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Review

Dietary polyunsaturated fatty acids and their metabolites: Implications for diabetes pathophysiology, prevention, and treatment

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1. Introduction

In 2013, the global burden of diabetes was estimated to be 382 million individuals, increasing to almost 592 million by 2035 [1]. The economic burden of diabetes is also high, in part due to chronic comorbidities such as cardiovascular and renal disease. US healthcare spending because of diabetes and its complications reached almost $306 billion in 2012 [2]. Of note, the aging population, specifically those over 65, are expected to experience the greatest increase in diabetes incidence, with a 134% increase by year 2030 [3]. Although the increased diabetes prevalence in the aged population may be explained partly by reduced all-cause mortality due to the advances of modern medicine, sedentary lifestyle and poor dietary habits are major risk factors for diabetes and are highly associated with the onset and rapid progression of diabetes.

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The modern food supply has evolved from that of our distant ancestors because of advances in agriculture, technology, and economic interest. Not only has an increased food supply made it easier for individuals in industrialized countries to consume a greater number of calories, but also the nutritional composition of that food supply continues to change. One class of nutrients that is drastically diverging from that of our ancestors is dietary fat, a fact that may play a key role in the rising prevalence and progression of certain diseases, particularly those of aging (Fig. 2) [4]. For instance, the ratio of diet-derived omega-6 to omega-3 polyunsaturated fatty acids (PUFAs) has been linked to the progression of a number of chronic diseases, including diabetes [5]. Long-chain PUFAs (LCPUFAs), such as arachidonic acid (AA) and eicosapentaenoic acid (EPA), have long been known to contribute to the structural integrity of cell membranes and provide a fuel source for the cell, but more recently their functional capacity as signal transduction mediators has come to light. Intact LCPUFAs can act as potent ligands for cellular and nuclear receptors, or can be modified into bioactive compounds to further cellular signaling cascades [6–8]. As we and others are actively studying signaling mediated by LCPUFAs and their metabolites,

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a research area ripe with conflicting results and recommendations, we sought to complete a comprehensive review of the published literature regarding what is currently known about the pro- and anti-diabetic actions of LCPUFAs and their metabolites in cells, model organisms, and humans. Ultimately, we also provide conclusions and future perspectives based on this comprehensive literature review, which describes the cellular signaling roles of LCPUFAs and their respective metabolites in the development, progression, and treatment of diabetes.

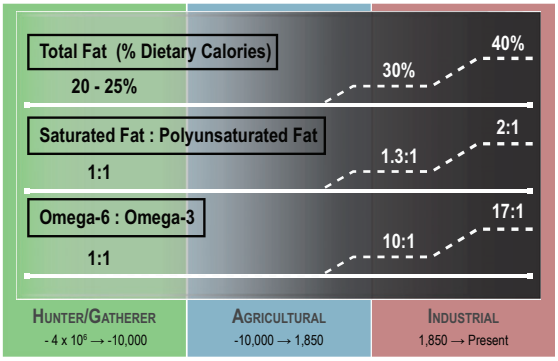

Fig. 1. Dietary fat composition changes over human existence. Human food composition has changed considerably over the course of time. Dietary fat accounted for at most 25% of total calories in the early Hunter/Gatherer time period but has increased to as much as 40% in the present day. The fat composition in the diet has also changed over time, with a higher ratio of saturated fat to polyunsaturated fat and a greater omega-6 to omega-3 ratio in the modern era when compared to earlier time periods. (Figure adapted from [4]).

2. Free fatty acids as signaling molecules

It is well documented that fatty acids contribute to blood glucose regulation and the pathogenesis of diabetes. Acute changes in circulating free fatty acids (FFAs), such as during the transition from a fasted to fed state, stimulate insulin secretion by directly acting on the β-cells of the pancreatic islet. FFAs can also maintain a basal level of insulin secretion during a prolonged fast to limit tissue lipolysis and, ultimately, ketoacidosis [9]. However, chronic exposure to FFAs blunts insulin secretion by potentially creating a lipotoxic environment, leading to increased β-cell cytotoxicity and apoptosis [10]. Chronically elevated FFAs also contribute to insulin resistance, as GLUT4 transport in muscle is blunted, interfering with peripheral glucose sensing [11, 12].

