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## Eicosanoids, $\beta$ -Cell Function, and Diabetes

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### Abstract

Arachidonic acid (AA) is metabolized by cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP) enzymes into eicosanoids, which are involved in diverse diseases, including type 1 and type 2 diabetes. During the last thirty years, evidence has been accumulated that suggests important functions for eicosanoids in the control of pancreatic  $\beta$ -cell function and destruction. AA metabolites of the COX pathway, especially prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), appear to be significant factors to  $\beta$ -cell dysfunction and destruction, participating in the pathogenesis of diabetes and its complications. Several elegant studies have contributed to the sorting out of the importance of 12-LOX eicosanoids in cytokine-mediated inflammation in pancreatic  $\beta$  cells. The role of CYP eicosanoids in diabetes is yet to be explored. A recent publication has demonstrated that stabilizing the levels of epoxyeicosatrienoic acids (EETs), CYP eicosanoids, by inhibiting or deleting soluble epoxide hydrolase (sEH) improves  $\beta$ -cell function and reduces  $\beta$ -cell apoptosis in diabetes. In this review we summarize recent findings implicating these eicosanoid pathways in diabetes and its complications. We also discuss the development of animal models with targeted gene deletion and specific enzymatic inhibitors in each pathway to identify potential targets for the treatment of diabetes and its complications.

### 1. Introduction

Between 2000 and 2010, the number of people with diabetes has more than doubled, from 121 million to 285 million. That number is expected to grow to 438 million by 2030 [1]. Currently, 23.4 million Americans have diabetes (American Diabetes Association, National Diabetes Fact Sheet, 2007). The Center for Disease Control (CDC) estimates that the current cost of diabetes is \$174 billion annually in the U.S.

Diabetes, which is characterized by hyperglycemia, is divided into type 1 (T1DM) and type 2 diabetes mellitus (T2DM). T1DM is characterized by autoimmune destruction of  $\beta$ -cells [2; 3]. Ultimately, circulating insulin concentrations are negligible or completely absent in patients with T1DM [4]. Obesity, which affects one in three Americans, is a serious health problem because it is often associated with T2DM [5; 6], which occurs because of insufficient generation of insulin and/or the inability of peripheral tissues, including skeletal muscle and adipose tissue, to respond to insulin efficiently. The development of T2DM is

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firmly associated with insulin resistance, a physiological condition in which insulin becomes less effective at lowering blood glucose [5; 6]. Diabetes shortens the life span as a consequence of cardiovascular disorders, including heart attack, hypertension, and stroke [7; 8]. Accordingly, diabetes-associated complications result in major expense for families and impose a major societal economic burden.

Since pancreatic  $\beta$ -cell dysfunction and destruction are the key events in the onset and progression of diabetes [2; 3; 9; 10], this review will focus on how arachidonic acid (AA)-derived lipid mediators affect insulin secretion and  $\beta$ -cell destruction as well as the role of these eicosanoids in diabetes. AA is a polyunsaturated fatty acid, which is esterified at the *sn*-2 position of the glycerol backbone of membrane phospholipids or other complex lipids [11]. AA is released from phospholipids by the action of phospholipase A<sub>2</sub> (PLA<sub>2</sub>), which specifically recognizes the *sn*-2 acyl bond of phospholipids and catalytically hydrolyzes the bond releasing AA and lysophospholipids.

As shown in Figure 1, AA is modified by three major pathways, including cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP), into biologically active eicosanoids (eicosa, Greek for 20, refers to 20 carbon fatty acids) [11–14]. The products of these pathways act as paracrine and autocrine factors and contribute significantly to the regulation of inflammation [13; 15], renal function [16; 17], and vascular function [18; 19]. Since novel receptors and metabolites of COX and LOX pathways are well defined, these two eicosanoid pathways are important therapeutic targets for inflammatory and cardiovascular diseases [13]. This review aims to provide important information related to brief background of biochemistry and function of eicosanoids, regulation of  $\beta$ -cell function by eicosanoids, regulation of  $\beta$ -cell destruction by eicosanoids, and the involvement of eicosanoids in diabetes.

## 2. Biochemistry and function of eicosanoids

### 2.1. COX-derived eicosanoids

The major COX-derived eicosanoids are prostaglandins (PGs) and thromboxane (TX). COXs are the enzymes that catalyze the first two steps of the enzymatic reaction to convert AA into PGH<sub>2</sub> [20]. Of note, PGH<sub>2</sub> is the precursor for the generation of PG<sub>2</sub> and TX by the activities of tissue-specific isomerases and synthases [21]. There are two isoforms of COX, COX-1 and COX-2. COX-1 is constitutively expressed in most cells, whereas COX-2 is inducible by inflammatory or stimulatory events in tissues and responds to specific inducers [22; 23]. The major PGs are PGD<sub>2</sub>, PGE<sub>2</sub>, PGI<sub>2</sub>, and PGF<sub>2 $\alpha$</sub> ; the major TX is TXA<sub>2</sub>. The action of these PGs and TXA<sub>2</sub> is mediated through the binding of these products into their membrane-bound receptors, including DP, EPs (EP<sub>1</sub> to EP<sub>4</sub>), IP, FP, and TP receptors (Fig. 1) [14; 23]. In the cardiovascular system, PGI<sub>2</sub> is a potent vasodilator and an inhibitor of platelet aggregation, whereas TXA<sub>2</sub> is a potent vasoconstrictor and a pro-aggregatory substance [24; 25]. Thus, the balance between PGI<sub>2</sub> and TXA<sub>2</sub> in the circulation is important for cardiovascular homeostasis [26]. In the kidneys, COX-eicosanoids are important in regulating renal function. Vasodilatory PGs, including PGI<sub>2</sub>, PGE<sub>2</sub>, and PGD<sub>2</sub>, increase renal blood flow and glomerular filtration rate. PGE<sub>2</sub> is a key regulator of sodium reabsorption in the distal tubules [21]. Therefore, these COX products are vital in the pathogenesis of cardiovascular [18; 19] and kidney diseases [14; 27].

