio are associated with obesity and inflammation [reviewed by (Simopoulos 2016)]. After being resorbed from the diet, PUFAs are either esterified and stored as triglycerides or incorporated into biological membranes as phospholipids. Prior to the generation of oxylipins, PUFAs must be released from these compartments upon cell activation. The cytosolic phospholipase A_2 ($cPLA_2$) enzyme is involved in the release of PUFAs from membrane phospholipids, which is traditionally perceived as the

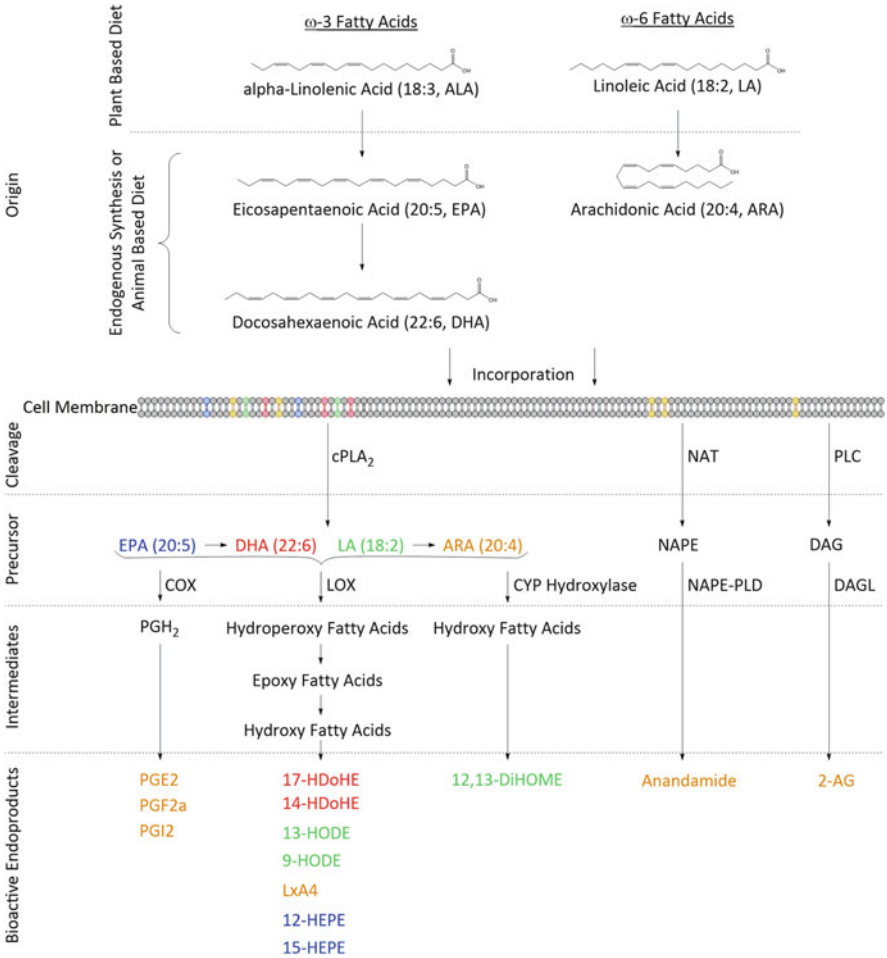

Fig. 1 Synthesis of oxylipins and endocannabinoids from membrane phospholipids. Diet-derived ω-3 and ω-6 fatty acids are incorporated into biological membranes. Through the action of various enzymes, membrane phospholipids are cleaved to release free fatty acids, *N*-arachidonoyl-phosphatidylethanolamine (NAPE) or diacylglycerols (DAG), into the cytosol. These precursors serve as substrates for different enzymatic pathways involved in the synthesis of oxylipins or endocannabinoids. Individual compounds derived from EPA, DHA, LA, and ARA are highlighted in blue, red, green, and orange, respectively. *$cPLA_2$* cytosolic phospholipase A2, *NAT* *N*-acyltransferase, *PLC* phospholipase C, *COX* cyclooxygenase, *LOX* lipoxygenase, *CYP* cytochrome P450, *NAPE-PLD* NAPE-phospholipase D, *DAG* diacylglycerol, *DAGL* DAG lipase

major origin of oxylipin precursor PUFAs. Deficiency of $cPLA_2$ is, however, not sufficient to entirely attenuate oxylipin production in mice and humans, suggesting the existence of alternative origins (Uozumi and Shimizu 2002; Adler et al. 2008). In fact, the adipose triglyceride lipase-mediated release of PUFAs from triglyceride-rich lipid droplets appears to constitute a novel route for the release of oxylipin

precursor fatty acids (Dichlberger et al. 2014; Schlager et al. 2015; Riederer et al. 2017). Subsequently, a vast diversity of oxylipins can be generated depending on the progenitor fatty acid released and on the metabolizing enzymes present in the cells. Based on the precursor PUFA, there are three classes of oxylipins to be distinguished: C18-derived octadecanoids, eicosanoids derived from C20 PUFAs, and C22-derived docosanoids. Fatty acids are converted to oxylipins by three types of enzymes, thus generating distinct oxylipin subclasses (Fig. 1).

The cyclooxygenase (COX) enzyme is responsible for the production of prostanoids and therefore an important mediator of inflammatory processes. Up to date, two COX isoforms have been identified. Although it is still a matter of debate, COX-1 is generally believed to be constitutively expressed in mammalian tissues, while COX-2 is regarded the inducible isoform being upregulated during states of inflammation. The COX-enzyme mainly facilitates the cyclization of its C20-PUFA substrate between C8 and C12, leading to the generation of the intermediary product prostaglandin H (PGH). Therefore, COX-1 and COX-2 are also known as prostaglandin H synthases (PGHS) 1 and 2, respectively. Depending on the substrate involved, PGH_1, PGH_2, or PGH_3 are generated from the C20 PUFAs dihomo-γ-linolenic acid (an intermediate in the synthesis of ARA from LA), ARA, or EPA, respectively. These intermediates serve as precursors for the formation of individual prostanoids of the 1-, 2-, and 3-series upon action of subsequent enzymes such as prostaglandin synthases, for instance. Among the different COX-substrates, ARA serves as the main substrate and precursor of 2-series prostanoids comprising various prostaglandins and thromboxanes [see Gabbs et al. (2015) for a comprehensive review about the generation of COX-derived oxylipins].

The lipoxygenase (LOX) isozymes represent a second oxylipin-producing enzyme class. There are six different human LOX genes (ALOX15, ALOX15B, ALOX12, ALOX12B, ALOXE3, and ALOX5), encoding for six functional isoforms. In contrast, ALOX15B is not found within the murine genome, which comprises the genes ALOX8 and ALOX12E instead. The common property of these enzymes is the introduction of dioxygen into PUFAs, thereby generating hydroperoxy, epoxy, and hydroxy fatty acids (Fig. 1). This includes the formation of hydroxyoctadecadienoic acids (HODEs), hydroxyeicosatetraenoic acids (HETEs), hydroxyeicosapentaenoic acids (HEPEs), and hydroxydocosahexaenoic acids (HDoHEs) from LA, ARA, EPA, and DHA, respectively. Additional products of the LOX pathway are leukotrienes, resolvins, and lipoxins (Kuhn et al. 2015; Gabbs et al. 2015).

Members of the cytochrome P450 (CYP450) system constitute the third class of enzymes able to generate oxylipins. In humans, there are 57 functional genes encoding for enzymes with hydroxylase or epoxygenase activity, while 102 functional genes have been identified in mice (Nelson et al. 2004). The hydroxylase activity of the CYP450 enzymes produces similar metabolite classes as LOX such as HODEs and HETEs, while epoxy fatty acids like ARA-derived epoxyeicosatetraenoic acids (EETs) are generated via epoxygenase activity (Konkel and Schunck 2011).

