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Role of cytochrome P450-derived, polyunsaturated fatty acid mediators in diabetes and the metabolic syndrome

Laila R.B. dos Santos[a,b], Ingrid Fleming[a,b,*]

[a] Institute for Vascular Signalling, Centre for Molecular Medicine, Goethe University, Frankfurt, Germany
[b] German Centre for Cardiovascular Research (DZHK) Partner Site Rhein-Main, Germany

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ABSTRACT

Over the last decade, cases of metabolic syndrome and type II diabetes have increased exponentially. Exercise and ω-3 polyunsaturated fatty acid (PUFA)-enriched diets are usually prescribed but no therapy is effectively able to restore the impaired glucose metabolism, hypertension, and atherogenic dyslipidemia encountered by diabetic patients. PUFAs are metabolized by different enzymes into bioactive metabolites with anti- or pro-inflammatory activity. One important class of PUFA metabolizing enzymes are the cytochrome P450 (CYP) enzymes that can generate a series of bioactive products, many of which have been attributed protective/anti-inflammatory and insulin-sensitizing effects in animal models. PUFA epoxides are, however, further metabolized by the soluble epoxide hydrolase (sEH) to fatty acid diols. The biological actions of the latter are less well understood but while low concentrations may be biologically important, higher concentrations of diols derived from linoleic acid and docosahexaenoic acid have been linked with inflammation. One potential application for sEH inhibitors is in the treatment of diabetic retinopathy where sEH expression and activity is elevated as are levels of a diol of docosahexaenoic acid that can induce the destabilization of the retina vasculature.

1. Introduction

The term "metabolic syndrome (MetS)" describes a collection of disorders that share common traits such as over nutrition, obesity/abdominal obesity, impaired glucose metabolism, hypertension, and atherogenic dyslipidemia as well as a more sedentary lifestyle (1, 2). It is, therefore, not surprising that exercise, caloric restriction and weight loss have proven to be the most effective strategies in combating the condition. MetS affects multiple organs and particularly their sensitivity to insulin. Indeed insulin insensitivity is a characteristic feature of MetS and reflects the fact that higher concentrations of insulin are required to initiate insulin-dependent signaling events as well as the removal of glucose from the bloodstream. In the liver, altered insulin signaling leads to increased glycogenolysis and gluconeogenesis, thereby raising blood glucose levels, whereas in adipose tissue insulin resistance leads to increased lipolysis, resulting in elevated circulating fatty acids [1]. The latter, in turn, promote lipid accumulation in the skeletal muscle and liver, and induce hepatic triglyceride synthesis which further aggravates hyperlipidemia. In order to compensate for peripheral insulin resistance, β cells in the pancreas increase insulin production. Should this overproduction become chronic the generation of reactive oxygen species (ROS) in the β cells increases and they develop endoplasmic reticulum (ER) stress, which can eventually result in dysfunction and cell death. Over time, therefore, there is a clear transition from MetS towards type 2 diabetes (Fig. 1).

While much research on diabetes has focused on glucose and the consequences of hyperglycemia the consequences of over nutrition on the accumulation of lipid intermediates in non-adipose tissue (liver, heart, kidneys skeletal muscle and pancreas) on cellular function are less appreciated. Although this lipid-induced dysfunction or "lipotoxicity" together with hyperlipidemia has been associated with the development of MetS and diabetes, not all fatty acids are equal. For example, an increase in the dietary intake of saturated fatty acids and ω-6 polyunsaturated fatty acids (PUFAs) has been associated with increased obesity, excessive visceral fat deposition, hypertension, endothelial damage, cardiovascular hypertrophy, inflammation, atherosclerosis, ventricular contractile dysfunction, fibrosis and fatty liver disease [2,3]. Diets enriched in ω-3 PUFAs (especially in fish oils), on the other hand, are generally thought to protect against the development of both diabetes and heart disease [4–8]. Certainly, levels of the ω-6 PUFA linoleic acid are over-represented in the Western diet, and recent studies indicate that dietary imbalance between ω-6 and ω-3 PUFAs in favor of

* Corresponding author at: Institute for Vascular Signalling, Centre for Molecular Medicine, Goethe University, Theodor Stern Kai 7, 60596 Frankfurt am Main, Germany.
E-mail address: fleming@em.uni-frankfurt.de (I. Fleming).

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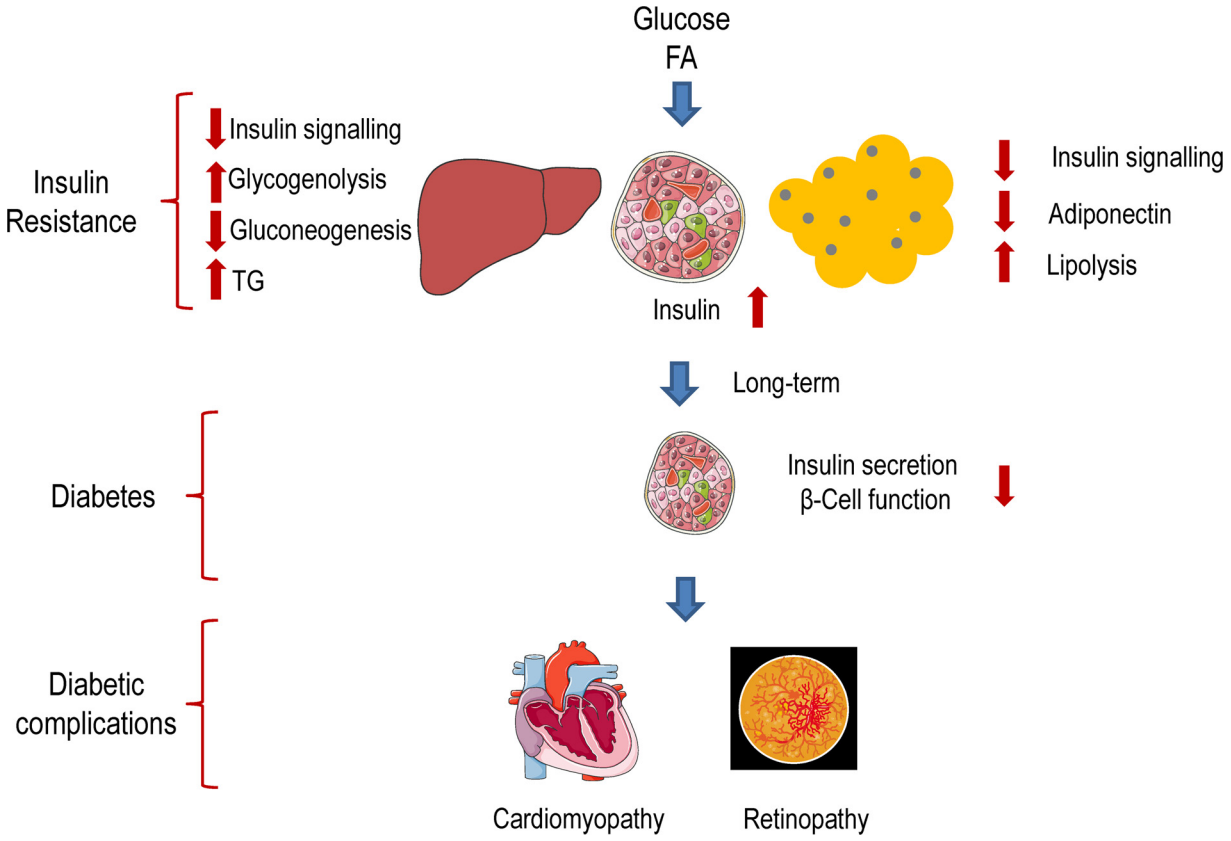

Fig. 1. General mechanism by which insulin resistance leads to diabetes type 2. In the liver, altered insulin signaling leads to increased glycogenolysis and gluconeogenesis, and triglyceride (TG) accumulation. In the adipose tissue, insulin resistance leads to increased lipolysis and decreased adiponectin. In pancreatic islets, higher insulin secretion is required to initiate insulin-dependent signaling events. Long-term insulin resistance leads to decreased β cell function as well as diminished insulin secretion thereby raising blood glucose levels resulting in complications such as retinopathy and cardiomyopathy.

the former leads to an adverse cardiovascular and metabolic profile, thereby contributing to the pathogenesis of nonalcoholic fatty liver disease, diabetes, and cardiovascular disease [9].