### 2.2. LOX-derived eicosanoids

The major LOX-derived eicosanoids are hydroxyeicosatetraenoic acids (HETEs) (12 (S)-HETE, 12 (R)-HETE, and 15 (S)-HETE), as well as leukotrienes (LTs) (LTA<sub>4</sub>, LTB<sub>4</sub>, LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub>) (Fig. 1). LOXs are enzymes that convert AA into different HETEs. In mammals, LOXs are categorized into 5-LOX, 8-LOX, 12-LOX, and 15-LOX, which are

classified according to the insertion site of the hydroperoxy group [28]. LOXs are non-heme iron-containing enzymes that insert a hydroperoxy group into AA [14]. 5-LOX metabolizes AA into 5-HPETE, which is the precursor for the generation of LTA<sub>4</sub>. Notably, the generation of LTA<sub>4</sub> requires the interaction of 5-LOX and 5-LOX-activating protein, which facilitates the transfer of AA to 5-LOX for the enzymatic reaction [27]. LTA<sub>4</sub> can be hydrolyzed to form LTB<sub>4</sub>, which then conjugates with glutathione to form cysteinyl-LTs (cysLTs), LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub> [27]. The action of these LTs is mediated through the binding of these products to their membrane-bound receptors, including BLT, cysLT, and LTE<sub>4</sub> receptors.

Of circulating cells, LTs are mainly synthesized by eosinophils, neutrophils, monocytes or macrophages, and mast cells [27]. Since LTs have a relative short half-life, these products act as autacoids near their synthesizing sites [29]. A substantial body of evidence indicates that 5-LOX products exert proinflammatory effects by increasing the production of proinflammatory cytokines; also, 5-LOX products act as chemotaxins to recruit inflammatory cells in the blood vessels [28; 29]. Accordingly, most investigators consider 5-LOX products to be detrimental factors in pathological conditions, including cardiovascular [28–30] and renal diseases [27; 31].

### 2.3. CYP-derived eicosanoids

The major CYP-derived eicosanoids are HETEs (16-, 17-, 18-, 19-, and 20-HETE) and epoxyeicosatrienoic acids (EETs) (5,6-, 8,9-, 11,12-, and 14,15-EET) (Fig. 1) [32]. EETs are formed endogenously in various tissues and exert potent biological effects on cellular functions. EETs are readily hydrolyzed by soluble epoxide hydrolase (sEH) to the corresponding dihydroxyeicosatrienoic acids (DHETs) [11; 13; 33]. In general, DHETs are much less biologically active than are EETs [13; 33]. Therefore, inhibition of sEH activity has been used as a means of studying the physiological function and cardiovascular benefits of EETs [13; 33]. The rapid development of selective inhibitors of sEH in the past decade is noteworthy. Moreover, sEH inhibitors have been consistently demonstrated to have cardiovascular benefits [13; 33].

Among HETEs, 20-HETE is the major metabolite in blood vessels and the kidneys [32]. Synthesis of 20-HETE is catalyzed by enzymes of CYP4A and CYP4F [32]. Synthesis of EETs is less specific and can be carried out by CYP1A, 2B, 2C, 2D, 2E, and 2J isoforms [13]. Accumulating evidence demonstrates that the major CYP epoxygenases for EETs synthesis are CYP2C and CYP2J isoforms [13]. These CYP products play an important role in the regulation of cardiovascular and renal function [13; 33]. 20-HETE and EETs have been implicated in the regulation of vascular tone [13]. 20-HETE is a vasoconstrictor in the renal and cerebral microcirculation and an important regulator of the myogenic tone [12]. Notably, EETs act directly on the afferent arteriolar smooth muscle cells to elicit relaxation and are considered to be endothelium-derived hyperpolarizing factors [34; 35]. EETs are anti-inflammatory and act as angiogenic factors [13; 33]. Although several studies have suggested that the action of EETs is mediated through an EET receptor [36–38], that receptor has yet to be identified.

In the renal tubules, 20-HETE and EETs are important mediators that inhibit sodium transport in proximal tubules [39; 40], the thick ascending limb [41; 42], and the collecting duct [43]. Accordingly, these CYP eicosanoids play a vital role in the pathogenesis of cardiovascular [13; 44] and renal diseases [27; 33]. The CYP eicosanoid pathway is currently being targeted for the treatment of hypertension and stroke [13].