2.2 Endocannabinoids and Endocannabinoid-Like Compounds

Like oxylipins, endocannabinoids and endocannabinoid-like compounds are derivatives of PUFAs. The endocannabinoids *N*-arachidonoyl-ethanolamide (anandamide, AEA) and 2-arachidonoylglycerol (2-AG) are derived from ARA via two distinct enzymatic pathways (Fig. 1). The synthesis of 2-AG is initiated via the transformation of the membrane phospholipid 2-arachidonoyl-phosphatidylinositol into diacylglycerol by phospholipase C. Subsequently, diacylglycerol is converted by diacylglycerol lipase into 2-AG, which is a short-lived molecule that is either isomerized to 1-arachidonoylglycerol or degraded to ARA by monoacylglycerol lipase. Anandamide is generated by the transfer of ARA from 1-arachidonoyl-phosphatidylcholine to phosphatidylethanolamine, a process catalyzed by the enzyme *N*-acyltransferase. *N*-arachidonoyl-phosphatidylethanolamine (NAPE) is the product of this reaction, which is further converted to anandamide via NAPE-phospholipase D (NAPE-PLD). The degradation of AEA into ARA is subsequently mediated by the action of the fatty acid amide hydrolase. Both AEA and 2-AG are ligands of the cannabinoid receptors 1 and 2 (CB1 and CB2) and therefore considered endocannabinoids.

Endocannabinoid-like compounds represent *N*-acylated-ethanolamides (NAEs) that are generated by the same enzymatic pathways as endocannabinoids. They are, however, not derived from ARA but from other PUFAs or saturated fatty acids. As such, docosahexaenoylethanolamide, eicosapentaenoylethanolamide, or oleoyl-ethanolamide (OEA) are derived from DHA, EPA, or oleic acid, respectively. Their structural similarities with the endocannabinoid AEA constitute their denomination as endocannabinoid-like compounds (although these metabolites barely bind to CB receptors).

3 Extraction and Analysis of Oxylipins and Endocannabinoids in Adipose Tissues

Over the years, several methods were developed for the quantitation of oxylipins and endocannabinoids in biological samples. The first analytical methods were based on gas chromatography coupled to mass spectrometry. Due to laborious sample preparation and the alteration of the lipid pattern based on degradation of specific compounds, these methods were mostly replaced by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). Advancements of analytical instruments allow the detection of hundreds of oxylipins and endocannabinoids simultaneously from the low nanomolar to the high millimolar range by mass spectrometry-based methods nowadays. Nevertheless, analyzing these metabolite classes, sample preparation, chromatographic separation, and detection of the desired analytes needs to be validated and optimized. For example, the oxylipin pattern can be altered through autoxidation mechanisms during sample storage. Therefore, antioxidants like butylated hydroxytoluene or ethylenediaminetetraacetic acid are added to the biological samples to minimize the change of the oxylipin pattern. The stable isotope dilution

assay is the method of choice for mass spectrometric methods; thus deuterated or 13C-labeled oxylipins or endocannabinoids are added to the samples as internal standards to correct for losses during sample preparation and matrix effects during measurements. One bottleneck is the limited availability of these standards and their high price. Therefore, a compromise often is to use one isotopically labeled standard per lipid class. The lipids are extracted by liquid-liquid extraction, solid-phase extraction, or a combination of both. For example, frozen adipose tissues can be crushed in balanced salt solution, extracted with cold methanol, and subjected to polymeric solid-phase extraction to quantify arachidonic acid metabolites in adipose tissue with LC-MS/MS (Pisani et al. 2014; Le Faouder et al. 2013). Most methods nowadays, where around 100 oxylipins and endocannabinoids can be quantified simultaneously, use LC-MS/MS with negative electro-spray ionization or atmospheric pressure chemical ionization (Strassburg et al. 2012; Dumlao et al. 2011; Krott et al. 2016). Usually, quantitative mass spectrometry is performed on a triple quadrupole mass spectrometer, which is operated in the multiple reaction monitoring mode (MRM) (Schuchardt et al. 2013). Here, the parent ion, often [M-H]-, is fragmented and a specific fragment is detected. The biggest challenge of oxylipins and endocannabinoids analysis is the differentiation of stereoisomers. Chiral chromatography methods have been developed to differentiate, for example, between (R)- and (S)-isomers (Mesaros and Blair 2012). Another example, where good chromatographic separation is needed, is the quantitation of the prostaglandins PGE_2 and PGD_2. These prostaglandins have the same chemical formula ($C_{20}H_{32}O_5$) and therefore the same mass-to-charge ratio and also the same MS/MS fragmentation pattern. In some cases, stereoisomers can be differentiated by a clever choice of mass transitions. For example, product ions of HETEs are formed through α-cleavage adjacent to a double bond, and therefore the individual oxylipins 5-HETE and 8-HETE can be distinguished by their fragment ions (Murphy et al. 2005). In general, MRM methods are sensitive, selective and the method of choice for quantitation of oxylipins and endocannabinoids in adipose tissues (Willenberg et al. 2015). One restriction of these LC-MRM-MS methods is that only compounds can be detected where reference material is available. To identify new lipids and to resolve additional structural information, liquid chromatography coupled to high-resolution mass spectrometry (LC-HRMS/MS) with data-dependent fragmentation is used (Lynes et al. 2017). These methods are less sensitive than the MRM methods but bear the advantage to obtain more structural information due to the recording of complete MS/MS spectra. MS/MS spectra are compared to lipid databases, and the lipid classes are tentatively annotated (Fahy et al. 2007). To verify the correct annotation and to quantify the candidates, reference standards are necessary (Masoodi et al. 2010). To use benefits of the targeted (LC-MRM-MS) and the untargeted (LC-HRMS/MS) approaches, the SWATH (sequential window acquisition of all theoretical mass windows) technology was recently applied to lipidomics and will in the future generate deeper insight into the complex regulation of lipids (Prasain et al. 2015).

Independent of the analysis technique, the interpretation of quantitative metabolite data requires their normalization to a reference quantity. A normalization to the applied mass is easily applicable when tissues are used as starting material but presumes the determination of the dissected tissue weight prior to the analysis. Metabolites expressed per milligram tissue can be extrapolated to depot size, thus providing information on the contribution of a tissue to the physiological metabolite production ("per animal") under the prerequisite that entire depots were dissected and weighed. Similarly, cell number may serve as reference quantity when cultured cells are subject to analysis. Additionally, the protein or lipid content of the material may be quantified to serve as alternative reference. However, the percentage of proteins and lipids may not only vary between different types of tissues but may also be influenced by treatment, which poses limitations to the interpretation of the results. This becomes particularly obvious in an exemplary, comparative analysis of oxylipins between WAT and BAT depots, which are well-known to differ in tissue mass (e.g., 250 mg vs. 65 mg depot mass for the inguinal WAT and interscapular BAT, respectively) and protein content (e.g., 2.5% vs. 7.25% of the respective, dissected tissue masses). Assuming that an oxylipin of interest is quantified with around 100 pg/mg protein in both tissues, a similar production rate would be a straightforward interpretation. However, when this production rate is extrapolated to the indicated tissue masses, the WAT depot is interpreted as a stronger contributor to the systemic synthesis of this oxylipin. In contrast, when the production rate is expressed per milligram tissue, BAT has an approx. threefold higher potency to produce this oxylipin. All normalization options provide valuable information but may result in over- or underestimation of metabolite production, which is particularly crucial when the analysis is applied to tissues of unknown mass or an undefined number of cells. Thus, oxylipin and endocannabinoid data should be analyzed in the light of all available normalization options to select the most reasonable option with regard to the scientific question.