2. PUFA metabolism

The most intensively studied PUFA is arachidonic acid, a 20-carbon, ω-6 PUFA that can be metabolized by a number of different enzymes including; cyclooxygenases (COXs), lipoxygenases (LOXs) and cytochrome P450 (CYP) enzymes. Arachidonic acid is the precursor of numerous bioactive modified PUFAs that make up the so-called "arachidonic acid cascade" that controls a wide array of cellular functions. In humans, most arachidonic acid is derived from linoleic acid (18:2, ω-6) which is enriched in nuts, seeds, vegetable oils and animal fats. Probably the best known arachidonic acid products are the prostaglandins generated by the COX enzymes and downstream prostaglandin synthases, which affect vascular reactivity as well as inflammation and platelet reactivity; for reviews see references [10,11]. Much less is known about the biological actions of arachidonic acid metabolites generated by CYP enzymes, or indeed the metabolites of other PUFAs that can also be used as substrates by these enzymes. This review, therefore, outlines some of the actions of CYP metabolites derived from PUFAs and their link to MetS/diabetes and its associated cardiovascular complications.

CYP enzymes are most highly expressed in the liver, a major site of lipotoxicity, but are also expressed in the kidney, heart, skeletal muscle, adipose tissue, pancreas and vasculature, making it tempting to speculate a central role for this class of enzymes in the generation of metabolites that contribute to the development of the MetS. The majority of CYP enzymes metabolize PUFAs to either epoxides or ω-hydroxides. For example, from the substrate arachidonic acid CYP enzymes can generate to epoxyeicosatrienoic acids (EETs) as well as 20-hydroxyeicosatetraenoic acids (20-HETE). While the former have been linked with vasodilatation and decreased blood pressure, the latter have been implicated in exactly the opposite and can elicit both vasoconstriction and an increase in blood pressure. Several CYP enzymes demonstrate a mixed function and can generate both metabolites with the ratio of EETs to 20-HETE varying between the specific CYP isoforms. As hinted at above, CYP enzymes accept several different ω-6 and ω-3 PUFAs as substrates and can, for example, also metabolize eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) to their respective epoxides (i.e. epoxyeicosatetraenoic acid or EEQs and epoxydocosapentaenoic acid or EDPs), which also have biological activity (Fig. 2). Importantly, many of these PUFA epoxides are rapidly hydrolyzed by the soluble epoxide hydrolase (sEH; gene name *Ephx2*) to their corresponding diols. For a long time, PUFA diols were assumed to represent an inactive end products and only to possess biological activity at high concentrations. It is now generally appreciated that these mediators also possess biological activity. Perhaps the most impressive link was made by studying patients with acute respiratory distress syndrome who generated high levels of 9,10-dihydroxyoctadecenoic acid (DiHOME) [12–14], and whose situation improved following inhibition of the sEH. Logically, reducing the concentration of the parent PUFA i.e., linoleic acid, in the parenteral nutrition resulted in marked benefits in gas exchange, ventilation requirement, and mortality [15]. While very high concentrations of linoleic acid-derived diols in critically ill patients are clearly detrimental, more recent studies indicated that low concentrations of 12,13-DiHOME inhibit rather than potentiate the respiratory burst in neutrophils [16]. Also, in zebrafish and mice 12,13-DiHOME was shown to activate Wnt signaling and be required for the regulation of

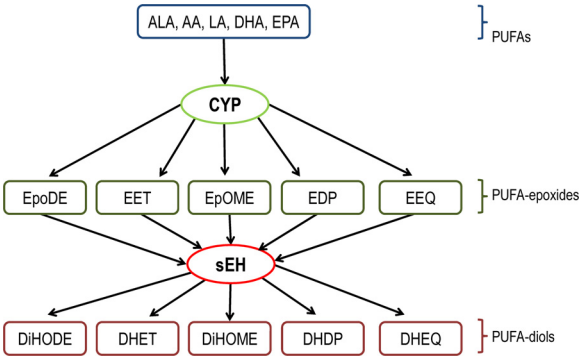

Fig. 2. CYP-sEH axis showing the CYP-dependent conversion of selected PUFAs (α-linolenic acid, ALA; arachidonic acid, AA; docosahexaenoic acid, DHA; linoleic acid, LA; eicosapentaenoic acid, EPA) into PUFA epoxides (EpODE, EET, EDP, EpOME and EEQ) and subsequent metabolism to diols (DiHODE, DHET, DHDP, DiHOME, DHEQ). EpODE: Epoxyoctadecadienoic acid, EET: epoxyeicosatrienoic acid, EDP: epoxydocosapentaenoic acid, EpOME: epoxyoctadecamonoenic acid, EEQ: epoxyeicosatetraenoic acid, DiHODE: dihydroxyoctadecadienoic, DHET: dihydroxyeicosatrienoic acid, DHDP: dihydroxydocosapentaenoic acid, DiHOME: dihydroxyoctadecenoic acid, DHEQ: dihydroxyeicosatetraenoic acid.

stem and progenitor cell proliferation and mobilization, as well as vascular repair after ischemia [17]. Thus, it seems that low concentrations of this particular linoleic acid diol are required for proper biological function but that higher concentrations can be detrimental. This is also an observation that hold true for DHA-derived diols generated by the CYP-sEH pathway (see below).

3. The CYP-sEH pathway and its biological actions

Of the PUFA epoxides studied to date, most is known about the biological actions of the epoxides of arachidonic acid i.e. the EETs. CYP enzymes can generate four EET regio–isomers; 5,6–, 8,9–, 11,12–, and 14,15– EET, that can also be metabolized by the sEH (although 5,6–EET seems to be a preferred substrate for COX enzymes) [18]. The EETs have been implicated in the nitric oxide and prostacyclin-independent regulation of vascular tone [19,20] and linked with anti-inflammatory effects [21]. The mechanism of action has yet to be definitively demonstrated but there is a growing body of evidence to indicate that a specific Gαs-coupled membrane receptor may mediate many of the protein kinase (PK) A-dependent effects of 11,12–EET [22]. In endothelial cells, for example, the rapid (within 10 s) PKA-dependent translocation of transient receptor potential C6 channels elicited by 11(R),12(S)-EET - but not its 11(S),12(R)-EET stereoisomer - was attributed to such a receptor [23]. Similarly, the presence of low-affinity G-protein coupled receptors that can be activated by 14,15-EET to increase cyclic AMP have been proposed [24], but their identification is outstanding. Whether or not GPR132, which was reported to mediate the effects of 11,12- and 14,15-EET in zebrafish [25], can account for the actions of the lipid mediators in the murine or human situation remains to be determined. However, given that GPR132 could also be activated by hydroxy-fatty acids [25], it may well turn out that low specificity receptors exist for PUFAs and/or PUFA metabolites in addition to a specific 11(R),12(S)-EET receptor.

A cell surface receptor may not be essential to initiate the biological actions of the PUFA-derived epoxides and diols as they can incorporate into membrane phospholipids and potentially influence cell signaling by modulating the lipid microenvironment therein [26]. Certainly, the fish oils EPA and DHA are readily incorporated into phospholipids and the resulting polyunsaturated phospholipids are able to infiltrate lipid rafts as well as form non raft domains [27]. There is also evidence that EETs and DHETs can be incorporated into the sn-2 position of phospholipids, especially phosphatidylcholine and phosphatidylinositol [28–32]. In endothelial cells the incorporation of EETs into a phospholipid pool was reported to be catalyzed by acyl coenzyme synthase [33], and a similar PKC-mediated phenomenon has been described in astroglia [34]. Although the physiological relevance of these processes remains to be determined, pre-loading isolated porcine coronary arteries with EET and DHET has been shown to enhance endothelium-dependent, but not endothelium-independent relaxations. Such observations suggest that these esterified lipids are an intracellular storage form of EET, from which they can be liberated upon cell activation, independently of CYP activity [22].