### 3. Regulation of $\beta$ -cell function by eicosanoids

Beta cells are a specific cell type in the pancreatic islets of Langerhans, making up about 50%–65% of the cells [45]. Pancreatic  $\beta$  cells produce insulin and secrete it at an appropriate rate to maintain blood glucose within a relatively narrow range [46]. In pancreatic  $\beta$  cells, glucose stimulates insulin secretion by two major pathways: the triggering and amplifying pathways [46].

The regulation of insulin secretion by these two pathways is shown schematically in Figure 2. In the triggering pathway, products of glucose metabolism enter the mitochondrial respiratory chain, which then uses them to generate adenosine triphosphate (ATP). Increased ATP levels close the  $K_{ATP}$ -sensitive channels. This is followed by plasma membrane depolarization and opening of the voltage-sensitive  $Ca^{2+}$  channels, which in turn increase the intracellular  $Ca^{2+}$  concentration and promote insulin secretion [47]. In this pathway, uncoupling protein 2 (UCP2) acts as a negative regulator of glucose-stimulated insulin secretion (GSIS) by decreasing the production of ATP [48]. The amplifying pathway augments insulin secretion independently from its action on  $K_{ATP}$ -sensitive channels. It is well recognized that the triggering pathway determines insulin secretion under physiological conditions, whereas the amplifying pathway optimizes the secretory response induced by the triggering signal [10]. In the following subsections, we will discuss the influence of COX-metabolites, LOX-metabolites, and CYP-metabolites on  $\beta$ -cell function.

#### 3.1. Influence of COX metabolites

Although  $PGE_2$  and  $PGF_{2\alpha}$  were identified in rat islets [49],  $PGE_2$  is the most predominant product of the COX pathway in  $\beta$  cells because  $PGE_2$  has been reproducibly shown to modulate  $\beta$ -cell function [45; 50; 51]. Thus, major research activities in this area have focused on the biochemistry and function of  $PGE_2$  in human and rodent islets [45; 51–54]. It is generally recognized that COX-1 is the constitutive isoform, while COX-2 is the inducible isoform in most tissues. In contrast, an earlier study demonstrated that COX-2 expression predominates over COX-1 in pancreatic islet cells under both basal and IL-1 $\beta$ -stimulated conditions [55]. Of note, the high basal expression of COX-2 in islets is probably due to the action of transcription factor, NF-IL6 [23]. Taken together, these results suggest that COX-2 is the major enzyme responsible for  $PGE_2$  production in  $\beta$  cells [23].

To understand the actions of  $PGE_2$  in the islets, islet expression of the mRNA of EP receptors has been studied by real-time RT-PCR. One interesting study showed that EP<sub>3</sub> is the most abundant EP receptor type in rat islets [51]. Similarly, EP<sub>3</sub> receptor is present in human islets [53]. Although results regarding the effects of COX metabolites on insulin secretion have been contradictory, the consensus is that  $PGE_2$  has inhibitory effects on insulin secretion in islets [50; 52]. For example, Robertson and colleagues [54] have demonstrated that in rat islets, NS-398 and SC-236, COX-2 selective inhibitors, prevented IL-1 $\beta$ -induced inhibitory effects on insulin secretion, and exogenously adding  $PGE_2$  reestablished the inhibition of insulin secretion by IL-1  $\beta$ . In addition, Fujita *et al.* [56] have demonstrated that COX-2 selective inhibitor (SC58236), but not COX-1 inhibitor (SC58560), inhibited  $PGE_2$  production and promoted GSIS in mouse islets. It is known that IL-1 $\beta$  activates COX-2 and EP<sub>3</sub> expression via the NF- $\kappa$ B pathway and that EP<sub>3</sub> has postreceptor activities resulting in a decrease in cAMP levels [51]. Thus, it has been postulated that during inflammation IL-1 $\beta$  promotes  $PGE_2$  levels via the induction of COX-2 in islets, after which increasing  $PGE_2$  binds to EP<sub>3</sub> receptor, resulting in a decrease in cAMP levels and a sequential decrease in GSIS [51]. However, this notion has not been confirmed in human islets because  $PGE_2$  did not inhibit insulin secretion in perfusion experiments with these islets [52]. A recent review article has pointed out that the main reason for the action of COX-2 inhibitor on insulin secretion is the increase in ambient

levels of AA in  $\beta$  cells [53]. Thus, the contribution of PGE<sub>2</sub> to the control of insulin secretion remains unresolved.

### 3.2. Influence of LOX metabolites

To study the effects of the LOX pathway on pancreatic  $\beta$ -cell function, earlier studies have determined the effects of various LOX metabolites on GSIS in rat islets [57; 58]. Metz and colleagues [58] have shown that 5-HETE and 12-HETE did not alter insulin secretion, whereas 15-HETE, LTB<sub>4</sub>, and LTC<sub>4</sub> inhibited insulin release. In addition, they showed that 12-HPETE acts as an important mediator that potentiates insulin secretion. Thus, it was postulated that LOX metabolites could provide an “on” signal for GSIS. However, during glucose metabolism, glutathione-derived metabolites convert this signal to an “off” response by a negative feedback loop [58]. This notion is supported by a recent publication [59] that siRNA to 5-LOX reduced GSIS and insulin gene expression in human islets. Although this notion was interesting, recent studies have not supported this hypothesis.