4 Mechanisms of Action

Oxylipins and endocannabinoids are thought to act locally in autocrine or paracrine manner, which is based on their short half-life resulting from rapid degradation of the free, active compounds. However, their occurrence within the blood circulation suggests a possible, endocrine function. Blood oxylipins predominantly occur as esterified or albumin-bound forms (Raz 1972a, b; Maclouf et al. 1980; Shearer and Newman 2008; Shearer et al. 2018). Lipoprotein particles comprise a large quantity of esterified oxylipins, which can be released by lipoprotein lipase (Shearer and Newman 2008; Schebb et al. 2014). Thus, blood lipoproteins may represent a storage compartment for oxylipins to facilitate their delivery and uptake by distant tissues. In contrast, the majority of blood endocannabinoids and endocannabinoid-like compounds does not seem to require lipoproteins as transport vehicle but may bind to serum albumin (Bilgin et al. 2015; Bojesen and Hansen 2003).

The transcellular exchange of oxylipins is likely mediated by plasma membrane transporters rather than diffusion. Several transporters have been identified, which mediate the exchange of prostaglandins and leukotrienes. These proteins regulate the secretion of these compounds into the extracellular space as well as their uptake, which serves the activation of intracellular signaling pathways or their degradation (Schuster et al. 2015; Zhou et al. 2008). The influx and efflux of endocannabinoids is discussed to involve different mechanisms such as specialized transporters, passive diffusion, or endocytosis (Fowler 2013).

Effects of oxylipins and endocannabinoids within the target cell are evoked by activation of receptor-mediated pathways. These compounds interact with different types of receptors located intracellularly or at the cell surface. The latter class includes several members of the transient receptor potential (TRP) ion channel family [for a comprehensive summary, see Kaneko and Szallasi (2014)]. Moreover, many oxylipin receptors as well as the endocannabinoid receptors CB1 and CB2 represent G-protein-coupled receptors of the plasma membrane that signal via intracellular calcium (G_q-protein) or cyclic adenosine monophosphate (cAMP). The cAMP response is triggered by inhibition (G_i-protein) or activation (G_s-protein) of the adenylyl cyclase. Elevation of cAMP levels activates protein kinase A, which subsequently triggers the p38 mitogen-activated protein kinases pathway to stimulate the expression of selected genes. Signaling via this pathway stimulates expression of the uncoupling protein 1 (Ucp1) gene, which classically occurs upon activation of β-adrenoreceptors under conditions of non-shivering thermogenesis (Cao et al. 2001). The same pathway is repressed upon inhibition of the adenylyl cyclase, e.g., upon activation of the CB1 and CB2 receptors (Howlett et al. 2002).

The occurrence of cannabinoid receptors is not restricted to the plasma membrane. Following their synthesis, cannabinoid receptors can be incorporated into endolysosomes of human and rodent cells. These receptors are functional, couple to G_i and/or G_q, and elicit calcium release from intracellular stores (Brailoiu et al. 2011, 2014; Rozenfeld and Devi 2008; Boon et al. 2014). The significance of intracellular vs. plasma membrane cannabinoid receptors for the mediation of physiological effects has not yet been elucidated.

Peroxisome proliferator-activated receptors (PPARs) are a family of ligand-activated nuclear receptors occurring as subtypes α, β/δ, and γ. Oxylipins and endocannabinoids serve as endogenous ligands for the γ-subtype (Bouaboula et al. 2005; Barquissau et al. 2017), which is the central regulator of adipose tissue development, thus regulating white and brown adipogenesis and browning of WAT [reviewed by Harms and Seale (2013) and Seale et al. (2009)]. After its heterodimerization with the retinoic x receptor, PPARγ is able to bind to the PPAR response element representing a DNA-binding domain. Such a PPAR response element is located in the promoter region of the Ucp1 gene, whose product essentially enables non-shivering thermogenesis in brown and brite adipocytes (Enerback et al. 1997; Li et al. 2014). Consequently, treatment of mice or cultured pre-adipocytes with the PPARγ agonist rosiglitazone induces the development of brown and brite adipocytes with marked Ucp1 expression (Carmona et al. 2007; Petrovic et al. 2010).

5 Effects of Individual Compounds on Brown/Brite Adipocytes

Brown and brite adipocytes are functionally thermogenic and provide Ucp1-dependent non-shivering thermogenesis within BAT and WAT (Li et al. 2014). The role of fatty acids for adipocyte-derived thermogenesis is not restricted to their quality as fuel for heat production, but comprises their function as important signaling molecules. Thermogenic signaling cascades may be initiated by fatty acids acting as primary effectors (Quesada-Lopez et al. 2016; Hu et al. 2016; Kim et al. 2016) or by their property to function as precursors for the formation of secondary thermogenic metabolites. The latter is contributed by their conversion into oxylipins and endocannabinoids representing a novel function of these fatty acid derivatives. Here we review the candidate compounds reported to influence the capacity for Ucp1-dependent non-shivering thermogenesis in BAT and WAT.

5.1 Prostacyclin

The two COX enzymes are an important hub of oxylipin synthesis in numerous cell types and tissues. Their abundance in murine WAT is under adrenergic control, rendering these enzymes crucial regulators of brite adipocyte formation (Madsen et al. 2010; Vegiopoulos et al. 2010). This function has been ascribed to the production of prostacyclin (PGI_2), which is a derivative of ARA obtained by the specific action of prostacyclin synthase on COX-derived PGH_2. As a ligand for its G_s-protein-coupled cell surface receptor (the IP receptor) expressed by numerous tissues and cell types, this prostaglandin is well-known to potently act on vasodilation and platelet aggregation. Browning of WAT constitutes a novel function affected by this oxylipin.

The production of PGI_2 in WAT under conditions of non-shivering thermogenesis is likely mediated by mature adipocytes as these cells show increased expression of COX-2 upon adrenergic stimulation (Vegiopoulos et al. 2010). As part of a straightforward signal transduction, the released PGI_2 likely acts in paracrine manner to stimulate Ucp1 expression and the sensitivity toward noradrenergic stimulation during the differentiation of adipocyte precursors (Vegiopoulos et al. 2010). This brite adipogenesis seems to specifically originate from the action of PGI_2 on committed precursor cells of the stromal vascular fraction as the effect is in vitro most efficiently inducible by treatment of purified $Lin^{-}Sca1^{+}$ primary cultures of the posterior subcutaneous fat depot with carbaprostacyclin ($cPGI_2$) (Babaei et al. 2017). The latter represents a chemically stable PGI_2-analogue as PGI_2 itself is quickly converted into the inactive metabolite 6-keto-$PGF_{1\alpha}$.

The $cPGI_2$-induced conversion of committed precursors into brite adipocytes in vitro is most efficient when the compound is added to the adipogenic culture medium during eight consecutive days (Babaei et al. 2017; Bayindir et al. 2015). Thermogenic maturation of these cells in response to $cPGI_2$ treatment is initiated

during an advanced stage of differentiation (Bayindir et al. 2015). This effect likewise seems to originate from an interaction of $cPGI_2$ with the cell surface IP receptor as well as with the nuclear receptor PPARγ since $cPGI_2$-induced Ucp1 expression is blunted during the differentiation of primary progenitors obtained from WAT of mice with heterozygous PPARγ ablation or in the presence of an IP receptor antagonist (Vegiopoulos et al. 2010). In fact, expression of the IP receptor is highest in pre-adipocytes and follows a reduction during the adipogenic differentiation of murine and human cells (Vassaux et al. 1992; Borglum et al. 1999). Thus, $cPGI_2$ may orchestrate brite adipogenesis via an initial activation of the IP receptor of committed pre-adipocytes to promote their thermogenic maturation in the further progress of differentiation via a predominant interaction with PPARγ.