Although chronic exposure to FFAs collectively contributes to blood glucose deregulation, certain FFA species, including LCPUFAs, can explicitly affect insulin secretion and sensitivity by binding to extracellular membrane receptors (Fig. 1). G-protein-coupled receptors (GPCRs) are ubiquitously expressed seven transmembrane receptors that, when bound by a ligand, change conformation to transmit an intracellular signal via guanine nucleotide-binding proteins (G-proteins) [13]. Collectively, there are four major groups of G-proteins–G_s, G_i, G_q, and G_{12}–each of which modulate different secondary messenger molecules and elicit different cellular responses [14]. G_s and G_i increase or reduce cAMP production by activating or deactivating adenylate cyclase activity, respectively. Moreover, G_q increases liberation of inositol triphosphate and diacylglycerol from the plasma membrane by activating phospholipase C while G_{12} activates the small G-protein Rho, which has been shown to play a role in cellular remodeling [14, 15].

Extensive work in isolated islets and β-cell models demonstrates the importance of the activation or repression of signaling through various GPCRs based on the G-proteins they couple to. For instance, the incretin glucagon-like peptide-1 (GLP-1) is released from L-cells of the intestine and enhances insulin secretion and β-cell replication and proliferation via the G_s-coupled GLP-1 receptor protein [16–19]. Also, extracellular nucleotides appear to play an important role in enhancing insulin secretion through the G_q-coupled P2Y6 receptor in islets [20]. Moreover, E-series prostaglandins reduce insulin secretion through the G_i-coupled E-prostanoid receptor 3 (EP3) in islets and multiple β-cell lines, which is upregulated in type-2 diabetes [21–23]. Much less known about the G_{12} group and β-cell function, but activation of receptors coupled to G_{12} proteins are linked to exocytosis and secretion [15, 24]. Thus, G-proteins serve important roles in mediating extracellular signals from GPCRs to modulate β-cell physiology.

A number of GPCRs specific for FFAs or their derivatives have been identified. Furthermore, a number of these receptors have been characterized as regulating glucose homeostasis. GPR41 and GPR43 bind short-chain fatty acids such as and have been implicated in insulin and leptin secretion and signaling [25]. GPR119 is a receptor for derivatives of phospholipids and sphingolipids, and has been shown to directly promote insulin and GLP-1 secretion