PUFA epoxides and diols may also possess intracellular receptors. For example, EETs can activate peroxisome proliferator-activated receptors (PPARs) [35], which may account for some of the EET-induced effects in hepatic and endothelial inflammation, as well as adipocyte differentiation [36–41]. PPAR activators enhance the expression of a number of genes encoding proteins involved in glucose and lipid metabolism and which PPAR plays the predominant protective role seems to be tissue-dependent [36,40,42]. For example, PPARα is highly expressed in the liver and promotes the activation of the PPARγ coactivator 1-α (PGC1α), which in turn regulates mitochondrial biogenesis [43,44]. Thus, in this setting EET-induced PPARα activation would result in a decrease in gluconeogesis and improved mitochondrial function due to enhanced fatty acid oxidation, as observed in obese animals treated with PPARα agonists [36,38]. PPARγ, on the other hand, is more abundant in adipose tissue and its activation induces adipocyte differentiation, increases lipid droplet size and decreases lipolysis [41]. Therefore, EET-induced PPARγ activation in adipose tissue would be expected to decrease circulating levels of fatty acids and improve insulin resistance, which fits with the reported beneficial effects of EETs on metabolism [40].

CYP-generated epoxides derived from other PUFAs have also been linked to PPAR activation. For example, the EPA epoxide; 17,18-EEQ, was shown to protect lungs against inflammation via a PPARγ-dependent mechanism [37]. Some diols e.g. 14,15-DHET, have also been shown to activate PPARs (in this case PPARα), to increase the expression of the carnitine palmitoyl transferase I. However, the DHET concentration used was extremely high (10 μM) suggesting possible off target effects [35,39]. Little is known about the effects of other PUFA epoxides or diols but it is assumed they act through similar pathways. PPAR activation may also regulate the expression of the sEH [45], implying that some of the effects induced by PPAR activators may be indirect. EETs have also been reported to activate the AMP-activated protein kinase (AMPK) [46], a kinase that plays a role in cellular energy homeostasis through stimulation of hepatic and muscle fatty acid oxidation, and the inhibition of lipogenesis, cholesterol synthesis, and triglyceride synthesis [47]. For example, the linoleic acid epoxide; 12,13-epoxyoctadecenoic acid (12,13-EpOME), has been shown to induce AMPKα phosphorylation in hepatocytes [48], suggesting a role of other PUFA-epoxides as regulators of cellular metabolism. For a more detailed analysis of the roles of the different CYP- and sEH-derived lipid mediators and their roles in physiology the reader is directed to a number of recent exhaustive reviews [18,49–51].

4. The CYP-sEH pathway in metabolic disease

Over nutrition in the form of a high fat diet impacts on the CYP-sEH axis in experimental animals. In ApoE$^{-/-}$ mice, feeding a high fat diet results in the suppression of hepatic CYP epoxygenase activity but the activation of renal CYP ω-hydroxylase activity, thus decreasing EET and increasing 20-HETE levels [52]. Interestingly, the angiotensin-converting enzyme inhibitor, enalapril, reversed the changes in CYP enzyme activity in both organs indicating that there may be a link between angiotensin II generation or bradykinin breakdown (both of which are catalyzed by the angiotensin-converting enzyme) and the CYP-sEH axis in situations associated with metabolic dysfunction. This is important given that angiotensin II is known to increase vascular sEH

expression in rats made hypertensive with angiotensin II [53]. In humans, recent clinical studies have linked obesity with low plasma EET levels and 14,15-EET:14,15-DHET ratios, which would fit with reports of elevated sEH levels. Age, diabetes, and cigarette smoking also were significantly associated with CYP and sEH activity, while only renin-angiotensin system inhibitor use was associated with CYP ω-hydroxylase activity [54]. Several studies have suggested a role of PUFA-epoxides in preventing the development of MetS [55], though with few exceptions [56], the majority of the studies did not assess the concentrations of PUFA epoxides and diols in the models studied.

CYP: On the whole the epoxides generated by CYP enzymes are reported to be protective and overexpression of the human CYP2J2 in mice made diabetic with streptozotocin was reported to attenuate diabetic nephropathy [57], and cardiomyopathy (58). The mechanisms implicated were many and varied and included the ability to decrease oxidative and ER stress, to reduce hyperglycaemia, and/or to improve mitochondrial function [58,59], together with anti-inflammatory effects and insulin sensitization [60]. Interestingly, a polymorphism in the *CYP2J2* gene that results in reduced gene expression and activity [61,62], has been linked with the risk of a younger onset of type II diabetes – at least in a Chinese population [63]. The same polymorphism has also been associated with an increased risk of coronary artery disease in Caucasian [61] and Chinese [62] subjects. The impression that CYP products are beneficial as far as insulin sensitivity is concerned is certainly strengthened by the fact that the overexpression of CYP2J3 increased EET generation, reduced blood pressure, and reversed insulin resistance in rats given a fructose-rich diet as well as in diabetic db/db mice [64]. CYP2J3 overexpression also enhanced the expression and secretion of the protective adipokine; adiponectin. At the molecular level the CYP2J3 products were shown to prevent the ER stress induced in adipose tissue by a high fat diet [65].

MetS and type 2 diabetes are generally secondary to increased abdominal fat accumulation and increased circulating levels of triglycerides. The reduction in plasma triacylglycerol is a sign of improved insulin sensitivity and decreased lipolysis and lipid release from adipose tissue. In hepatocytes, EET treatment was reported to attenuate insulin resistance induced by the saturated fatty acid palmitic acid [66]. In addition, in $sEH^{-/-}$ mice plasma triacylglycerol cholesterol ester and phosphatidylcholine levels were significantly decreased [67]. In HepG2 cells and differentiated adipocytes, EETs and EpOME attenuated insulin resistance by enhancing the insulin-stimulated phosphorylation of the insulin receptor and Akt, whereas DHET and DiHOME tended to blunt insulin signaling [68]. This suggests an important role of PUFA-epoxides in insulin insensitivity induced by a high fat diet. In fact, CYP2J2 overexpression and 14,15-EET treatment both resulted in the activation of the hepatic and endothelial AMPKα, which in turn increased acetyl-CoA carboxylase phosphorylation, thus, decreasing the activity of the enzyme responsible for malonyl-CoA production and carnitine palmitoyltransferase I inhibition. Moreover, 14,15-EET increased expression of carnitine palmitoyltransferase I and PPARα, and lowered plasma and liver triglycerides, liver cholesterol and fatty acids [47].