It has been demonstrated that 5-LOX products improve rather than decrease islet function in rodents. Also, there have been conflicting reports about whether or not 5-LOX is expressed in islets [15; 60]. Accumulating evidence indicates that 12-LOX is expressed in human islets and 12-HETE has been detected in human islets [15]. Thus, 12-HETE probably is the major LOX product in islets that regulates GSIS [49; 60].

The islet production of 12-HETE is elevated in Zucker rats, a model of T2DM. In diabetic Zucker rats, an inhibitor of 12-LOX activity inhibited AA-stimulated insulin secretion, implying that 12-LOX products are involved in the deficits in insulin secretion [61]. To study the effects of 12-LOX metabolites on  $\beta$ -cell function during basal and inflammatory conditions, Bleich *et al.* [62] determined GSIS in 12-LOX knockout (KO) and control islets in the absence or presence of cytokines. They showed that in the absence of cytokines, 12-LOX KO did not affect GSIS, whereas deletion of 12-LOX significantly improved GSIS in the presence of cytokines [62]. These results provided novel evidence that the deletion of 12-LOX is an effective approach improving  $\beta$ -cell function during inflammation. To investigate the importance of 12-LOX-derived lipid mediators in diabetes, a recent publication examined the effects of 12-LOX products on  $\beta$ -cell function in human islets [63]. In this report, Ma and colleagues [63] showed that at 1 nM, 12-HPETE and 12 (S)-HETE produced substantial reductions in insulin secretion. Taken together, these findings provide evidence that 12-LOX products are important negative mediators of insulin secretion in human islets. The importance of the LOX pathway on  $\beta$ -cell function has been reviewed previously [15; 60].

### 3.3. Influence of CYP metabolites

Less investigation has been devoted to the influence of CYP metabolites on pancreatic  $\beta$ -cell function. The relevance of EETs to pancreatic function is documented in a study by Falck and colleagues who demonstrated that EETs stimulate insulin secretion in isolated rat islets [64]. Regioselectively, only 5,6-EET (1  $\mu$ M), but not 8,9-EET, 11,12-EET, or 14,15-EET, directly induce the release of insulin [64]. This report provided the first evidence that CYP metabolites are involved in regulating pancreatic  $\beta$ -cell function.

To advance this research area, Zeldin and colleagues [65] have investigated the expression profile of CYP epoxygenase, CYP2J, in human and rat pancreatic tissues. Using immunohistochemical analysis, they showed that CYP2J is highly expressed in the cells of islets, with minimal staining in pancreatic exocrine cells. They also showed that a significant amount of EETs are produced in human and rat pancreas [65], providing biochemical evidence that CYP epoxygenase products may regulate  $\beta$ -cell function. It is difficult to study

the physiological function of EETs *in vivo* because these products are rapidly degraded by sEH to DHETs. Moreover, sEH inhibitors and KO are widely used to enhance the biological and cardiovascular actions of EETs [13; 66; 67].

Interestingly, using a hyperglycemic clamp approach, recent work by Luo *et al.* [68] has provided the first evidence that the genetic deletion and pharmacological inhibition of sEH promote insulin secretion *in vivo*, resulting in the prevention of hyperglycemia in diabetic mice. They showed that sEH KO and the selective inhibitor (*trans*-4-[4-(3-adamantan-1-ylureido)-cyclohexyloxy]-benzoic acid; *t*-AUCB) augmented GSIS in mouse islets [68]. Mechanistically, this report also demonstrates that the enhancement of GSIS by sEH KO in  $\beta$  cells is mediated through the amplifying pathway, which is an important target for the development of therapeutic insulin secretagogues [10]. Taken together, these findings support the notion that sEH KO or inhibition would increase pancreatic EET levels and contribute to the enhancement of GSIS. Nevertheless, it remains unclear which CYP epoxygenases are responsible for the production of EETs and whether EETs are able to promote insulin secretion in mouse and human islets.

#### 4. Regulation of $\beta$ -cell destruction by eicosanoids

T1DM, which occurs in 5%–10% of the diabetic patients, causes the loss of 70%–80% of pancreatic  $\beta$ -cell mass by the time of diagnosis [3]. There is no practical method of preventing or curing T1DM, which impairs the overall quality of life because patients require daily insulin administration. Pancreatic islet transplantation (PIT) has been used clinically in efforts to treat T1DM patients [69]. The average human pancreas has about 300,000 to 1.5 million pancreatic islets. It is estimated that about 60% of pancreatic islet cell mass is needed to maintain normal glucose metabolism [69]. Therefore, there is great demand for T1DM patients to obtain healthy islets from donors. However, significant numbers of islets undergo apoptosis, an important mechanism of  $\beta$ -cell destruction, after PIT procedures. It has been estimated that the rate of apoptosis following PIT is 10 times higher than the rate in native pancreatic islets [69]. Because transplanted encapsulated islets are encircled by reactive macrophages and T-lymphocytes, which secrete cytokines into the internal core of the islet capsule, inflammatory cytokine-induced  $\beta$ -cell apoptosis appears to be the major mechanism that mediates  $\beta$ -cell damage [60]. Thus, approaches to inhibit inflammatory cytokine actions have become important to improve the function of islets after PIT [69].