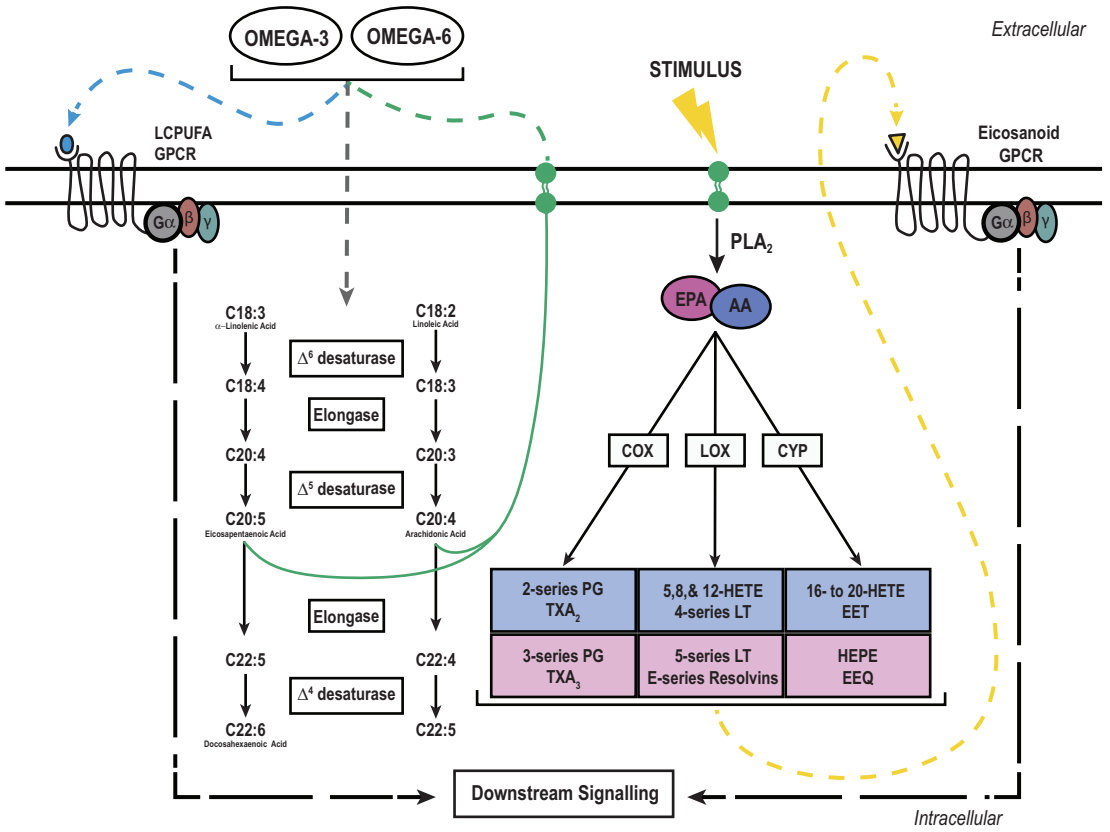

Fig. 2. Long chain polyunsaturated fatty (LCPUFA) signaling and metabolism: LCPUFAs, namely omega-6 and omega-3, must be derived from the diet to elicit intracellular signaling cascades through G-protein coupled receptors (GPCRs) or be incorporated into the cellular membrane for future use. Shorter omega-6 or -3 LCPUFAs like linoleic or α-linoleic acid, respectively, can be further metabolized by the same enzymes to yield the longer LCPUFAs arachidonic acid (AA) or eicosapentaenoic acid (EPA). Newly formed AA and EPA can then be incorporated into the phospholipid membrane for future use. Upon an external stimulus like a cytokine or growth factor, AA and EPA can be liberated from the membrane by phospholipase A_2 (PLA_2) and metabolized into bioactive compounds by the rate limiting enzymes cyclooxygenase (COX), lipoxygenase (LOX), or cytochrome P450 (CYP). These bioactive compounds can then activate extracellular GPCRs in an autocrine or paracrine fashion to elicit downstream signaling cascades.

[26–29]. Extensive reviews of these and other GPCRs, G-proteins and their downstream targets are beyond the scope of this review but can be found elsewhere [30, 31].

Like the FFA species described above, LCPUFAs are endogenous ligands for a subset of GPCRs that are found in unique expression patterns across tissues and play important roles in regulating glucose metabolism. GPR40 is a known lipid-binding GPCR and is highly expressed in the pancreas, with highest concentrations in the insulin-secreting β-cells [32–34]. When GPR40 is bound to one of a number of LCPUFAs, such as linoleic acid or AA, insulin secretion is potentiated from the MIN6 mouse insulinoma β-cell line [33]. Additionally, GPR40 knockout mice experience fasting hyperglycemia, insulin resistance, and obesity as compared to their wild-type littermate controls, indicating an important role for GPR40 in whole body glucose metabolism [35]. The notion that activators of GPR40 are essential fatty acids and must be derived from the diet makes it a potential target for a dietary therapeutic intervention as a treatment for diabetes. A recent human study revealed short-term improvements in insulin secretion with GPR40 agonist treatment, although other results were mixed [36–39]. Furthermore, thiazolidinediones, an established class of insulin-sensitizing diabetes therapeutics known primarily as peroxisome proliferator-activated receptor ligands, also appear to activate GPR40, providing an additional explanation to the drugs' action and efficacy [34].

GPR120 is another receptor for LCPUFAs linked to the development of obesity and diabetes in both mice and humans [40, 41]. Of the LCPUFA family, GPR120 has the highest affinity for omega-3 PUFAs [41, 42]. GPR120 expression is limited to lung, adipose tissue, macrophages, and enteroendocrine cells, and its signaling capability at these tissues is quite high [41, 43–45]. With high expression levels in enteroendocrine cells, LCPUFA signaling through GPR120 increases secretion of a number of incretin hormones, including cholecystokinin (CCK), gastric inhibitory peptide (GIP), and GLP-1 [43–45]. Moreover, GPR120 expression in macrophages helps promote a key anti-inflammatory signaling cascade that enhances insulin-sensitizing effects, preventing glucose intolerance [41].