PPAR activators have been used in the clinic to reverse the effects of insulin resistance, mainly to control glycaemia and triglycerides. In adipose tissue, the overexpression of CYP2J2 in endothelial cells reduced inflammation and reestablished PPARγ levels [69]. One potentially interesting link between CYP metabolite generation and insulin resistance involves long chain acyl-CoA synthetases (ACSLs). It appears that while unesterified EETs inhibit glucose-stimulated insulin secretion, the generation of EET-CoAs by ACSL4 results in EET esterification into glycerolipids thus alleviating the intrinsic inhibitory mechanism and promoting glucose-stimulated insulin secretion [70]. The prolonged exposure (72 h) of INS 832/13 cells to arachidonic acid or linoleic acid resulted in decreased ACSL4 expression and a parallel decrease in glucose-stimulated insulin secretion [70]. However, the physiological relevance of the latter observations remains to be demonstrated but silencing of ACSL4 and ACSL3 in human pancreatic islets was shown to decrease insulin secretion [71]. Consistent with their preference for unsaturated fatty acids, ACSL4- and ACSL3-deficient cells demonstrated a greater reduction in acyl-CoA synthetase activity when arachidonic acid was provided as substrate versus palmitate [71]. One word of caution should be stated regarding the consequences of increased CYP enzyme expression; as in addition to generating PUFA epoxides with anti-inflammatory properties, these enzymes can also generate superoxide anions. The consequence of this being a decrease in the bioavailability of nitric oxide, which precipitates endothelial dysfunction [72,73]. To-date this link has only been addressed with respect to vascular disease but is more than likely to contribute to the cardiovascular complications of MetS and diabetes in other organs.

sEH: There have been numerous reports of an increase in sEH expression in conditions associated with metabolic stress. Indeed, over nutrition in the form of a high fat diet has been linked with elevated sEH expression [74], and/or activity [75] in adipose tissue and in mesenteric arteries from obese Zucker rats [64]. Moreover, sEH inhibition can ameliorate diet-induced-MetS in animal models [74,76]. The sEH has also been linked with type 1 diabetes as sEH expression is reportedly elevated in the hearts [77] and retinas [78] from Ins2Akita type 1 diabetic mice, and macrophages from non-obese diabetic mice [79], as well as in livers [80] and cerebral vessels [81] from animals made diabetic with streptozotocin. sEH inhibition may therefore be an attractive strategy to address some of the complications of the MetS. To-date there is convincing evidence that inhibition of the sEH and a decrease in the generation of the DHA-derived diol; 19,20-DHDP, can prevent the development of diabetic retinopathy [78]. sEH inhibition has also been reported to enhance the CD36-mediated recognition and degradation of oxidized LDL and improve cholesterol efflux via the upregulation of ABCA1 expression. Furthermore, sEH inhibition attenuated the ER stress induced by a high-fat diet [68], and blocked tumor necrosis factor α and adiponectin secretion by cultured adipocytes [82]. Longer term *in vivo* studies are however required as although sEH expression increases, it is not known how long the activity of the protein is maintained. This may be a particularly important consideration in view of the fact that the sEH can be tyrosine nitrated and inhibited *in vivo* in diabetic mice [83]. The molecular events underlying the change in sEH expression in MetS and diabetes are currently unclear. However, there is a potential link to heme oxygenase (HO)-dependent signaling. For example, EETs increase the expression of the inducible HO-1 [84] and at least partially account for the positive effects of sEH inhibition on renal function [85]. Also, while HO induction attenuated the development of the MetS in obese mice [86], HO inhibition negated the protective effects of sEH inhibition in diabetic rats [87]. Thus, there seems to be an intricate interplay between the CYP/sEH axis and the HO pathway.

Despite interest in the sEH as a drugable target, surprisingly little is known about the mechanisms regulating sEH expression, apart from its regulation by hypoxia [88] and PPARγ [45]. The human promoter lacks a TATA box and contains several transcription factor SP-1 sites [88], one of which lies immediately upstream of the transcription start site. This particular site is required for minimum promoter expression and its methylation is involved in sEH gene silencing, at least in HEPG2 cells. Other factors reported to affect expression are unfolded protein response elements and activating transcription factor (ATF)-6 [89]. More recently, the histone demethylase Jarid1b was found to prevent the angiotensin II-stimulated induction of sEH [90]. Mechanistically, Jarid1b maintained the length of the 3′untranslated region of the sEH mRNA, thereby increasing its stability and thus sEH protein expression. Loss of Jarid1b activity therefore resulted in sEH mRNA destabilization. However, currently no specific link has been made between these mechanisms and the MetS or diabetes.

Given that sEH inhibition increases tissue and circulating levels of PUFA-epoxides, the association of sEH inhibitors and PPARγ agonists would be an interesting approach to reverse diabetes. In fact, a dual-

target ligand that simultaneously activates PPARγ and inhibits sEH was able to reduce plasma triglycerides and cholesterol levels, improve hyperglycemia and hyperinsulinemia and reduce lipid accumulation in liver of diabetic and obese animals [41,91].

5. PUFA epoxides and diols as regulators of mitochondria and endoplasmic reticulum function

5.1. Mitochondria

Mitochondrial activity is essential to maintain energy production in mammalian cells but in diabetes and metabolic diseases, mitochondrial function is significantly altered and associated with increased oxidative stress and cell death. This mitochondrial stress is associated with hepatic insulin resistance [92], and with β cell dysfunction [93].

Perhaps most is known about the role of the CYP-sEH pathway in cardiac mitochondrial metabolism, particularly following ischemia and reperfusion. The opening of the mitochondrial permeability transition pore (mPTP) following an ischemic insult facilitates the passage of small molecules and ions, such as Ca^{2+}, and the generation of ROS, prior to mitochondria and cardiomyocyte death [94]. The targeted disruption of the sEH, cardiomyocyte-specific overexpression of CYP2J2 or perfusion with EETs have all been reported to improve recovery following ischemia and to significantly decrease mPTP opening [95]. Thus, protection against injury has also been attributed to a delayed loss of the mitochondrial membrane potential [96], an increase in the ADP/ATP ratio [97], as well as decreased ROS production [98]. The mechanism by which EETs and sEH inhibitors protect mitochondria against the mPTP opening remains to be clarified. In retinal astrocytes, 19,20-DHDP was found to protect against apoptosis in a mouse model of retinopathy of prematurity. Mechanistically 19,20-DHDP prevented astrocyte loss by targeting the mitochondrial membrane to prevent the hyperoxia-induced dissociation of presenilin-1 and presenilin-1-associated protein to attenuate poly ADP-ribose polymerase activation and mitochondrial DNA damage [99]. Effects on mitochondria may well be cell type- (or receptor-) dependent as in vascular smooth muscle cells, the β1 subunit of the large conductance Ca^{2+}-activated potassium (BK) channels is localized to the inner mitochondrial membrane [100,101]. In these cells, 11,12-EET was able to induce the association of the BK α and β1 subunits and elicit loss of the mitochondrial membrane potential [102]. EETs also target PGC1α, which is considered to be the master regulator of mitochondrial biogenesis and respiration [103], the activation of which may result in an enlarged mitochondrial pool and increased in cellular metabolism [43,60,103]. Other mechanisms have been linked to HO-1, which increases antioxidant activity and therefore reduces oxidative stress and mitochondrial dysfunction [104]. Indeed, HO–1 activity is decreased by dyslipidemia and restored by EET agonists [105]. Putting all of this together, it seems that EETs can improve mitochondrial metabolism by activating PGC1α and HO-1, which in turn result in reduced oxidative stress and improved Ca^{2+} handling.

In humans there is evidence for a relationship between mitochondrial function and insulin resistance, implying that approaches aimed at boosting mitochondrial function might be beneficial to patient health [106]. Even though most of the data regarding mitochondrial function and PUFA epoxides are restricted to cardiomyocytes, other tissues with high mitochondrial activity could also benefit from PUFA epoxides. As β cell malfunction and diabetes development are linked with altered mitochondrial dysfunction, and sEH inhibition is known to improve β cell function (at least in mice), it seems to be a safe bet that either the accumulation of a PUFA epoxide of the depletion of a PUFA diol may protect against diabetes development.

5.2. ER stress

A fully functional ER is required for the synthesis, folding and transport of proteins, as well as for lipid synthesis and Ca^{2+} homeostasis. The ER becomes stressed when unfolded proteins accumulate as a consequence of increased protein synthesis and is regularly observed in β cells exposed to saturated fatty acids for prolonged periods [93,107]. Several enzymes involved in lipogenic pathways also reside in the ER e.g. the fatty acid elongation machinery, enzymes involved in cholesterol and triglyceride biosynthesis and the assembly of very low density lipoprotein particles. This is important as an alternative form of ER stress can be induced by over nutrition and the accumulation of fatty acids and can be observed in the livers of individuals with non-alcoholic fatty liver disease. Interventions such as chemical chaperones aimed at enhancing protein folding and diminishing ER stress, normalized hyperglycemia and systemic insulin sensitivity in diabetic and obese mice. In parallel fatty liver disease was resolved, and the actions of insulin in liver, muscle, and adipose tissues enhanced [108].