In T2DM patients, it has been shown that about 25% to 50% of  $\beta$ -cell loss is found in initial pathological studies. As in T1DM,  $\beta$ -cell apoptosis is the main reason for  $\beta$ -cell loss [3]. Therefore, both T1DM and T2DM are associated with a significant loss of  $\beta$  cells [3]. In the following subsections, we will review the impact of COX-metabolites, LOX-metabolites, and CYP-metabolites on  $\beta$ -cell destruction.

##### 4.1. The impact of COX metabolites

Since it is widely accepted that COX-2 is induced by inflammatory cytokines [21; 31], a lot of research effort has focused on the role of COX-2 in the pathogenesis of T1DM and T2DM. Studies have demonstrated that a high glucose level (25 mM) induces the expression of COX-2 in the human islets [70; 71]. Shanmugam and colleagues [71] have demonstrated increased expression of COX-2 in db/db mice, a mouse model for T2DM. Growing evidence demonstrates that COX-2 promoter contains NF- $\kappa$ B, IL-6, activated protein-1, and cAMP-response element [72].

Interleukin-1 (IL-1), an inflammatory cytokine, is released in islets by both T lymphocytes and activated macrophages. Treatment of islets with IL-1 causes transient induction of

COX-2 expression; it peaks within 2–4 hr and decreases to basal levels after 24 hr of exposure [55]. Similarly, EP receptor promoter contains an NF- $\kappa$ B binding site [73]. The inhibition of NF- $\kappa$ B by sodium salicylate results in decreased expression of EP<sub>3</sub> receptor [51]. Accordingly, it has been postulated that COX-derived PGE<sub>2</sub> is the important lipid mediator for  $\beta$ -cell destruction.

Noteworthy, earlier work by Rabinovitch and colleagues [74] has demonstrated that indomethacin, a non-selective COX inhibitor, concentration-dependently protects rat islets from cytokine-induced destruction. More importantly, Oshima and colleagues [75] have used rat insulin-2 promoter to overexpress COX-2 and microsomal PGE synthase-1 in mouse  $\beta$  cells. They provided the first evidence that overexpressing COX-2 and PGE synthase in  $\beta$  cells causes increased levels of PGE<sub>2</sub>, which have deleterious effects on  $\beta$ -cell mass in the transgenic mice. Nevertheless, the reduction of  $\beta$ -cell mass is due to the inhibition of  $\beta$ -cell proliferation [75].

Further investigations of COX-2 in transplanted islets have tested whether selective COX-2 inhibitors improve the survival and function of transplanted islets in non-obese diabetic (NOD) and streptozotocin (STZ) models [76; 77]. These studies have shown that COX-2 inhibitor does not have a significant effect on initial graft loss, blood glucose levels, glucose tolerance, or insulin content of the grafts [76; 77]. Of note, acetylsalicylic acid, a non-selective COX inhibitor, significantly reduces initial graft loss and prolongs the survival of islet grafts in NOD mice [77]. However, the dose of acetylsalicylic acid used in these experiments was at least 10-fold higher than that required to inhibit PG synthesis. These results suggest that the effects of acetylsalicylic acid are due to COX- and PG-independent mechanisms [77]. Taken together, these previous reports [76; 77] have failed to show that COX-2 inhibitors have any beneficial effect in PIT.

#### 4.2. The impact of LOX metabolites

Extensive research activities have focused on the effect of 12-LOX products on pancreatic  $\beta$ -cell function and destruction [15; 63]. There are three types of 12-LOX: platelet, leukocyte, and epidermal. Leukocyte 12-LOX is the major enzyme expressed in pancreatic islets [78]. 12(S)-HETE is the major product of leukocyte 12-LOX [78]. It is recognized that 12-LOX products, which are proinflammatory, are important in the pathogenesis of T1DM and T2DM [15; 63]. A study by Laybutt and colleagues [79] has demonstrated that 12-LOX expression is induced in islets of a partial pancreatectomy model of diabetes. Similarly, the production of 12-LOX products is induced in the islets of Zucker rats [61]. To determine the importance of 12-LOX in  $\beta$ -cell destruction, Chen and colleagues [78] showed that 12-LOX is expressed in human islets and the combined treatment with inflammatory cytokines induced the production of 12(S)-HETE in these islets. Similarly, 12(S)-HETE induces apoptosis in  $\beta$ -TC3 cells [78], providing direct evidence that leukocyte 12-LOX product has a deleterious effect on  $\beta$  cells.

Another aspect of LOX products acting as pro-apoptotic agents is indicated by Rabinovitch and colleagues who showed that nordihydroguaiaretic acid (NDGA), a lipoxygenase inhibitor, inhibits cytokine-induced  $\beta$ -cell destruction in rat islets [74]. To elucidate the protective role of LOX inhibitors in transplanted islets, Fu and colleagues [80] have tested whether NDGA protects the graft survival of neonatal pig pancreatic cell clusters in alloxan-diabetic mice. They showed that NDGA prevented  $\beta$ -cell toxicity and preserved function of xenografts early after transplantation [80]. Taken together, these findings suggest that LOX inhibitor exerts a beneficial effect in PIT.