Collectively, GPCRs activated by FFAs or their derivatives, including LCPUFAs, serve as excellent targets to help regulate blood glucose. Whether signaling through these GPCRs directly affects β-cells, enhances insulin sensitivity, or regulates weight gain, targeting these receptors may be beneficial as diabetes therapeutics.

3. Eicosanoids as mediators of blood glucose

In conjunction with LCPUFAs acting as signaling molecules in their unaltered form, the essential omega-3 and -6 LCPUFAs can be metabolized into bioactive compounds termed eicosanoids (Fig. 1). Although eicosanoids derived from the omega-6 LCPUFA arachidonic acid (AA) are traditional focal points in the literature, having been linked with inflammation and exacerbation of many chronic diseases, emerging evidence regarding EPA (i.e., omega-3)-derived eicosanoids has shown these may have a protective effect, even competing with omega-6-derived eicosanoids.

AA and EPA may be consumed in the diet and can be metabolized to form bioactive eicosanoids. However, the 18-carbon omega-3 and -6 LCPUFAs, α-linolenic and linoleic acid, respectively, represent a larger portion of the diet and can be elongated and desaturated in mammalian systems to produce the required substrates for eicosanoid production. Interestingly, omega-3 and -6 LCPUFAs compete for the same elongase and desaturase enzymes, linking dietary LCPUFA composition to substrate availability and eicosanoid production [46, 47]. But, this process is severely limited in mammalian systems and only accounts for a small amount of AA and EPA. γ-Linoleic acid (GLA), AA, and EPA are 20-carbon LCPUFAs that can be metabolized into bioactive eicosanoids such as prostaglandins, leukotrienes, and hydroxyeicosatetraenoic acids [47]. Eicosanoid production initiates with an external stimulus, such as a cytokine or hormone, and leads to the hydrolysis of GLA, AA, or EPA from the phospholipid membrane by phospholipase A_2 [7]. After liberation from the membrane, LCPUFAs may still act as signaling molecules and effect cellular function or be metabolized by cyclooxygenase (COX), lipoxygenase (LOX), or cytochrome P450 (CYP450) into substrates for a number of eicosanoid specific enzymes [7, 48]. However, this process is tightly controlled to prevent aberrant eicosanoid production.

The initiation of eicosanoid production comes from an extracellular stimulus, such as a cytokine, which promotes the activation of multiple downstream enzymes [49]. Phospholipase A_2 (PLA_2) is the class of enzymes responsible for liberating LCPUFAs from the phospholipid membrane to initiate eicosanoid biosynthesis, and activation of PLA_2 is modulated by phosphorylation [50, 51]. Moreover, eicosanoid production is limited to discrete locations in the cell, as most eicosanoid production occurs in close proximity to the PLA_2 enzymes at specific organelles [49]. In conjunction with the distinct location of substrate and enzymes within the cell, eicosanoids have a relatively short half-life, which limits continuous agonism of receptors and propagation of intracellular signals [52]. Therefore, strict regulation of eicosanoid production prevents perturbed signaling.

Eicosanoids can be transported from the cell and agonize receptors in a paracrine or autocrine manner to alter cellular function. A number of these compounds are linked to diabetes and have profound effects on insulin sensitivity and secretion in obesity-linked type 2 diabetes and β-cell health in autoimmune-linked type 1 diabetes. First, we will discuss the much more widely-studied AA-derived eicosanoids, finishing with what is currently known about the effect of EPA-derived eicosanoids on factors contributing to diabetes pathophysiology.

4. Cyclooxygenase (COX) metabolites

Prostaglandins are eicosanoids derived from the cyclooxygenase (COX) biosynthetic pathway. COX enzymes exist in two isoforms: the constitutive form, COX-1 and the inducible form COX-2. In most

cell types the induction of COX-2 occurs following activation by certain pro-inflammatory cytokines and growth factors [53]. Interestingly, COX-2 is the dominant and constitutively expressed isoform expressed in β-cells, having a profound influence on prostaglandin formation and insulin secretion [54, 55]. Collectively, there are 5 major AA-derived, or 2-series, prostaglandins that bind to distinct GPCRs that are linked to inflammation and disease [56]. It is well documented that prostaglandin production and signaling occurs in both healthy and diabetic islets and can lead to a profound influence on function, proliferation, and survival [21, 57–60]. Prostaglandin production and signaling influences both insulin secretion and sensitivity, making them a popular target for therapeutic intervention in diabetes.