In several different animal models of diabetes, increased expression of the sEH has been associated with increased ER stress in hepatic and adipose tissue [67,108]. Rather than being parallel event, there may be a cause and effect relationship as PUFAs such as EPA and DHA can blunt the appearance of ER stress markers and caspase expression induced by simvastatin [109]. Also, EET and EpOME were able to improve insulin sensitivity and reverse ER stress while the respective diols did the opposite and potentiated ER stress [68]. Additional evidence for a role of ω-3 PUFA derived epoxides in regulating the ER stress response comes from experiments using fat-1 mice. These mice express a ω-3 PUFA desaturase that is capable of increasing intracellular concentrations of ω-3 PUFAs. Inhibition of the sEH in fat-1 mice effectively increased levels of ω-3 PUFA-derived epoxides such as 17,18-EEQ and 19,20-epoxydocosapentaenoic (19,20-EDP) in insulin sensitive tissues, thereby decreasing ER stress [56,110,111]. Not only are ω-3 PUFA-derived epoxides protective in the early stages of diabetes, but sEH inhibition in the later stages of the disease also decreased ER stress in hepatocytes and delayed the development of hepatic fibrosis [112]. Pancreatic islets are known to be sensitive to ER stress induced by chronic exposure to high concentrations of glucose and fatty acids [107], and PUFA epoxides may play also protect against ER stress in β cells. Indeed, sEH inhibition or deletion attenuates hyperglycemia and stimulates insulin secretion as well as reducing ER stress markers and subsequently improving β cell survival during the development of type 2 diabetes [74]. Taking all of this information together, it seems that even though the molecular mechanisms that underlie these phenomena remain to be elucidated in detail, PUFA-epoxides protect diverse tissues against diabetes and insulin resistance by reducing ER stress.

An additional function of the ER that is potentially important is its role in Ca^{2+} homeostasis. The ER contains a high concentration of Ca^{2+} that is maintained largely by the activity of the sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA) [113]. There are several cell types in which altered SERCA expression and/or activity has been linked with diabetes or the complications thereof. For example, the expression of SERCA2b and SERCA3 in β cells is decreased in MetS and to result in diminished insulin secretion [114], and in the heart the expression of SERCA is decreased in hyperglycemic rats a response that was attenuated in animals receiving an sEH inhibitor [98]. These changes may be secondary to post-translational modification as diabetes induces the tyrosine nitration of SERCA2 and a decrease in its activity which in turn results in increased cytoplasmic Ca^{2+} [111]. In platelets this increase in Ca^{2+} is followed by the activation of the calpain family of cysteine proteases and the limited proteolysis of a series of proteins involved in the regulation of platelet function, including SERCA2 [115,116]. Importantly, calpain inhibition *in vivo* protects against the development of endothelial dysfunction [117], as well as platelet activation in animals made diabetic with streptozotocin [116]. Although there is currently no link between the CYP-sEH pathway and calpains, 11,12- and 14,15-EET regulate SERCA2a expression and activity, as well as maintain cardiac myocyte mitochondrial potential [96,118]. Given that SERCA2 is a PPARγ-regulated gene [119] and PPARγ activators such as rosiglitazone

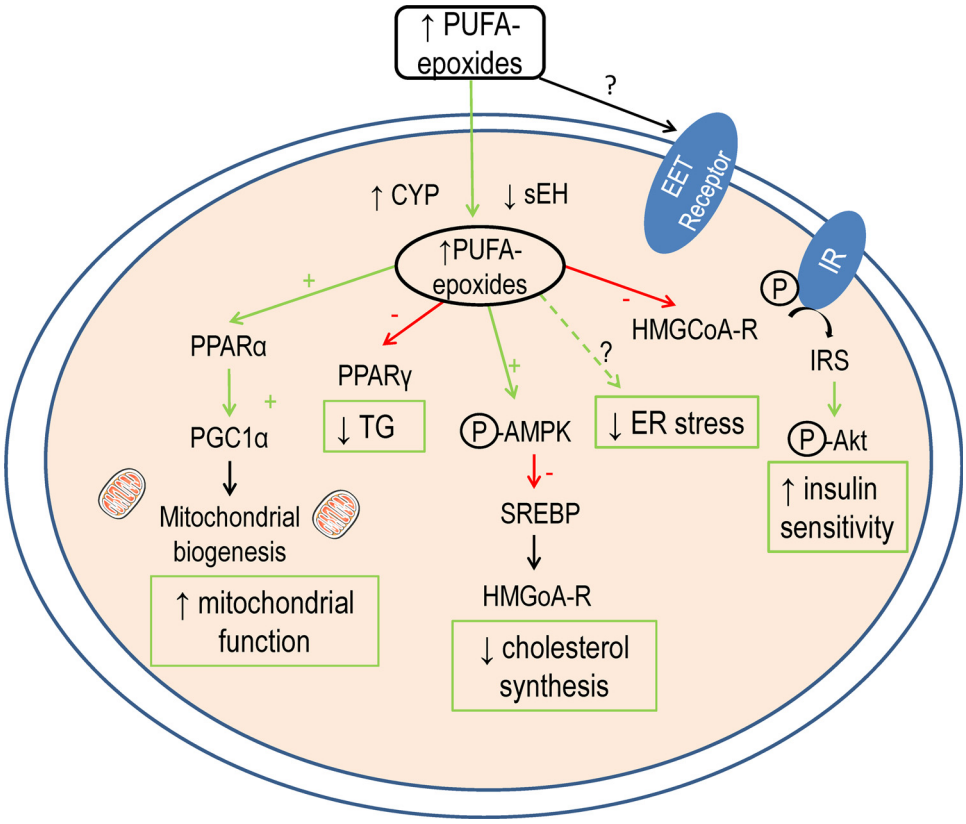

Fig. 3. Mechanism by which PUFA-epoxides protect liver against metabolic syndrome. Increased CYP expression or sEH inhibition increase PUFA-epoxide levels intracellularly as well PUFA epoxides in the circulation can diffuse into the cell or activate specific membrane receptors. The role and expression of membrane receptor has not been clarified in the context of metabolic syndrome. Once inside the cell PUFA-epoxides are able to activate the phosphorylation of the insulin receptor and activate the cascade responsible for the insulin signaling. PUFA-epoxides activate PPARγ resulting in PGC1α stimulation and mitochondrial biogenesis. Altogether PUFA epoxides induce increased insulin signaling and mitochondrial biogenesis and function as well as reduce triglycerides (TG) accumulation, cholesterol synthesis and ER stress. Green arrows: positively regulated, red arrows: negatively regulated.

are able to increase SERCA2 expression in diabetic individuals [116], one other possibility is that EETs could regulate SERCA2 levels via their effects on PPARγ.

6. PUFA epoxides and diols in different organs

6.1. Pancreas

β cells are responsible for the secretion of insulin and thus the maintenance of blood glucose within the normal range [120]. In general unsaturated fatty acids ameliorate β cell function [121]. For example, the monounsaturated fatty acid; oleic acid, stimulates insulin secretion at least partially through regulation of ROS production [121]. PUFAs and monounsaturated fatty acids protect β cells against ER stress and inflammatory cytokines [122–124]. The exact mechanisms are unclear but, fat-1 mice were protected against ER stress via inhibition of SREBP, a known PUFA epoxide target [48]. When administered together with saturated fatty acids, PUFAs may antagonize the deleterious effects of the former. For example, the monounsaturated fatty acid oleic acid was found to increase triacylglycerol accumulation – an effect that correlated with its ability to reduce palmitate cytotoxicity [125]. Additional effects may be related to protection against apoptosis as when challenged with inflammatory cytokines, islets from fat-1 transgenic mice were resistant to cell death [126]. Nothing much is known about PUFA epoxide levels in pancreatic islets or β cells but pancreatic islets express both CYP enzymes as well as the sEH [74,127]. CYP and sEH-derived PUFA mediators may well have functional consequences as 8,9-, 11,12-, and 14,15-EETs were able to augment insulin secretion [128], a phenomenon also observed in $sEH^{-/-}$ mice [129]. Given that pancreatic β cell dysfunction and loss is a characteristic of diabetes, strategies to prevent β cell failure in diabetes are essential to delay the need for insulin supplementation [120]. Therefore, the use of different CYP-derived PUFA metabolites in the first stages of insulin resistance may have a potential to protect β cell function and delay the development of diabetes type 2.