Intriguingly, $cPGI_2$-induced brite adipogenesis is not restricted to murine adipocytes but reproducible in human mesenchymal stem cells involving similar signal transduction, either during a continuous treatment or upon 3 days of exposure in the final stage of the adipogenic differentiation (Vegiopoulos et al. 2010; Ghandour et al. 2016). The $cPGI_2$-induced expression of Ucp1 in human and murine cells is rather moderate compared to the potent effect of the PPARγ agonist rosiglitazone (Ghandour et al. 2016; Babaei et al. 2017). This relative difference in potency may be counterbalanced under physiological conditions since the naturally occurring PGI_2 is considered ten times more potent than its synthetic analogue (Aiken and Shebuski 1980; Whittle et al. 1980). However, the physiologic contribution of this system to the recruitment of brite adipocytes in vivo is to date virtually unexplored. The production of PGI_2 in WAT of COX-2 overexpressing mice correlates well with their increased abundance of brite adipocytes. This phenotype is associated with thermogenesis and resistance to diet-induced obesity (Vegiopoulos et al. 2010). Moreover, adrenergically induced browning of WAT is impaired in IP receptor knockout mice and in mice with heterozygous ablation of PPARγ, indicating PGI_2 signaling to be a modulator of systemic energy expenditure (Vegiopoulos et al. 2010).

The effect of PGI_2 on browning of murine adipocytes remains to be corroborated by more studies. The author's laboratories were not able to fully reproduce these findings using our own proven protocols. Prostacyclin-mediated browning of murine cells appears to require very precise culture conditions and may thus not constitute a common, robust effect. Moreover, IP receptor knockout mice appear to be protected from the adipogenic effect of a diet rich in ARA precursors, indicating PGI_2 signaling to promote energy storage and fat mass expansion (Massiera et al. 2003). This observation is well in line with enhanced adipogenic differentiation of cultured cells in the presence of PGI_2 (Negrel et al. 1989; Catalioto et al. 1991). Altogether, these findings indicate a bifunctional role of PGI_2 for adipocyte identity with an effect on both brite and white adipogenesis. The underlying reasons remain to be clarified but may involve, for instance, the PGI_2 target cell itself, the abundance of committed precursors within a tissue or a culture, or the presence of other adipogenic factors in blood or cell culture sera, respectively. Further studies are needed to corroborate the browning potential of PGI_2 and to further explore its specific effect on energy balance regulation under in vivo conditions.

5.2 Prostaglandin E_2

As member of the various prostaglandins produced via the COX pathway, prostaglandin E_2 (PGE_2) specifically arises from the action of the PGE synthase isozymes on ARA-derived PGH_2. As for other prostaglandins, the physiological effects of PGE_2 originate from its interaction with at least four cognate cell surface PGE receptors (EP1-EP4). The individual physiological responses evoked by PGE_2 are not only the result of cell type-dependent variations in receptor expression but also influenced by the specific signaling cascade of the receptor subtypes. While the EP1 subtype is G_q-coupled, the EP2 and EP4 subtypes couple to G_s, whereas the EP3 subtype couples to G_i. The latter is involved in mammalian febrile response (Ushikubi et al. 1998; Lazarus et al. 2007), which is an indirect consequence of central PGE_2 signaling on BAT function. In a healthy organism, the hypothalamic preoptic area (POA) translates the environmental temperature sensed by cutaneous thermoreceptors into an appropriate physiological response to maintain normothermia. In a cold environment, this involves an inhibition of efferent POA neurons culminating in the excitation of sympathetic nerves to activate BAT thermogenesis. The activity of these efferent POA neurons is likely influenced by the EP3 receptor [for a comprehensive review, see Morrison and Madden (2014)]. During febrile response (e.g., to infection), elevated levels of central PGE_2 act on the same neuronal pathways mediating an increase in body temperature and energy expenditure via the stimulation of BAT activity (Morrison 2016; Nakamura et al. 2002; Scammell et al. 1996).

Reduced systemic levels of PGE_2 have been hypothesized to participate in the afebrile regulation of body temperature (Foster et al. 2015). Besides centrally mediated mechanisms, there is evidence for a direct interaction of PGE_2 with adipocytes affecting thermogenesis. In fact, exogenous PGE_2 acutely increases the oxygen consumption of brown adipocytes (Nagai et al. 1996). The administration of 16,16-dimethyl-PGE_2 (a stable analogue of PGE_2) to C57BL/6J mice enhances the expression of Ucp1 mRNA in WAT suggesting an effect on brite adipocyte recruitment (Madsen et al. 2010; Xue et al. 2016). This PGE_2-mediated browning appears to involve a coordinated interaction of distinct molecular effectors (Garcia-Alonso and Claria 2014; Garcia-Alonso et al. 2013). Mice with an adipocyte-specific knockout of PPARγ have elevated adipose tissue levels of PGE_2 besides an increased expression of its synthesizing enzymes COX and microsomal PGE synthase 1 (mPGES1). This indicates a repressive effect of PPARγ on the PGE_2-synthesis pathway, confining the physiological origin of adipose tissue PGE_2 production to a cell type with low or absent PPARγ expression. In line with this, cells of the stromal vascular fraction from murine subcutaneous adipose tissue show higher PGE_2 secretion compared to mature adipocytes (Ying et al. 2017). Exogenous PGE_2 is able to suppress PPARγ expression in murine cells and to stimulate COX-2 and mPGES1 expression of WAT explants, indicating the existence of an autocrine positive feedback loop within the secreting cell to further elevate its own PGE_2 production (Garcia-Alonso et al. 2013). Whereas the presence of PGE_2 during the adipogenic differentiation of primary epididymal pre-adipocytes enhances Ucp1

expression over that of vehicle-treated wild-type cells, Ucp1 expression is unaltered in PPARγ-ablated cells (Garcia-Alonso et al. 2013). Thus, the browning effect of PGE_2 appears to require the presence PPARγ within the target cell, although the underlying mechanism is not yet conclusive in the light of its suppressive effect on PPARγ expression. Moreover, the specific cell type responding to PGE_2 has not yet been determined and may differ between species. Adipocyte progenitors seem to be a plausible target for the murine tissue as an acute treatment with PGE_2 is capable of increasing Ucp1 mRNA levels in cells of the stromal vascular fraction (Vegiopoulos et al. 2010). Conversely, primary mature adipocytes derived from human omental fat respond to acute PGE_2 treatment with an increase in Ucp1 mRNA expression, suggesting PGE_2-mediated browning to arise from trans-differentiation of white adipocytes (Garcia-Alonso et al. 2016). Such hypothesis is, however, not supported by experiments with human multipotent adipose-derived stem (hMADS) cells that serve as an established model system for human brite adipogenesis in culture (Elabd et al. 2009; Pisani et al. 2011). The white-to-brite adipocyte conversion of these cells is dose-dependently inhibited when 16,16-dimethyl-PGE_2 is present in the culture medium during an advanced stage of the adipogenic differentiation (Pisani et al. 2014).

The physiological effects of PGE_2 are mediated via its interaction with the four EP receptors, all of which are expressed in murine adipose tissue. The EP4 receptor has been suggested to be responsible for the browning effect (Madsen et al. 2010), which was further explored in EP4 receptor knockout mice recently (Ying et al. 2017). In fact, these mice show a more pronounced delipidation of their subcutaneous WAT depot than wild-type littermates after 10 days of repeated β_3-adrenergic stimulation. Interestingly, this phenotype is not related to the abundance of Ucp1 but rather originates from mitochondrial biogenesis and a disequilibrium between lipid droplet breakdown and synthesis. Thus, ablation of the EP4 receptor enhances murine WAT remodeling, suggesting this receptor as a negative regulator of adrenergically stimulated WAT browning. In contrast, the inhibitory effect of 16,16-dimethyl-PGE_2 on brite adipogenesis of hMADS cells is even more pronounced in the presence of an EP4 receptor inhibitor, indicating a supportive effect on the trans-differentiation of human adipocytes (Pisani et al. 2014).