It was initially demonstrated that one particular class of bioactive LCPUFA metabolites, called E-series prostaglandins, reduce insulin secretion both *in vitro* and *in vivo* [61, 62]. Moreover, it is well characterized that the AA-derived prostaglandin E2 (PGE_2) is the predominant E-series prostaglandin formed by COX-2 in islets [7, 54]. PGE_2 binds to a class of ubiquitously expressed GPCR E-prostanoid receptors (EP) that vary in their signaling cascades [56]. Previous work indicates that the EP_3 isoform, which couples to an inhibitory G-protein, is the most highly expressed E-prostanoid receptor in islets and we, along with others, have shown that agonism of EP_3 in β-cells with PGE_2 leads to a reduction in insulin secretion [21, 63]. Moreover, we confirmed that PGE_2 production and EP_3 expression are both increased in type 2 diabetic human and mouse islets, and that this production was a significant contributor to diabetic β-cell dysfunction [21].

In addition to directly limiting insulin secretion, PGE_2 may also have a profound influence on insulin sensitivity, although its exact effect remains controversial. It has been shown that PGE_2 disrupts insulin signaling and glycogen synthesis via the EP_3 receptor in cultured hepatocytes [64]. Moreover, PGE_2 production in liver Kupffer cells disrupts hepatocyte insulin signaling and promotes insulin resistance. It is postulated that altered cytokine production in non-parenchymal cells may contribute to insulin resistance [65]. In another study, rats fed a high fat diet with selective COX-2 inhibitors were less insulin resistant and had reduced hepatic glucose production compared to their control counterparts [66]. Similar results were demonstrated in high fructose- and high fat-fed rats given a selective COX-2 inhibitor [67, 68]. In contrast, others have demonstrated PGE_2 may have protective effects on insulin sensitivity. In one study, FFA-induced COX-2 activity and PGE_2 production in muscle cells led to improved insulin sensitivity, whereas treatment with a COX-2 inhibitor reversed this protection [69]. Another group demonstrated that increased hepatic COX-2 expression and PGE_2 production protected against insulin resistance in diet-induced obese in mice [70]. Therefore, the influence of PGE_2 on insulin resistance is controversial and warrants future investigation.

Since PGE_2 is the most abundant endogenous AA-derived prostaglandin, the others have received considerably less attention in the literature. However, emerging evidence indicates other AA-derived prostaglandins may prove beneficial for insulin secretion and sensitivity. These additional AA-derived prostaglandins include PGD_2, $PGF_2\alpha$, PGI_2, and thromboxane A_2 (TXA_2).

Like PGE_2, PGD_2 appears to be fairly abundant in isolated rat islets and is produced in human islets incubated with AA [71, 72]. Evidence for a direct effect of PGD_2 on insulin secretion from β-cells is weak, although there is stronger evidence of a role for PGD_2 in regulating islet α-cell glucagon secretion, the counter-regulatory hormone to insulin [73]. Moreover, a mouse model that over-produces PGD_2 gained more weight on a high-fat diet when compared to their wild-type counterparts but had enhanced insulin sensitivity [74]. When a form of PGD_2 synthase is knocked out in mice fed a high-fat diet they become insulin insensitive, further indicating the importance of PGD_2 in insulin signaling [75].

$PGF_2\alpha$ is also expressed in rodent and human pancreatic islets [71, 72]. $PGF_2\alpha$ appears to directly stimulate insulin and glucagon secretion in rat pancreases perfused with $PGF_2\alpha$ [76]. However, an isomer of $PGF_2\alpha$, 8-epi- $PGF_2\alpha$, is elevated in plasma from type 2 diabetics and may contribute to the progression of the disease [77, 78].

Classic studies demonstrating the influence of PGI_2 on insulin secretion are fairly ambiguous. PGI_2 infusion increases blood glucose in rabbit and human test subjects, but this was not linked to changes in insulin secretion [79, 80]. Moreover, the influence of PGI_2 on insulin secretion was dependent not only on its own concentration, but also that of glucose, in an isolated rat islet model [81, 82]. More recently, when production of PGI_2 was upregulated in an insulinoma cell line, there was a concomitant increase in insulin secretion in the presence of stimulatory glucose [83].