6.2. Liver

Non-alcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis are a consequence of the accumulation of fat in the liver and are associated with insulin resistance and MetS. Although the exact mechanism(s) that precipitate the initiation of NAFLD have not been defined, the exacerbated release of fatty acids and concomitant decrease in the release of adiponectin from adipose tissue has a direct impact on liver cells [130]. For example, adiponectin regulates hepatic glucose and lipid metabolism, decreasing gluconeogenesis and stimulating glucose and fatty acid oxidation. Excessive triglyceride accumulation in the liver is the trigger for insulin resistance in this organ and can lead to steatohepatitis and fibrosis. Therefore, decreased triglyceride accumulation in the liver can improve insulin sensitivity. Despite the fact that the liver is enriched in CYP enzymes as well as the sEH, few studies have determined the effects of PUFA epoxides in insulin-resistant hepatocytes. It is however appreciated that a hepatocyte component must contribute to the beneficial effects of sEH inhibition on insulin sensitivity and glucose tolerance, at least in animal models. For example, while hepatic lipid accumulation was lower in $sEH^{-/-}$ mice than wild-type mice, sEH overexpression in the liver increased both triglyceride uptake and hepatic inflammation [131]. Also here, potential beneficial effects of PUFA epoxides could be linked to the activation of PPARγ [37,131,132], and/or the AMPK [40,47,133].

Approximately 80 % of cholesterol synthesis takes place in the liver through the activity of the hydroxymethylglutaryl coenzyme A (HMG CoA) reductase. There are close links between sEH activity and whole body cholesterol metabolism, as plasma total cholesterol levels were significantly decreased in male $sEH^{-/-}$ mice [67], a fact that could at least be partially attributed to decreased hepatic expression of the HMG CoA reductase [134]. At the level of PUFA-derived mediators, the linoleic acid epoxide 12,13-EpOME was found to attenuate the expression of the HMG CoA reductase via the activation of AMPK and inhibition of SREBP1/2 [48]. The effects were not limited to the HMG CoA reductase as sEH deletion also affected the basal and insulin-

induced expression of the low density lipoprotein receptor and fatty acid synthase. The mechanisms by which PUFA epoxides potentially protect liver against metabolic syndrome are outlined in Fig. 3.

6.3. Adipose tissue

Adiponectin is a hormone produced by adipose tissue under control conditions but its expression and release are decreased as a consequence of obesity, MetS and type 2 diabetes [135]. Adiponectin activates AMPK and PPARα which promote fatty acid oxidation and reduced lipid accumulation in tissues as liver and skeletal muscle [135]. Interestingly, both 11,12-EET and 14,15-EET have been reported to prevent the decrease in circulating adiponectin levels [65], possibly via anti-inflammatory actions of the EETs [59]. PUFA epoxides and diols may also play a role in adipocyte differentiation as the process of adipogenesis was reported to be concomitant with an increase in sEH expression [75]. Whether or not epoxides or diols are true adipogenic factors remains to be determined. Adipocytes are the clearance site for oxidized low-density lipoprotein (oxLDL) in the circulation and thereby also contribute to the cholesterol balance. In adipocytes from mice given a sEH inhibitor the recognition and degradation of oxLDL was enhanced by the action of the cluster of differentiation 36 (CD36) through a PPARγ dependent pathway [82]. sEH inhibitors were also found to enhance the expression of the ATP-binding cassette transporter (ABCA1), which mediates the efflux of cholesterol and phospholipids to apolipoproteins (Apo-A1 and ApoE) by the formation of high-density lipoproteins. Consistent with the latter observations mice treated with a sEH inhibitor responded with an increased cholesterol efflux from adipose depots and developed smaller atherosclerotic plaques [136]. Thus, sEH inhibition or deletion seems to act simultaneously in liver and adipose tissue in order to maintain stable levels of cholesterol.

There are a number of potential mechanisms by which CYP-derived PUFA epoxides could protect adipose tissue against the metabolic syndrome (Fig. 4). As EETs are fatty acid–derived mediators, it is not surprising that they bind to fatty acid binding proteins (FABPs) [137] which play an important role in the intracellular transport of fatty acids [138]. Whether PUFA epoxides could affect the activity of these transporters is not clear but FABP4 inhibitors have been reported to reduce fatty acid uptake and lipid accumulation in adipose tissue, and to decrease adipocyte triglyceride levels without changing circulating levels of fatty acids [137]. FABP4 inhibition also increased insulin and circulating adiponectin levels, indicating a potential increase in systemic insulin sensitivity [139]. Thus, the development of novel EET agonists that bind or inhibit FABPs may offer therapeutic opportunities for the MetS and insulin resistance, as well as atherosclerosis.

7. CYP-sEH axis in the cardiovascular consequences of MetS

7.1. Blood pressure

Since EETs elicit vasodilation and increase renal sodium excretion, they have been attributed anti-hypertensive effects [18]. Certainly, inhibition of the sEH increases epoxide levels and lowers blood pressure in spontaneously hypertensive rats. Similarly, CYP2J2 overexpression decreases blood pressure in spontaneously hypertensive rats and hypertensive mice [140]. Altered CYP and sEH activity may contribute to the hypertension that frequently accompanies MetS as obesity induced by a high fat diet and hypertension were concomitant with a decrease in renal Cyp2c23 and EET generation [141]. Other PUFA epoxides may well also have anti-hypertensive properties, at least following the activation of the renin-angiotensin system [7,49,142]. These fatty acids may alter blood pressure as a result of increased membrane fluidity and altered lipid raft composition, which can potentially increase the permeability of the membranes and leakage of cellular components [8]. While the majority of vascular studies performed with PUFA epoxides have focused on the actions of the EETs and their role as endothelium-derived hyperpolarizing factors [143], EPA and DHA-derived epoxides may well turn out to be more potent vasodilators than the EETs