A question of profound interest is whether PGE_2 is of any physiological relevance for the recruitment of brite adipocytes in vivo. Pertaining to mice, reported effect sizes on Ucp1 mRNA expression are rather small, and none of the aforementioned studies provides information on Ucp1 protein expression, PGE_2-induced oxygen consumption of brite cultures or tissues, or physiological estimates of thermogenic capacity depending on the size of the affected depot. Studies in COX-2 transgenic mice or in mice with genetically or pharmacologically induced deficiency of COX-2 only provide limited information as physiological effects associated with brown/brite adipocyte-derived thermogenesis (e.g., body temperature, whole-body energy expenditure, body mass development) may be influenced by altered production of various COX-metabolites (Vegiopoulos et al. 2010; Madsen et al. 2010). Altogether, the observations currently available suggest PGE_2 to constitute a candidate compound that may mediate the recruitment of non-shivering thermogenesis in WAT, whose

potential requires comprehensive characterization in vitro and in vivo with particular focus on species-specific effects.

5.3 Prostaglandin $F_{2\alpha}$

Together with PGI_2 and PGE_2, prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) represents another COX-derived prostaglandin produced by adipose tissues. The synthesis originates from the metabolization of ARA into PGH_2, which serves as a direct or indirect (via the intermediate production of PGE_2 and PGD_2) substrate for the downstream production of $PGF_{2\alpha}$ by members of the aldo-keto reductase enzyme family. Its cognate receptor (the FP receptor) is abundant in adipose tissues (Volat et al. 2012), located at the cell surface, and couples to G_q, thus mediating the physiological effects of $PGF_{2\alpha}$ via an increase in intracellular calcium. This signaling pathway attenuates Ucp1 expression during brite adipogenesis, thus rendering this compound a negative regulator of thermogenic adipocyte function (Pisani et al. 2014). Intriguingly, the effect of $PGF_{2\alpha}$ on adipocyte browning has not yet been investigated in murine cells but is evident in hMADS cells. These cells can be differentiated into white or brite adipocytes under serum-free conditions depending on the presence (brite) or absence (white) of the PPARγ-activator rosiglitazone during the last days of the differentiation phase. Co-administration of the stable $PGF_{2\alpha}$-analogue fluprostenol during that phase dose-dependently blunts the levels of Ucp1 mRNA and protein in brite hMADS adipocytes (Pisani et al. 2014). The effect is mediated via activation of the FP receptor resulting in intracellular calcium oscillations with subsequent phosphorylation of extracellular signal-regulated kinases (ERK). In line with this, differentiation of brite hMADS in the presence of an ERK inhibitor or a calcium-chelator restores fluprostenol-induced effects on Ucp1 expression. As $PGF_{2\alpha}$ signaling in adipocytes inhibits the activity of PPARγ (Reginato et al. 1998), the repressive effect of this compound on Ucp1 expression may be explained by an antagonization of rosiglitazone during the conversion of white into brite hMADS adipocytes.

Physiologic effects of $PGF_{2\alpha}$ in adipose tissue may comprise both mature and pre-adipocytes as responsive cell types. In fact, $PGF_{2\alpha}$ signaling in cultured 3T3-L1 pre-adipocytes results in an inhibition of adipogenesis (Annamalai and Clipstone 2014; Liu and Clipstone 2007; Ueno and Fujimori 2011), which could be hypothesized to limit the de novo maturation of thermogenic cells in vivo in the long term. Genetically induced reduction of $PGF_{2\alpha}$ production in mice, however, results in the excessive accumulation of adipose tissue and adipocyte hypertrophy (Volat et al. 2012) and thus appears to primarily promote general adipogenesis. As brite adipogenesis in hMADS cells can be interpreted as a model system for trans-differentiation, the thermogenic function of adipocytes may rather be affected by reduced conversion of mature white into brite adipocytes in the presence of $PGF_{2\alpha}$ (Pisani et al. 2014). The increased production of this compound by adipose tissues may antagonize the browning effect of other oxylipins and therefore limit adaptive heat production under conditions of non-shivering thermogenesis.

5.4 Lipoxin A_4

The ARA-derivative lipoxin A_4 (LXA_4) is an eicosanoid belonging to the subclass of lipoxins, whose biosynthesis is mediated via alternative routes within the LOX pathway. The formation of LXA_4 via the LOX-15 isozyme involves the intermediate formation of 15-hydroperoxyeicosatetraenoic acid, whereas the metabolization of ARA via LOX-5 results in the intermediate synthesis of leukotriene A_4 serving as precursor for the subsequent formation of both leukotriene B_4 and LXA_4. The activity of LOX-5 is tightly controlled by interaction with its activating protein ALOX5AP (Dixon et al. 1990; Miller et al. 1990). Overexpression of this protein in adipose tissue of mice increases the levels of LXA_4 but not leukotriene B_4 in BAT, subcutaneous WAT, and within the circulation (Elias et al. 2016). The subcutaneous WAT of these mice is characterized by an increased abundance of multilocular cells and elevated expression of Ucp1 protein under obesogenic and non-obesogenic conditions. Although elevations in WAT Ucp1 expression are reproducible on mRNA level during a 2-day injection of LXA_4 in wild-type mice, it remains to be determined whether adipose tissue browning in ALOX5AP transgenic mice is entirely related to elevated LXA_4 levels. In fact, LOX-5 is involved in the synthesis of a number of oxylipins, some of which may complement the effect of LXA_4 via a direct or indirect interaction with cells of white adipose tissue.

A possible, direct action of LXA_4 on cultured adipocytes has not been investigated, but this oxylipin appears to influence the number and activity of Ucp1-positive cells in ALOX5AP transgenic mice via a secondary mechanism. Cultivation of the liver cell line HepG2 in the presence of LXA_4 results in higher mRNA levels of bile acid synthesizing enzymes. In line with this, ALOX5AP transgenic mice have higher levels of circulating bile acids as well as a higher fecal bile acid excretion (Elias et al. 2016). Intriguingly, systemic bile acid levels have been associated with elevated energy expenditure and reduced propensity to diet-induced obesity (Watanabe et al. 2006, 2011, 2012; Teodoro et al. 2014; da-Silva et al. 2011; Zietak and Kozak 2016). These effects have been hypothesized to originate from Ucp1-dependent thermogenesis based on the ability of bile acids to activate brown adipocytes and to increase the abundance of brite adipocytes (Velazquez-Villegas et al. 2018; Zietak and Kozak 2016; Teodoro et al. 2014; Watanabe et al. 2006). In line with these studies, ALOX5AP transgenic mice have a higher BAT expression of the G-protein-coupled bile acid receptor 1 and display higher energy expenditure that translates into attenuated body mass accumulation upon high-fat diet feeding (Elias et al. 2016). However, the physiological relevance of Ucp1-dependent thermogenesis, activated or recruited via such LXA_4-bile acid-mediated mechanism, requires careful elucidation in further studies. Bile acid-mediated effects on energy expenditure seem to require the presence of Ucp1 (Zietak and Kozak 2016), while such relationship was not reproduced in our own laboratory (manuscript submitted). Thus, the currently available data do not support a direct thermogenic function of LXA_4 for brown and brite adipocytes, while its possible secondary effect on Ucp1-dependent energy expenditure may be of minor physiological relevance.