Finally, thromboxane A_2 (TXA_2), does not appear to have an influence on insulin secretion as demonstrated in perfused rat pancreases [73]. However, TXA_2 may have a more important role in the cardiovascular disease risk, as type 2 diabetic platelets have enhanced TXA_2 production leading to increased activation and aggregation [84–86].

5. Lipooxygenase (LOX) metabolites

Lipooxygenase (LOX) enzymes, which include 5-LOX, 8-LOX, 12-LOX, and 15-LOX, utilize AA to synthesize hydroxyeicosatetraenoic acids (HETEs) and leukotrienes (LTs) and are categorized based on where they oxygenate AA [7, 87]. Similarly to prostaglandins, HETEs and LTs bind to GPCRs, and can play a role in regulating blood glucose by influencing insulin secretion and sensitivity.

In rat islets, 12-HETE is the most abundant product of the LOX pathway and is produced in fairly large quantities during glucose-induced insulin secretion, whereas 5-HETE and 15-HETE could not be detected or were only minor species [88–91]. Moreover, the addition of exogenous 5-, 12-, or 15-HETE did not result in enhanced insulin secretion, indicating that the production of HETEs alone may not directly impact insulin secretion [91]. This is in contrast to another study, where rat islets treated with exogenous 11-HETE or 15-HETE both had reduced insulin secretion [92]. Interestingly, mice lacking 5-LOX have β-cell hyperplasia and hypertrophy but have blunted insulin secretion and are not insulin resistant. Moreover, insulin secretion is reduced when 5-LOX is knocked down by siRNA in human islets. These results suggest an important role for 5-HETE production and signaling for islet function in both humans and mice [93].

Interestingly, an unstable intermediate of HETE metabolism, 12 hydroperoxyeicosatetraenoic (12-HPETE), potentiated insulin secretion in the presence of glucose, suggesting that labile products from this pathway may play a greater role in β-cell function [58, 92]. Conversely, it was shown in human islets that exogenous treatment with the 12(S)-HETE stereoisomer reduces insulin secretion and increases cell death [94]. Similarly, 12-HETE production is closely linked to β-cell destruction by immune cells in mouse islets and mice lacking the 12-LOX enzyme are protected from chemically-induced type 1 diabetes [95, 96]. Thus, the production of 12-HETE may be important for immune modulation as opposed to function during β-cell glucose metabolism.

In adipocytes, both 12- and 15-HETE may contribute to insulin resistance. Mice fed a high fat diet have an upregulation of 12-LOX and 15-LOX in adipose tissue, and insulin signaling was impaired when adipocytes were treated with either 12- or 15-HETE [97]. Remarkably, 12-LOX knockout mice are protected from developing insulin resistance and β-cell destruction when fed a high-fat diet [98]. 12-LOX gene expression and 12-HETE production is upregulated in adipose tissue and islets from the Zucker diabetic rat, linking this pathway to the progression and development of insulin resistance in type 2 diabetes [99, 100]. Moreover, it was shown that rat islets treated with exogenous 11-HETE, 15-HETE, LTB_4, and LTC_4 all inhibited insulin secretion [92]. Although they may not appear to be endogenous islet products, islet immune cell infiltration and subsequently eicosanoid production during diabetes may contribute to defects in insulin secretion or β-cell destruction, as demonstrated in a mouse model of type-1 diabetes [101].

6. Cytochrome P450 (CYP) metabolites

Similarly to LOX enzymes, CYP enzymes can also synthesize HETEs from AA, but also generate epoxyeicosatrienoic acids (EETs), with number designations for the site of epoxidation [7, 102]. However, much less is known regarding the influence of CYP450 metabolites and their impact on insulin secretion.