### 4.3. Influence of CYP metabolites

Little research has been done on the role of CYP metabolites in pancreatic  $\beta$ -cell destruction. Several studies have indicated that EETs have anti-apoptotic effects in different cell types [81; 82]. For example, Yang and colleagues showed that overexpression of CYP epoxygenase significantly increased endothelial cell viability and inhibited TNF  $\alpha$ -induced endothelial apoptosis. Simpkin *et al.* [82] have recently shown that the inhibition of sEH by 12-(3-adamantane-1-yl-ureido)dodecanoic acid decreased the expression of pro-apoptotic genes in neural tissues. Luo and colleagues [68] investigated the relevance of EETs to pancreatic  $\beta$ -cell destruction by determining the effects of sEH KO on islet cell apoptosis in STZ-induced diabetes. They showed that STZ-sEH ( $-/-$ ) mice exhibited less islet cell apoptosis than did STZ-sEH ( $+/+$ ) mice [68]. This was the first report to show that sEH is involved in  $\beta$ -cells apoptosis. Since sEH is expressed in human pancreas [83] and mouse  $\beta$  cells [68], it is possible that the blockade of sEH will be an important approach to increasing the bioavailability of EETs in  $\beta$  cells. Nevertheless, no study has directly addressed the role of EETs in protecting transplanted islets. Taken together, the preceding results suggest that EETs are important in protecting  $\beta$ -cells from apoptosis.

## 5. Eicosanoids and diabetes

Insulin resistance, which has large roles in both T2DM and T1DM [84–87], is characterized by impaired sensitivity to insulin in its main target organs. After insulin is produced and released from pancreatic  $\beta$  cells, it binds to its receptor and helps the liver, muscle, and fat to take up glucose from the blood, storing it as glycogen in the liver and muscle. Insulin also increases fatty acid synthesis and inhibits gluconeogenesis and lipolysis [87].

Early in the development of T2DM, compensatory insulin hypersecretion maintains normoglycemia, but progressive insulin resistance and/or  $\beta$ -cell dysfunction eventually lead to overt hyperglycemia. Chronic hyperglycemia, a major cause of the death in diabetic individuals, damages the kidneys, blood vessels, and other organs. In recent years, it has been postulated that low-grade inflammation contributes to insulin resistance [88]. Accumulating evidence from rodents to large-scale studies of populations has demonstrated that AA-derived eicosanoids regulate inflammatory cytokines and chemokines and contribute to the pathogenesis of insulin resistance and diabetes-related complications.

### 5.1. COX and diabetes

COXs, which are widely distributed enzymes, are activated by mechanical, chemical, and immunological stimuli. PG synthesis often accompanies the inflammatory response [89; 90]. Studies have shown that increased PGE<sub>2</sub> is involved in insulin-regulated glycogen synthesis and gluconeogenesis in the liver [91; 92]. The expression of COX-2 is closely correlated with plasma leptin levels and Homeostasis Model of Assessment - Insulin Resistance (HOMA-IR), which is an index of whole-body insulin resistance [93]. In addition, hyperglycemia induces COX-2 expression [94–96] and activates the receptors for advanced glycation end products (RAGE), which therefore could be involved in vascular and renal diseases [94; 97].

Diabetes also causes chromatin remodeling and histone acetylation of the COX-2 gene promoter at NF- $\kappa$ B binding sites [98]. In diabetes, RAGE overexpression is associated with inflammation and COX-2 expression, which is significantly correlated with hemoglobin A1c [99]. A selective COX-2 inhibitor improves peripheral and hepatic insulin resistance and decreases plasma cytokines [93; 100; 101]. Indomethacin, a non-selective COX inhibitor, prevents hyperglycemia-induced tachyarrhythmia [102]. Although early reports showed that PGs have a protective role during inflammation [103; 104], some COX-2 inhibitors, including nimesulide, endotoxin, and metformin, lead to intensified inflammation and



impaired glucose metabolism [105; 106]. This discrepancy may be due to inhibitor selectivity and variability in the amount of AA that is available to LOXs, CYPs, or non-enzymatic oxidative modification. The association between COX genetic polymorphism and diabetes has been investigated. The COX rs20417 variant has 30% higher T2DM prevalence in Pima Indians [107]. COX-2 polymorphism also increases the risk of cardiovascular disease [108]. Patients with T1DM display a lower frequency of the protective CC genotype of the -765G>C COX-2 polymorphism [109].

## 5.2. LOX and diabetes

LOX enzymes catalyze the oxygenation of AA into lipid mediators [110]. LOX enzymes and their products regulate cytokine and chemokine expression in many tissues and organs, including pancreatic islets and adipose tissue, the respective sites where insulin is produced and acted on [15; 111].

Increasing evidence suggests that the 12/15-LOX pathway is involved in the pathogenesis of insulin resistance and adipose tissue inflammation [112–114]. High glucose levels enhance 12/15-LO pathway activation and expression in vascular smooth cells [115] and endothelial cells [116], as well as 15-HETE production in porcine aortic endothelial cells [117]. 5/12-LOX enzymes and products as well as 5-LO-activating protein (FLAP) are upregulated in adipocytes from diabetic animals [118; 119]. Increased production of 12/15-LOX eicosanoids accelerates monocyte or endothelial interactions in diabetes [120]. Moreover, 5-LOX knockout mice do not develop diabetic retinopathy [121]. Therefore, the LOX pathway could play a vital role in diabetic complications.