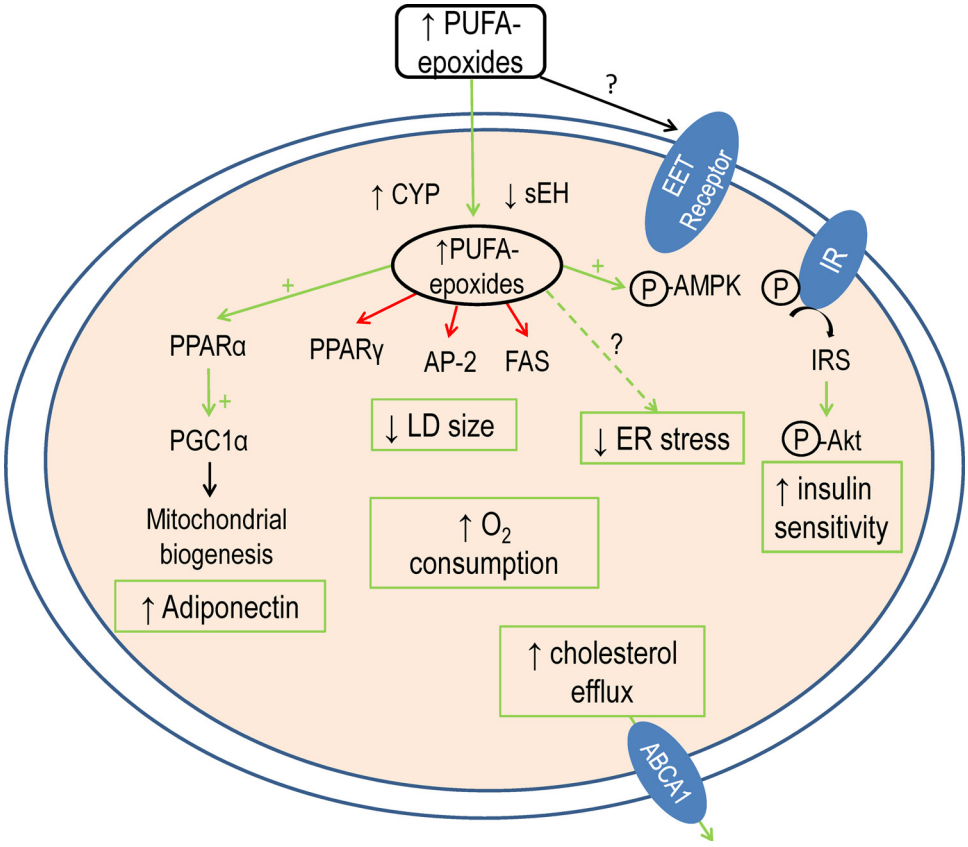

Fig. 4. Mechanism(s) by which PUFA-epoxides protect adipose tissue against metabolic syndrome. Increased CYP expression or sEH inhibition increases PUFA epoxide levels intracellularly as well PUFA epoxides in the circulation that can diffuse into the cell or activate specific membrane receptors. A specific 11,12-EET receptor has been proposed but its identity remains to be convincingly demonstrated as does its link to the metabolic syndrome. Once inside the cell PUFA epoxides are able to activate the phosphorylation of the insulin receptor and activate the insulin signaling cascade. PUFA epoxides activate PPARα resulting in PGC1α stimulation, mitochondrial biogenesis, and increased adiponectin levels. PPARγ, fatty acid synthase (FAS) and fatty acid binding protein (FABP4 or AP-2) are proteins involved in the reduction of lipid droplet size. Altogether, PUFA epoxides increase insulin signaling, cholesterol efflux and mitochondrial biogenesis as well as reduce lipid droplets size and ER stress. Green arrows: positively regulated, red arrows: negatively regulated.

[5,143,144].

7.2. Diabetic cardiomyopathy

Insulin resistance, hyperinsulinemia and hyperglycemia are risk factors for the development of diabetic cardiomyopathy [145]. The latter condition is characterized by ventricular dilation, enlargement of heart cells and prominent fibrosis. Oxidative stress, inflammation and inappropriate activation of the renin-angiotensin system are involved in the development of the pathology and are, at least in part, reversed by sEH inhibition [146,147]. As in other diabetes-induced pathologies, sEH expression is increased in hearts of Ins2Akita mice corroborating the importance of the CYP-sEH axis in the regulation of cardiomyopathy [77]. Decreased subcutaneous and total fat levels, increased insulin sensitivity and adiponectin levels, as well as decreased inflammation are all effects that have been linked with EETs and/or the CYP-sEH axis and all linked to improved cardiac function. EET and sEH inhibitors are also known to reverse endothelial dysfunction and hypertension, and to delay cardiac remodeling, which is a characteristic of the cardiomyopathy that develops as a consequence of MetS and diabetes [148,149].

7.3. Retinopathy

Diabetic retinopathy is an important cause of blindness in the adult population [150,151], and is characterized by a progressive loss of vascular cells and the slow dissolution of inter-endothelial tight junctions resulting in vascular leak and retinal edema [152]. Later stages of the disease are characterized by inflammatory cell infiltration, tissue destruction and neovascularization [153,154]. Given that the early initiating event(s) of the disease are unknown, no effective treatment exists that can be applied to effectively stop or delay degeneration. DHA levels are known to be higher than those of arachidonic acid in the retina [155,156], and the DHA-derived diol; 19,20-DHDP, was recently implicated in the development of diabetic retinopathy [78]. Although, CYP enzyme expression is reported to increase in diabetes, and murine retinal Müller cells were found to express Cyp2c44 [157], there is no information available to link a specific change in CYP enzyme expression or activity to diabetic retinopathy. However, a pronounced increase in the expression of the sEH was detected in diabetic mice and increased 19,20-DHDP levels were reported in retinas from mice as well as vitreous humor from diabetic human subjects. High concentrations of 19,20-DHDP were detrimental to vascular integrity and barrier function as it interacted with cholesterol in the cell membrane to alter the localization of cholesterol-binding proteins. As such, 19,20-DHDP interfered with the association of presenilin 1 with N-cadherin and VE-cadherin to compromise pericyte-endothelial cell as well as inter-endothelial cell junctions and promote the dissolution of the blood-retinal barrier. Not only did the overexpression of the sEH in healthy non-diabetic mice induce a retinopathy very similar to that of non-proliferative diabetic retinopathy but the treatment of diabetic mice with a sEH inhibitor prevented the pericyte loss and vascular permeability that characterize diabetic retinopathy [78]. The potential importance of sEH for retinal disease is highlighted by the fact that a chemical proteomics approach identified the sEH as a target of the antiangiogenic homoisoflavonoid, SH-11037 which had a potent anti-angiogenic effect in the laser-induced choroidal neovascularization mouse model [158]. Given that the sEH is also overexpressed in human eyes with wet age-related macular degeneration [159] it seems that similar mechanisms may also be implicated in the development of wet age-related macular degeneration as well as diabetic retinopathy.

The latter studies focused on the early non-proliferative form of diabetic retinopathy, but as PUFA epoxides have been implicated in angiogenesis [160], is there any evidence that they contribute to the later stages of the disease usually characterized by retinal hypoxia and an increase in vascular endothelial cell growth factor (VEGF) production? This would be an attractive hypothesis given that VEGF increases the activity of the CYP2C promoter to enhance CYP2C expression and activity and increase intracellular EET levels in endothelial cells. In fact, EETs seem to be a functional component to the VEGF signaling cascade as an inhibitory EET analogue or “EET antagonist” prevented VEGF-induced endothelial cell tube formation. This effect was specific to VEGF–induced responses but was unrelated to altered phosphorylation of the VEGF receptor 2 and was unaffected by basic fibroblast growth factor [46,161]. In a potential positive feedback mechanism EETs were also reported to increase VEGF expression and further increase endothelial cell proliferation and angiogenesis [162], a response that may be related to the ability of EETs to activate hypoxia-inducible factor [163]. While the epoxides of arachidonic acid promote angiogenesis, the CYP2C-derived epoxides of ω-3 PUFAs appear to have the opposite effect. For example, the EPA-derived epoxide 17,18-EEQ (but not other EEQ regioisomers) was found to activate the growth-suppressing p38 MAP kinase and downregulate cyclin D1 thereby resulted in the inhibition of cell proliferation in an immortalized endothelial cell line [164].

Relatively little is known about the biological actions of the DHA-derived epoxides and diols but the epoxides (EDPs) were reported to inhibit inflammation in human retinal microvascular endothelial cells [165] as well as in a mouse model of choroidal neovascularization [78], and have also been linked to increased pathological neovascularization [166,167]. For example, 19,20-EDP, was reported to inhibit the expression of VEGFC mRNA, while not affecting that of VEGFA, and to attenuate the VEGF-induced phosphorylation of its receptor; effects coupled to inhibitory effects on tumor growth and metastasis [168]. Although the detailed mechanism(s) linking 19,20-EDP with VEGF signaling remain to be determined, the finding that 19,20-EDP inhibits VEGFC expression is significant as the latter VEGF isoform is an important mediator of lymphatic endothelial cell migration, proliferation, and outgrowth [169]. However, it is not possible to generalize and state that all ω-3 PUFA epoxides inhibit angiogenesis as recent studies in a mouse model of retinopathy of prematurity revealed that retinal neovascularization was increased in mice with a Tie2-driven overexpression of human CYP2C8, fed with an ω-3 PUFA-rich diet [166]. The angiogenic effect was correlated with increased plasma levels of 19,20-EDP as well as increased retinal VEGFA mRNA expression [166]. Moreover, the inhibition of Cyp2c, which reduced EDP levels, suppressed neovascularization in the mouse model of retinopathy of prematurity as well as in a model of choroid injury. Inhibition of the sEH to prevent the metabolism of EDP in the retina, on the other hand, resulted in increased neovascularization [167].