One of the initial studies assessing the influence of CYP450 metabolites on β-cell function only found 5,6-EET to potentiate insulin secretion whereas 8,9-, 11,12-, and 14,15-EET had no effect on insulin secretion but did increase glucagon production in rat islets [103]. Moreover, it was shown that a prominent CYP enzyme, CYP2J2 in humans and CYP2J3 in rats, is highly expressed in islets in addition to endogenous production of EETs as determined by gas chromatography/mass spectrometry indicating a potential role for EET biosynthesis in islets [104]. Unfortunately, EETs are short-lived *in vivo* making it difficult to accurately quantify them. Recent work, however, determined that selectively inhibiting or knocking out a soluble epoxide hydrolase (sEH), an enzyme responsible for the metabolism of EETs, protected mice from chemically induced glucose intolerance and enhanced insulin secretion [105]. This phenotype

was further recapitulated in a diet-induced obese mouse model treated with selective sEH inhibitors or with sEH-null mice, which led to improved insulin sensitivity and greater islet size [106]. Furthermore, a genetic mutation in the human sEH gene EPHX2 that reduces the efficacy of the enzyme improves insulin sensitivity and increases EET production [107]. Thus, it appears that EET degradation may be a critical component in glucose regulation and may serve as a potential target for the treatment of diabetes.

7. Omega-3 fatty acids: From mouse models to eicosanoids

Similarly to the competition between omega-3 and -6 fatty acids for the elongase and desaturase enzymes, EPA and AA utilize and compete for the same enzymes required for eicosanoid biosynthesis [46]. Generally, omega-3 derived eicosanoids are considered less inflammatory compared to omega-6 derived eicosanoids and are shown to be protective in many cardiovascular based diseases including atherosclerosis, hypertension, and thrombosis [108]. In contrast to the strong evidence supporting the benefits of omega-3 LCPUFAs on cardiovascular function, the current evidence regarding the beneficial effect of increased omega-3 fatty acid consumption as a method to enhance insulin secretion and sensitivity is controversial [109–114]. Unfortunately, high omega-3 fatty acid feeding studies in rodents tend to hinder weight gain, making it difficult to attribute metabolic findings to omega-3 fatty acids or lack of weight gain [115]. Furthermore, the direct role of EPA-derived eicosanoids on insulin secretion and insulin sensitivity is poorly characterized. However, emerging work utilizing transgenic mouse models engineered to shift the endogenous ratios of omega-3 and -6 fatty acids may provide a better understanding of how omega-3 metabolites and eicosanoids contribute to protection from and progression of diabetes.

A mouse model engineered to express the *fat-1* gene from *Caenorhabditis elegans* is capable of desaturating omega-6 into omega-3 fatty acids, reducing the ratio of omega-6 to -3 ratios from upwards of almost 49 : 1 in some tissues to less than 1 : 1 [116, 117]. Interestingly, islets isolated from *fat-1* mice secrete more insulin at sub-stimulatory and stimulatory concentrations of glucose when compared to wild-type islets, indicating a potential role for islet LCPUFA composition in insulin secretion [117]. Moreover, *fat-1* islets produced less AA-derived PGE_2 compared to wild-type controls, suggesting a shift in prostaglandin production due to changes in LCPUFA composition [117]. When subject to diet-induced obesity, *fat-1* mice are protected from glucose intolerance and overt diabetes [118–121]. Part of this protection is due to enhanced liver insulin sensitivity and improved β-cell morphology when compared to wild-type controls [119, 120]. Moreover, the AA derived eicosanoids PGE_2 and LTB_4 were reduced in livers from *fat-1* mice, indicating a potential reduction in inflammation and shift in eicosanoid production [119]. To ascertain whether *fat-1* mice would be protected from age-related blood glucose impairment, *fat-1* mice were placed on non-obesogenic diet for 2 and 8 months. Interestingly, *fat-1* mice were protected from developing glucose intolerance due in part to endogenous blood glucose production, indicating a potential benefit of enhanced omega-3 fatty acids in preventing age-related metabolic disease [122]. Lastly, when *fat-1* is strictly expressed in adipocytes, only male mice are protected from glucose intolerance (presumably due to enhanced insulin secretion) suggesting both sex- and tissue-specific effects of omega-3 fatty acids [123].

In addition to diet-induced glucose intolerance mouse models, *fat-1* mice are protected from β-cell destruction in mouse models of type-1 diabetes. When *fat-1* mice are treated with streptozotocin (STZ) to induce type-1 diabetes, they do not become glucose intolerant and β-cell structure and function is preserved [120, 124]. Furthermore, there was a reduction in islet cell apoptosis and markers of inflammation, including reduced production of the AA-specific eicosanoids PGE_2 and 12-HETE [120, 124]. Interestingly, enhanced production of the EPA-specific eicosanoid 18-HEPE, which has anti-inflammatory properties, was also upregulated in *fat-1* mice treated with STZ, suggesting a shift in eicosanoid production based on substrate availability [124]. When isolated islets were subject to cytokine-induced destruction, *fat-1* islets were protected from cell death indicating a role for LCPUFAs in apoptosis [117].