Direct evidence demonstrates that cells overexpressing 12/15-LOX secrete MCP-1 and osteopontin, which participate in the development of insulin resistance [112]. 12- and 15-HETEs induce inflammatory cytokine expression and impair insulin action in adipocytes [122–124]. Moreover, deletion of 12/15-LOX in mice improves high-fat-diet-induced inflammation and insulin resistance [112]. LOX inhibition decreases triglycerides and free fatty acids, and improves insulin action in both fructose-fed and fat-fed rat models of insulin resistance and T2DM [125; 126]. 12-LOX products also downregulate glucose transport in VSMC, which may lead to insulin resistance [127]. Moreover, deletion of 12-LOX resists T1DM induction in mice [62].

In obese subjects, different adipose tissues seem to express different LOX enzymes. For example, 15b-LOX and 12-LOX are expressed in both subcutaneous and omental fat, but 15a-LOX is expressed only in subcutaneous fat, predominantly in CD34-positive cells [128]. The increased mRNA expression of LOX5AP in subcutaneous adipose tissue observed in obese populations is associated with HOMA-IR [129]. In diabetic patients, urinary excretion of 12(S)-HETE is increased as compared with that in matched non-diabetic controls [130].

LOX5AP polymorphism is associated with increased risk of atherothrombotic cerebral infarction in Japanese people who have metabolic syndrome [131]. It has also been revealed that Japanese T2DM patients with the polymorphism have increased susceptibility to chronic kidney disease [132]. Similarly, 12-LOX is associated with diabetic nephropathy in European-American T2DM patients [133]. Further, 12-LOX, 5-LOX, and LOX5AP polymorphisms are associated with subclinical atherosclerosis in European-Americans with T2DM [134].

## 5.3. CYP and diabetes

As compared to COX and LOX pathways, less is known about the role of the CYP pathway in diabetes. AA is metabolized to 20-HETE by CYP4A families and to EETs by CYP2C and

2J families. EETs are further metabolized to DHETs by sEH. Diabetes and obesity are associated with reductions in the expression of CYP2C isoforms [135–137], but increases in the expression of CYP4A isoforms and sEH [136; 138; 139]. EETs are decreased in diabetic vitreous [121] and glomeruli [140]. It seems that insulin is involved in the regulation of these enzymes. Direct evidence shows that insulin reverse increased hepatic CYP4A isoforms in diabetic rats [139].

It has been demonstrated that the inhibition of CYP epoxygenase did not affect relaxation in insulin-resistant blood vessels [141; 142], suggesting that vasodilation induced by CYP-derived EETs is impaired in T2DM. Since EETs are produced by CYP2C/2J and degraded by sEH, CYP2C/2J induction or sEH inhibition is expected to enhance the beneficial properties of EETs. *In-vivo* CYP2J3 gene delivery has been shown to increase EET generation, reduce blood pressure, and reverse insulin resistance [143]. Furthermore, overexpression of CYP2J3 prevented fructose-induced decreases in insulin receptor signaling and phosphorylation of AMP-activated protein [143]. sEH genetic deletion or pharmacological inhibition decreases hyperglycemia in STZ and obese models [68; 144; 145]. Interestingly, Sodhi and colleagues have demonstrated that EETs agonist rescues the metabolic syndrome phenotype of heme oxygenase-2 knockout mice [146]. In addition, db/db obese mice lacking sEH have lower blood glucose than do db/db mice (M. H. Wang, unpublished data).

PPAR- $\alpha$  agonist, which induces CYP enzymes, attenuates hypertension and glomerular damage in diabetic rats [147]. Inhibition of 20-HETE production or reduction of EET degradation may have therapeutic potential to prevent erectile dysfunction associated with diabetes [148].

There are also reports of a close association between the sEH G860A (Arg287Gln) polymorphism and insulin resistance in T2DM patients [149]. CYP2C9 polymorphism displays a better response to anti-diabetic medicine in T2DM patients [150; 151], but carries a high risk of hypoglycemia, raising the possibility of a pharmacogenetic interaction [152]. Increased prevalence of the CYP2C8\*4 mutation has been found in T2DM patients [153]. CYP2J2 G-50T polymorphism seems to contribute to the pathogenesis in patients with T2DM of early onset [154]. CYP2C9\*2 and CYP2C9\*3 alleles currently appear to have no clinical implications for dosing of sulfonylureas in patients with T2DM in the Netherlands [155]. There is also no association between CYP2C9, CYP2C19, or CYP2D6 genotype and diabetes susceptibility in Bosnian populations [156]. Moreover, CYP2C9 variant seems to have lower response to losartan in T1DM patients with nephropathy [157]. CYP2J2 has no association with T1DM or T2DM in Caucasians [158]. However, these results reflect the use of limited study populations. Large-scale studies are required to reveal potential relationships between CYP genetic variants and diabetic risk.

#### 5.4. Omega 3-derived eicosanoids and diabetes

Besides generating from omega 6 ( $\omega$ -6) polyunsaturated fatty acids (PUFAs), eicosanoids can also be produced from  $\omega$ -3 PUFAs. Numerous studies demonstrate that lipid mediators generated from  $\omega$ -3 PUFAs, which include eicosapentaenoic acid (EPA, 20:5 n-3) and docosahexaenoic acid (DHA, 22:6 n-3), possess anti-inflammatory and protective effects in diverse diseases including diabetes [159; 160].