8. Fish oil therapy

Omega-3 PUFAs are usually attributed anti-inflammatory effects – particularly when considering the metabolic syndrome, type 2 diabetes and cardiovascular disease [153,170–174]. Early findings associating a diet rich ω-3 PUFAs with protection against cardiovascular disease boosted the research field but more recent clinical trials failed to demonstrate any significant benefit of fish oil supplements. Although ω-3 levels were low in patients with type 2 diabetes and non-alcoholic fatty liver disease [6], ω-3 PUFA intake failed to reduce abdominal fat in overweight/obese subjects [175]. Also supplementation with a low dose (1 g/day) of EPA and DHA failed to demonstrated cardiovascular benefit in large clinical trials [176–178]. Why did ω-3 PUFA supplementation failed to obtain significant effects? Firstly, the different studies performed failed to determine the optimal concentration of each ω-3 PUFA, or the ratios of ω-3/ω-6 PUFAs required to obtain protective effects. Second, there is a large variability of quality of the supplements in the market. The analysis of the most sold fish oil dietary supplement in the US, for example, revealed a high percentage of other fatty acids than EPA and DHA in these supplements. In one of the products analyzed the saturated fatty acid palmitic acid, accounted for 19 % of total

fat content, and exceeded the DHA content [179], also many EPA and DHA formulations are bound either to triacylglycerol or ethyl esters. The formulation of the preparations may be important as the accumulation of EPA and DHA in red blood cell membranes in individuals receiving dietary supplementation with identical doses of EPA and DHA (1.67 g/day) was higher in those that received the PUFAs in a triacylglycerol-bound rather than ethyl ester-bound formulation [180]. Indeed, new EPA and DHA ethyl ester formulations have achieved high availability in red blood cells at lower dose than known available formulation [181]. The mixture of EPA and DHA may be a problem as EPA (in the absence of DHA) in combination with statin therapy gave protective effects in a Japanese clinical trial [182]. In particular, the randomized Reduction of Cardiovascular Events with EPA Intervention Trial (REDUCE-IT) showed that icosapent ethyl, which is the ethyl ester form of the EPA induced a significant reduction in cardiovascular events. In the latter trial a dose of 4 g /day of a highly purified EPA ethyl ester revealed a decrease in triglycerides levels as well as a reduced the risk of ischemic events [183,184]. This suggests that the discrepancy in previous studies could be a result of low EPA amounts in formulations, which contained both EPA + DHA. Unfortunately, it appears that there is a surprisingly high degree of inter-individual variability in certain aspects of lipid metabolism [185], that renders responsiveness to ω-3 PUFA supplementation probably too variable to ever see clear effects in large population studies. Indeed, variables such as age, the underlying health status of individuals, the dose, duration of exposure, and relative proportion of EPA and DHA in the supplements given [170,186–188] can complicate the situation. However, assessing individual responsiveness to ω-3 PUFAs may be a way to increase the effectiveness of dietary supplementation [185].

How could fish oils exert an anti-inflammatory effect? This is difficult to answer as much less is known about the mechanism of action of the ω-3 PUFAS at the molecular level than the ω-6 PUFAs. However, ω-3 PUFAs can modify tissue and blood lipid metabolism, blood lipid concentrations, blood coagulation, immune function, inflammation and endothelial function [189]. EPA and DHA are readily incorporated into cells and tissues to modify membrane properties in lipid rafts as well as non-raft domains [27]; including the cholesterol content, eicosanoid profiles, signal transduction processes and gene expression [187]. It should also not be forgotten that EPA also serves as a substrate for the formation of the specialized pro-resolving mediator resolvin E1. The latter is an anti-inflammatory metabolite that has been shown to promote the resolution of inflammation in diverse disease models. Resolvins are reported to exert their effects at very low concentrations (pico to nanogram), making them potentially more efficient than their parent PUFA, EPA, as anti-inflammatory mediators [190].

Retinopathy: Retinopathy of prematurity is a complication of treating preterm infants with high concentrations of O_2. It is estimated that as many as 10 % of very premature infants become blind as a consequence of aberrant retinal neovascularization that leads to fibrovascular retinal detachment [191]. Treatment strategies have focused on vascular ablative therapy and more recently on anti-VEGF-based approaches, but recurrence of disease and adverse effects are a cause of concern [192,193]. Another potential contributor to the disease is a deficiency of PUFAs, particularly DHA [191,194]. Indeed, DHA is abundant in the retina [155] and is a fundamental structural component of neuronal and endothelial cells, required to maintain optimal retinal function [195]. Although dietary supplementation has shown some promise in preventing retinopathy [196], and has been linked with a coincident normalization of circulating adiponectin levels by modulating endoplasmic reticulum stress in white adipose tissue [197]. Recent evidence has hinted that O_2-induced retinal damage may be linked to altered PUFA metabolism as the nitrosative stress associated with O_2 therapy in a mouse model of retinopathy of prematurity resulted in the tyrosine nitration of the sEH [99], which is known to inhibit its activity [83]. Fitting with this, retinopathy was more prominent in $sEH^{-/-}$ mice than in wild-type mice and in both cases low concentrations of 19,20-DHDP were able to protect the retina, an effect attributable to the prevention of astrocyte apoptosis. These observations led to the suggestion that 19,20-DHDP may be more effective than DHA as a nutritional supplement at preventing retinopathy in preterm infants. However, the protective effect of 19,20-DHDP was observed following the application of low doses of the diol, while higher concentrations elicited vascular abnormalities – fitting with the link between elevated 19,20-DHDP and vascular instability in diabetic retinopathy [78].

9. Outlook

Over the next decade, it will be interesting to assess the importance of the CYP-sEH pathway in as yet under investigated areas, such as in the gut microbiome. This is potentially important as over nutrition, MetS, insulin resistance, hyperlipidemia and atherosclerosis are frequently accompanied with alterations in the gut microbiota [198–200], and an increase in pro-inflammatory/pathogenic bacteria [201,202]. Interestingly, meals can affect the intestinal CYP-sEH pathway as postprandial sEH activity was significantly reduced in rats, resulting in a decrease in plasma levels of 17 diols [203]. In the same study, animals treated with antibiotics to deplete their gut bacteria did not show reduced diol levels, implying that the sEH is expressed by gut microbiota. Given the different species of bacteria in the gut, it would be interesting to investigate whether there is a differential expression of the sEH by probiotics and inflammatory/pathogenic bacteria in health and diabetes. The finding that diabetic rats exhibited low gut microbiota diversity and that diet with a low ω-6/ ω-3 ratio could improve glucose homeostasis [204,205], implies that ω-3 PUFA also exert beneficial effects on the microbiota. Certainly, feeding mice a high fat diet rich in krill and fish oils reversed the effects on gut microbiota diversity and resulted in a decreased weight gain. The ω-3 rich diet also resulted in lower plasma triglyceride levels than those measured in mice on a ω-3 poor high fat diet [206]. Moreover, microbiota transfer from fish-oil-fed mice attenuated lard-induced inflammation [207].

Based on the evidence outlined above it is clear that the CYP-sEH pathway is intimately involved in regulating metabolic pathways and that this pathway is altered in MetS and diabetes. Indeed an increase in sEH expression may account for some of the organotypic changes usually linked with the development of insulin resistance. While local (e.g. vitreal) administration of sEH inhibitors may find an application in diabetic retinopathy, it is questionable whether the already developed sEH inhibitors will ever be tested clinically in metabolic diseases, given potential side effects accompanying the global inhibition of the enzyme. Strategies to optimize the supplementation of fish oils will certainly be of benefit, but require more detailed studies on the ω-3 PUFA species that are stable enough to be administered and transferred to tissues to result in the generation of protective metabolites.

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