5.5 12,13-Dihydroxy-9Z-Octadecenoic Acid

Besides the eicosanoids described above, there are several compounds belonging to the class of octadecanoids recently associated with an impact on thermogenic adipocyte function. Among them, 12,13-dihydroxy-9Z-octadecenoic acid (12,13-DiHOME) represents a potent modulator of non-shivering thermogenesis as recently demonstrated by Lynes and coworkers (Lynes et al. 2017). This compound occupies a unique role among the oxylipins described herein as it exclusively influences the thermogenic function of brown but not brite adipocytes. The metabolite is generated in a two-step reaction from LA firstly forming its epoxide-precursor 12,13-epoxy-9Z-octadecenoic acid via the CYP450 pathway, which is subsequently converted into the diol 12,13-DiHOME via four epoxide hydrolase isozymes (Ephx1–4). Transcript levels of the Ephx1 and 2 genes are upregulated in murine BAT in a cold (4°C) environment, rendering BAT an important source of circulating 12,13-DiHOME levels under conditions of non-shivering thermogenesis. In vivo, the cold-induced release of 12,13-DiHOME appears to initiate an autocrine/paracrine feedback reaction to enhance the thermogenic function of BAT. The causative signal transducer has not yet been addressed but may involve PPARγ since such an interaction has been described for its isomer 9,10-DiHOME (Lecka-Czernik et al. 2002). Interestingly, the thermogenic effect of 12,13-DiHOME does not result from a direct effect on Ucp1 expression but rather originates from an immediately augmented membrane translocation of adipocyte fatty acid transporters facilitating the lipid absorption of mature brown adipocytes. Consequently, repeated administration of 12,13-DiHOME to diet-induced obese mice results in enhanced BAT-specific uptake of triglycerides and free fatty acids, thus affecting oral lipid tolerance and serum triglyceride levels. This facilitated lipid uptake appears to improve adaptive heat production as 12,13-DiHOME-treated cold-exposed mice show an attenuated reduction of body temperature, an increased oxygen consumption, and a reduction of the respiratory exchange ratio indicative of lipid oxidation. Thus, 12,13-DiHOME supports non-shivering thermogenesis by increasing the supply of BAT with circulating lipids. The molecular fate of internalized lipids, however, remains subject to further experiments since fatty acids do not exclusively serve as fuel for thermogenesis but also as direct activators of Ucp1. Moreover, further studies are required not only to clarify whether this thermogenic mechanism is dependent on the presence of Ucp1 but also to determine the most effective therapeutic dosage of the oxylipin. In fact, supraphysiological concentrations of LA-diols interfere with the mitochondrial function of mammalian cells (Moran et al. 1997; Sisemore et al. 2001). Although the chronic treatment of diet-induced obese mice with 12,13-DiHOME does not affect body mass development (Lynes et al. 2017), this compound may have therapeutic relevance in the context of dyslipidemia. Intriguingly, circulating 12,13-DiHOME levels in humans correlate with BAT activity in response to acute cold exposure (14°C), emphasizing the translational significance of this novel effector (Lynes et al. 2017).

5.6 Hydroxyoctadecadienoic Acids

Recruitment of brite adipocytes in response to cold exposure involves interleukin-4 (IL-4) dependent, adipose-directed migration of alternatively activated M2 macrophages. This brite adipogenic mechanism has been ascribed to the local production of macrophage-derived catecholamines (Nguyen et al. 2011; Qiu et al. 2014), but this was questioned lately (Fischer et al. 2017). A recent publication suggests the octadecanoids 9-hydroxyoctadecadienoic acid (9-HODE) and 13-HODE as alternative mediators of macrophage-dependent adipose tissue browning (Lee et al. 2016). In their study, Lee and coworkers observed a transiently increased number of lipid-laden, cluster of differentiation 44 positive ($CD44^+$) F4/80 macrophages in the stromal vascular fraction of murine gonadal WAT upon 3 days of β_3-adrenergic treatment. This particular macrophage fraction is characterized by an increased production of 9-HODE and 13-HODE. In vivo, this macrophage-derived secretion of 9-HODE and 13-HODE could be supported by adipocyte-derived fatty acids as $CD44^+$ macrophages accumulate their triglycerides during the clearance of dying adipocytes. This hypothesis is supported by the observation that β_3-adrenergic treatment causes F4/80 macrophages to form crown-like structures in adipose tissue with elevated expression of the genes cluster of differentiation 36 (Cd36) and arachidonate 15-lipoxygenase (Alox15) in the $CD44^+$ fraction. Whereas the first encodes a fatty acid transporter that may catalyze the uptake of adipocyte-derived fatty acids, the second encodes a LOX-enzyme involved in the biosynthesis of HODE from LA. The expression of macrophage Alox15 protein increases during co-culture with dying adipocytes along with the accumulation of markers typical for alternative macrophage activation. As these events occur in the presence but not absence of IL-4, the production of 9-HODE and 13-HODE likely represents a downstream event mediated by $CD44^+$ macrophages following their targeted M2 polarization.

Alternatively activated M2 macrophages not only form crown-like structures to clear the tissue from dying adipocytes but also recruit adipocyte progenitors expressing the platelet-derived growth factor receptor A (Lee et al. 2013, 2014). This particular fraction is capable of undergoing brite adipogenesis (Lee et al. 2012). Indeed, adipogenic differentiation of these precursor cells in the presence of 9-HODE, 13-HODE, or rosiglitazone for 3 days results in an increased sensitivity toward β-adrenergic stimulation characterized by elevated Ucp1 mRNA levels, lipolysis, and Ucp1-dependent oxygen consumption following isoproterenol treatment (Lee et al. 2016). It remains to be determined whether these effects originate from an interaction with either PPARγ, the cation channel TRP vanilloid 1 (TRPV1), or the G-protein-coupled receptor 132, all of which serving as receptors for these oxylipins (Nagy et al. 1998; Obinata et al. 2005; Patwardhan et al. 2009; Huang et al. 1999).

Thus, 9-HODE and 13-HODE represent candidate compounds for the browning of WAT likely acting in a paracrine manner following their orchestrated production from immune cells. The latter fraction complements mature and pre-adipocytes as source of adipose-derived oxylipins with brite adipogenic potential.

5.7 10-Oxo-12(Z)-Octadecenoic Acid

The intestinal microbiome has been repeatedly hypothesized to be a significant contributor to systemic energy balance regulation [see Moran-Ramos et al. (2017) and Zhang et al. (2017) for recent reviews]. This relationship appears to be contributed by the bacterial turnover of dietary LA affecting energy expenditure. Lactic acid bacteria are capable of producing the octadecanoid 10-oxo-12(Z)-octadecenoic acid (KetoA) and further structurally related LA metabolites (Kishino et al. 2013). Considerably higher levels in colon, small intestine, and plasma of conventional vs. germ-free mice render the intestinal microbiome a significant source of these compounds (Kishino et al. 2013). In their recent study, Kim and coworkers show that KetoA represents an activator of TRPV1 (Kim et al. 2017). Physiological effects of oral KetoA administration investigated in the same study rely on the TRPV1-dependent initiation of an afferent signaling cascade within the gastrointestinal tract as demonstrated by the use of TRPV1 knockout mice and mice subjected to gastric vagotomy. Afferent signaling of KetoA via the nervus vagus results in the excitation of efferent sympathetic pathways. KetoA-induced, sympathetic signaling may selectively target BAT and WAT but not the cardiovascular system as the turnover of norepinephrine is elevated locally in these tissues but not in the heart. Moreover, this sympathetic norepinephrine release translates acutely and chronically into elevated Ucp1 expression in BAT and WAT under obesogenic and non-obesogenic conditions. In line with an elevated capacity for non-shivering thermogenesis, KetoA-supplemented mice of the C57BL/6 and KK-Ay strains but not TRPV1 knockout mice show reduced propensity to diet-induced obesity, elevated rectal body temperature and energy expenditure.