There is very little evidence regarding the influence of specific EPA-derived eicosanoids and insulin secretion or sensitivity. However, in addition to GPR119 serving as a receptor for phosphatidylcholine and ethanolamide compounds, it can also be activated by 5-hydroxy-eicosapentaenoic acid (5-HEPE), an EPA-derived eicosanoid formed by 5-LOX [125]. In a mouse insulinoma cell line, it was shown that 5-HEPE bound specifically to GPR119

and enhanced insulin secretion, suggesting GPR119 can be activated by a diverse set of ligands including eicosanoids [125]. Additionally, further metabolism of eicosanoids derived from EPA and docosahexaenoic acid (DHA) into compounds termed resolvins and protectins, respectively, may confer benefits to glucose homeostasis [126]. A hyperphagic mouse model fed a diet high in omega-3 fatty acids had enhanced production of resolvins and protectins, which ultimately led to increased insulin sensitivity [127]. Another study demonstrated that exogenous treatment with resolvin D1 improved insulin sensitivity and reduced fasting hyperglycemia in a hyperphagic mouse model further supporting the beneficial role for omega-3 eicosanoid metabolism in protection from glucose intolerance [128].

8. Conclusions and future perspectives

During the past several decades in the U.S., high dietary fat consumption was considered detrimental to health, even with poor or uncertain scientific justification, leading to a drastic and questionable shift in dietary recommendations for fat intake [129]. Ultimately, this shift did not reduce caloric intake or the prevalence of metabolic diseases, such as obesity and diabetes [130, 131]. It is now becoming evident that a shift in the types of fats consumed may be far more important than an overall reduction in fat intake. This is particularly true with the bioactive LCPUFAs, with their potential role in contributing to or ameliorating chronic conditions such as obesity and diabetes [4, 5, 129, 132].

Traditionally, omega-6 fatty acids are considered more detrimental to health and promote disease primarily due to their pro-inflammatory properties. However, omega-6 LCPUFAs are absolutely required for the development, maturation, and function of the immune system [133]. Moreover, many human studies assessing the impact of omega-6 LCPUFA intake and cardiovascular risk fail to demonstrate any significant changes in AA content in cells or changes in pro-inflammatory markers [134–136]. Similar findings demonstrate that omega-3 supplementation does not appear to change morbidity or mortality or inflammatory markers associated with type-2 diabetes [137]. Therefore, the essentiality of omega-6 fatty acids and limited evidence linking omega-6 LCPUFAs to inflammation in human studies hinder the direct link between omega-6 LCPUFAs and disease. But, the divergence in the ratio of omega-6 to omega-3 fatty acids may inherently be the root of the problem as opposed to any quantity of omega-6 LCPUFAs.

Perhaps more important than the species of LCPUFAs is the bioactive compounds they create. Pharmaceutical interventions to limit eicosanoid production, such as COX-2 inhibitors, are efficacious in potentiating insulin secretion and may provide additional benefits in insulin sensitivity in human patients [63, 138–140]. However, cardiovascular risk factors are a cause for concern regarding this treatment, as COX-2 inhibitors in type 2 diabetic patients may lead to adverse cardiac events, particularly in a population with increased basal risk [141, 142]. Moreover, antagonizing eicosanoid receptors as a therapeutic intervention is growing in interest and may be more efficacious in diabetic treatment [14, 21, 143].

In an age where disease therapy is closely linked to pharmaceutical treatment, a dietary intervention promoting a LCPUFA profile similar to our ancestors may also prove beneficial in the prevention and treatment of both type 1 and 2 diabetes. The previously mentioned transgenic mouse models demonstrate the importance of the omega-6 to omega-3 ratios in directly and indirectly altering insulin sensitivity and secretion. Future dietary interventions designed to transform our eicosanoid profiles may prove to be a potential therapy for the long-term treatment of diabetes.

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