The TRPV1 receptor is expressed by adipose tissue, and treatment of cultured cells with the TRPV1 agonist capsaicin affects brown and brite adipogenesis (Kida et al. 2016; Baboota et al. 2014). KetoA may thus be able to complement Ucp1-dependent non-shivering thermogenesis via a direct interaction with TRPV1 of adipocytes upon spillover into the bloodstream. Such direct effect may be supported by its property to interact with PPARγ (Goto et al. 2015), although the knockout of TRPV1 is sufficient to explain the majority of physiologic effects induced by oral KetoA (Kim et al. 2017). In fact, Kim and coworkers report KetoA to be undetectable in plasma of KetoA-supplemented mice (Kim et al. 2017), indicating the physiologic effects induced by this compound to entirely rely on secondary signaling upon activation of TRPV1 in the intestine. The effect of KetoA, however, has not been investigated upon administration via other peripheral routes (e.g., intraperitoneal or subcutaneous) or with cultured adipocytes.

Although the actual relevance of Ucp1-dependent thermogenesis remains to be assessed, the oxylipin KetoA appears to be a potent modulator of systemic energy expenditure of microbial origin. The physiological relevance of this microbiome-host-interaction should be further addressed in studies using KetoA-supplemented conventional and germ-free mice under conditions (e.g., cold exposure) that promote Ucp1-dependent non-shivering thermogenesis.

5.8 Endocannabinoids

The endocannabinoid system is well-known for its implication in energy homeostasis [reviewed by Matias and Di Marzo (2007), Silvestri and Di Marzo (2013), Richard et al. (2009)]. The best studied entity in this regard is the CB1 receptor expressed by various brain areas associated with the regulation of food intake and energy turnover. Its activation increases body mass by elevated food intake as well as reduced energy expenditure and thus centrally signals a positive energy balance (Kirkham et al. 2002). In line with this, treatment of mice with the synthetic CB1 antagonist rimonabant decreases food intake and body mass (Jbilo et al. 2005) and increases glucose and lipoprotein clearance by BAT (Bajzer et al. 2011; Boon et al. 2014).

While the importance of the endocannabinoid system for the regulation of energy homeostasis is strongly supported by the aforementioned studies, it is still a matter of debate (1) whether effects on energy expenditure are exclusively or only partially mediated by central cannabinoid receptors and (2) whether effects on energy expenditure originate from brown and brite adipocyte-derived thermogenesis. On the one hand, exclusive stimulation of peripheral CB1 in diet-induced obese mice is sufficient to reduce their body mass and to increase their energy expenditure, suggesting the occurrence of cannabinoid-dependent thermogenesis in the absence of central signaling (Boon et al. 2014). On the other hand, a genetically induced decrease of 2-AG levels (an endogenous CB1 agonist) in the murine forebrain results in elevated mitochondrial abundance and Ucp1 protein expression in BAT, increased body temperature upon adrenergic stimulation, and reduced body mass accumulation under obesogenic and non-obesogenic conditions (Jung et al. 2012), thus arguing for a central regulation of peripheral energy expenditure by the cannabinoid system. This is further supported by studies in mice with forebrain-specific CB1 deletion, which are resistant to diet-induced obesity and show higher body temperature under cold stimulation (Quarta et al. 2010). Elevated Ucp1 mRNA expression and glucose uptake in BAT of these mice indicates the recruitment of BAT-derived thermogenesis via central cannabinoid signaling (Quarta et al. 2010). Moreover, treatment of cultured murine white and brown adipocytes with a synthetic CB1 agonist decreases Ucp1 protein levels, suggesting a direct regulation of adipocyte-derived thermogenesis by the peripheral endocannabinoid system (Perwitz et al. 2006; Boon et al. 2014). In line with this, the adipose-specific knockout of the CB1 receptor is sufficient to induce a lower body mass in mice and to reduce the propensity to diet-induced obesity (Ruiz de Azua et al. 2017). Rimonabant-treated mice show increased Ucp1 mRNA in BAT independent of sympathetic innervation (Bajzer et al. 2011), providing additional evidence for the importance of peripherally expressed CB1. Hypothesizing the adipocyte CB1 receptor as direct repressor of Ucp1-dependent thermogenesis, ablation of its ligands should be expected to mimic the effect of the CB1 knockout. Such relationship was further investigated in mice with an adipocyte-specific knockout of NAPE-PLD, representing the enzyme that synthesizes the endocannabinoid AEA and endocannabinoid-like compounds (Geurts et al. 2015). As expected, the knockout translates into reduced levels of

the respective metabolites. Surprisingly, these mice have reduced Ucp1 mRNA expression and elevated body mass under obesogenic and non-obesogenic conditions, suggesting the endocannabinoid system as a positive regulator of adipocyte-derived thermogenesis. Thus, the significance of the endocannabinoid system as a direct or indirect regulator of Ucp1-dependent thermogenesis requires further deciphering as it appears to involve a complex regulation of the implicated effectors.

The potential of individual endocannabinoids or endocannabinoid-like compounds to activate or recruit Ucp1-dependent non-shivering thermogenesis is largely unexplored. Stimulation of mice by cold exposure or with a β_3-adrenergic agonist increases the levels of endocannabinoids and NAEs like OEA in BAT and especially in WAT (Krott et al. 2016). Krott and coworkers hypothesize this regulation of the endocannabinoid system to mediate an autocrine negative feedback mechanism limiting the capacity for Ucp1-dependent thermogenesis during the recruitment of brown and brite adipocytes. However, mice supplemented with OEA exhibit increased thermogenic capacity in BAT, energy expenditure, and BAT temperature after β_3-adrenergic treatment, suggesting this compound to potentiate the recruitment of Ucp1-dependent heat production (Suarez et al. 2014). As OEA is unable to bind cannabinoid receptors (Fonseca et al. 2013), this effect may be mediated by an interaction with PPARα of brown and brite adipocytes (Fu et al. 2003). Further studies are needed to manifest the positive regulatory role of OEA on Ucp1-dependent non-shivering thermogenesis and to elucidate the potential of other endocannabinoids and endocannabinoid-like compounds.

6 Nutritional Interventions to Modulate Oxylipin Formation and the Thermogenic Capacity of Adipose Tissues

Dietary PUFAs constitute an important part of the human nutrition. The dietary ω-6/ω-3 ratio has shifted from approx. 1:1 during the Paleolithic period to 15:1 and higher in modern societies, which is associated with the occurrence of obesity related to adipose tissue dysfunction (Simopoulos 2016). Concomitantly, the activity of BAT among adult humans is highest in lean and lowest in obese subjects (Saito et al. 2009; Cypess et al. 2009; van Marken Lichtenbelt et al. 2009; Vijgen et al. 2011). Treatment of hMADS cells with ARA blunts Ucp1 expression during brite adipogenesis, which is prevented upon co-treatment with EPA (Ghandour et al. 2018; Pisani et al. 2014). Thus, a causal relationship between dietary PUFA-uptake, the abundance and activity of thermogenic adipocytes, and energy expenditure may be hypothesized.

Evidence supporting a role of fatty acids and their metabolites in the activation of BAT and the recruitment of brite adipocytes has accumulated during recent years (Okla et al. 2017). Several studies have particularly investigated the effects of ω-3 fatty acids and show that supplementation of mice with fish oil comprising diets rich in EPA and DHA results in an elevated expression of Ucp1 in BAT and/or WAT (Kim et al. 2015, 2016; Bargut et al. 2016a, b). These in vivo findings are further

supported by in vitro experiments. Treatment of murine primary white and brown pre-adipocytes with EPA increases thermogenic gene expression and concomitantly enhances markers of mitochondrial abundance and function (Kim et al. 2016; Zhao and Chen 2014). Similarly, EPA elevates Ucp1 expression of human primary adipose tissue-derived stem cells, but the same effect is not observed in the presence of DHA (Fleckenstein-Elsen et al. 2016). Thus, ω-3 fatty acids and particularly EPA appear to beneficially affect the recruitment of Ucp1-positive cells in vivo and in vitro. Mechanistically, such effect may be mediated by a direct interaction of EPA with free fatty acid receptors (Quesada-Lopez et al. 2016; Kim et al. 2016), for instance, or via their conversion to bioactive metabolites. In fact, the fatty acid composition of membranes and thus the endogenous oxylipin profile changes upon nutritional interventions. Accordingly, the systemic production of ω-3-derived metabolites is enhanced upon dietary supplementation of ω-3 PUFAs [for a review, see Ostermann et al. (2017)].

The potential of nutritional interventions to modulate the abundance or activity of Ucp1-positive adipocytes as a direct consequence of altered oxylipin production is virtually unexplored. Recent studies support the hypothesized role of the dietary ω-6/ω-3 ratio in this context (Pisani et al. 2014; Ghandour et al. 2018). Mice were subjected to chow diets supplemented with ω-6 or ω-3 PUFAs to achieve a dietary ω-6/ω-3 ratio of 30 or 3.7, respectively. After 11 weeks of feeding, mice were treated with a β_3-adrenergic agonist for another week to stimulate the recruitment of non-shivering thermogenesis in BAT and WAT. The expression of Ucp1 is more pronounced in BAT and WAT of ω-3-supplemented mice. This effect is hypothesized to originate from $PGF_{2\alpha}$, whose production is reduced in both tissues of ω-3- vs. ω-6-supplemented mice upon β_3-stimulation. This reduced production is reproducible in ARA-treated brite hMADS cells upon co-incubation with EPA accompanied by a restoration of Ucp1 expression. As described above (Sect. 5.3), $PGF_{2\alpha}$ is a negative regulator of Ucp1-dependent thermogenesis in hMADS cells. In line with this, the capacity for non-shivering thermogenesis is impaired under conditions that favor the production of this compound. Mice on a chow diet supplemented with ARA have a higher WAT-production of $PGF_{2\alpha}$ compared to mice receiving oleic acid supplementation. This production rate of $PGF_{2\alpha}$ remains elevated following β_3-adrenergic treatment. This regulation is well in line with the impaired recruitment of Ucp1 protein and the reduced abundance of multilocular adipocytes in WAT of ARA-supplemented vs. oleic acid-supplemented mice. Thus, these studies support the hypothesis that non-shivering thermogenesis is modifiable by the oxylipin pattern produced in response to a dietary intervention. These studies suggest this effect to primarily result from an antagonistic mechanism that reduces the production of individual ω-6-derived compounds rather than originating from an elevated abundance of ω-3-derived compounds acting as thermogenic effectors. This regulation may constitute one possible mechanism to explain the beneficial effect of dietary ω-3 supplementation on energy expenditure and cold tolerance (Kim et al. 2015, 2016). A possible relationship between dietary PUFA supplementation, changes in the endocannabinoid profile of adipose tissues, and the induction or activation of thermogenic adipocytes remains to be assessed.

7 Conclusion

Oxylipins and endocannabinoids represent two metabolite classes originating from the metabolic conversion of ω-3 and ω-6 PUFAs. These bioactive compounds affect a plethora of physiological processes constituting their role as essential regulators of metabolic control. Since only a few years, there is accumulating evidence for a novel role for these effectors as regulators of Ucp1-dependent non-shivering thermogenesis. Several individual compounds with the potential to affect brown and brite adipocytes have been identified (Fig. 2). These compounds appear to modulate thermogenic adipocytes on multiple levels by acting as (1) upstream effectors influencing non-shivering thermogenesis via a secondary mechanism, (2) direct effectors of adipocyte identity and function, or (3) sensitizers to enhance Ucp1-derived heat production in response to a thermogenic stimulus. Thus, they can act directly in adipose tissues or indirectly via central or peripheral circuitries. Accordingly, the production of thermogenic effector compounds is not restricted to local entities such as mature adipocytes, pre-adipocytes, or immune cells, but involves distant sites such as the central nervous system or the intestinal microbiota, which may in turn facilitate the delivery of effectors via the blood circulation. Their production and their biological effect are regulated in a complex manner affected

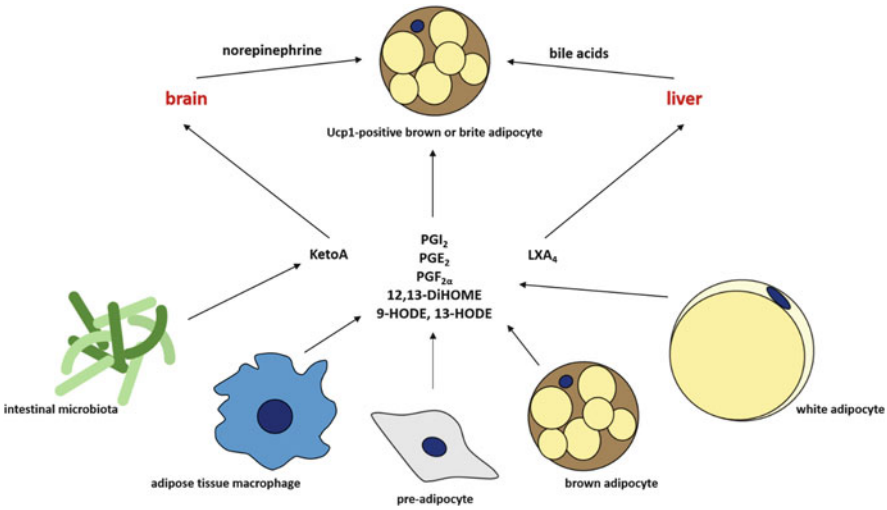

Fig. 2 Schematic summary of oxylipins affecting the recruitment or function of Ucp1-positive brown and brite adipocytes. The compounds PGI_2, PGE_2, $PGF_{2\alpha}$, 12,13-DiHOME, 9-HODE, and 13-HODE likely act in autocrine or paracrine manner upon their local production in adipose tissues by mature adipocytes, pre-adipocytes, or immune cells. The compound LXA_4 produced in BAT and WAT is thought to affect hepatic bile acid production, which is in turn hypothesized to signal Ucp1-dependent thermogenesis. The microbial-derived compound KetoA stimulates gastrointestinal afferences to signal thermogenesis via sympathetic pathways. Endocannabinoids and endocannabinoid-like compounds (not depicted) may complement oxylipin-mediated effects on brown and brite adipocytes via direct or centrally mediated pathways.

by multiple variables such as the abundance of the precursor fatty acid, the enzymatic pathway involved, the responding cell type, and the implicated receptor and signaling pathway. Future studies may not only focus on the physiological potential of such compounds to affect parameters associated with Ucp1-dependent energy expenditure (such as adrenergically induced heat production, cold tolerance, or the regulation of body mass) but also on the manipulation of their production and signaling pathways. Nutritional interventions seem to represent a useful tool, although their effect is not restricted to the modulation of a single compound but may trigger the systemic generation of a profile that favors the abundance or activity of thermogenic adipocytes. Sophisticated analysis techniques with a high sensitivity will not only help to decipher effects of oxylipins and endocannabinoids on brown and brite adipocyte function in the future but also facilitate the identification of further compounds with thermogenic potential.

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