To investigate the importance of  $\omega$ -3 PUFAs in diabetes, investigators have studied the effects of overexpression of fat-1, a *C. Elegans* gene encoding an  $\omega$ -3 fatty acid desaturase catalyzing the conversion of  $\omega$ -6 to  $\omega$ -3 PUFAs, in different diabetic models [161; 162]. Stable production of  $\omega$ -3 PUFAs in transgenic mice carrying fat-1 gene enhances GSIS and protects  $\beta$  cells from cytokine-induced destruction [161]. Similarly, fat-1 transgenic mice

have significantly higher levels of  $\omega$ -3 PUFAs in the pancreases and are protected from STZ-induced diabetes [162]. These novel studies [161; 162] demonstrate that endogenously synthesized  $\omega$ -3 PUFAs are  $\beta$ -cell protective. Similarly, an earlier study has demonstrated that  $\omega$ -3 PUFA-enriched diet reduces hyperglycemia in STZ diabetes [163]. Moreover,  $\omega$ -3 PUFAs intake alleviates obesity-induced insulin resistance and hepatic steatosis through upregulation of insulin sensitivity related genes, such as glucose transporter-2 and -4, insulin receptor substrate-1 and -2 [164] and intake of  $\omega$ -3 PUFA-rich diet prevents obesity [165] and improves insulin sensitivity [166]. In T1DM patients,  $\omega$ -3 PUFA treatment reduces cholesteryl ester transfer (CET) and increased concentrations of CET protein, which mediates lipid metabolism [167]. However, these studies are based on small size of populations and short following-up time, large-scale studies are necessary to establish the importance of  $\omega$ -3 PUFAs in diabetes.

## Conclusion

Pancreatic  $\beta$ -cell dysfunction and insulin resistance are important in causing the onset and progression of T1DM and T2DM. During diabetes, AA and its lipid metabolites, eicosanoids, have an important role in inflammation-induced  $\beta$ -cell dysfunction and insulin resistance. We have outlined the functions of COX-, LOX-, and CYP-derived eicosanoids that are produced in pancreatic islets under normal and disease conditions.

PGE<sub>2</sub>, the most important COX product found in islets, reduces insulin secretion and insulin sensitivity during cytokine-induced inflammation. The action of PGE<sub>2</sub> on  $\beta$ -cell dysfunction during inflammation is probably mediated through the binding of PGE<sub>2</sub> to EP<sub>3</sub> receptor, causing a reduction in cAMP levels. Overproduction of PGE<sub>2</sub> can also promote the loss of  $\beta$ -cell mass through the inhibition of  $\beta$ -cell proliferation. Nevertheless, it appears that COX-2 inhibitors do not exert any beneficial effects in pancreatic islet transplantation. Also, the effects of COX-2 inhibitors on insulin sensitivity need to be validated. Although it has been demonstrated that COX-2 inhibitor prevents hyperglycemia in the STZ-diabetic mouse model [168], more research is needed to establish the importance of COX-2 in human diabetes.

12-HETE is the most important LOX product in islets. Deletion of the 12-LOX gene increases insulin secretion in the presence of cytokines, suggesting that 12-LOX products are involved in  $\beta$ -cell dysfunction during inflammation. There is direct evidence that 12(S)-HETE, a 12-LOX product, promotes  $\beta$ -cell destruction. Animal and human studies have shown that the LOX pathway contributes to insulin resistance and diabetic complications. LOX inhibitors show the beneficial effects in pancreatic islet transplantation. Although selective 15-LOX inhibitors have been recently developed [169], no highly selective 12-LOX inhibitor is yet available for *in vitro* and *in vivo* studies. Selective 12-LOX inhibitors must be developed if we are to fully understand the importance of 12-LOX products in  $\beta$ -cell function and destruction.

EETs are the most important CYP products in islets. Although there is some evidence that EETs promote insulin secretion, there is still a deficit in current knowledge regarding the function of EETs with regard to  $\beta$ -cell destruction. A recent study has demonstrated that increasing EETs by inhibiting sEH promotes insulin secretion and reduces  $\beta$ -cell destruction, indicating EETs are a potential therapeutic target for the treatment of diabetes. Although these findings are interesting, we still need to prove the direct effects of EETs on  $\beta$ -cell function and destruction. Given the important effects of EETs on anti-inflammation, it is likely that EETs contribute to the control of insulin sensitivity. The development of novel pharmacological tools such as EET analogs for use in *in vivo* studies, as well as the development of molecular biology tools such as mouse models for  $\beta$ -cell-specific

overexpression of CYP epoxygenases, is necessary to fully delineate the importance of the EETs pathway in diabetes.

Although growing evidence supports the existence of strong relations between eicosanoids and diabetes, the detailed mechanism whereby eicosanoids contribute to diabetes needs to be further explored. Identification of the putative EETs receptor will facilitate future studies in the CYP pathway. A recent study has clearly demonstrated that rats given dietary EPA/DHA supplementation promote the synthesis of pancreatic  $\omega$ -3-derived epoxyeicosatetraenoic acids (EEQs) [170]. Since EPA/DHA supplementation reduces hyperglycemia in STZ diabetes [163], it is possible that EEQs may have potential to regulate  $\beta$ -cell function and destruction.

#### Highlights

- Cyclooxygenase (COX) products, specifically PGE<sub>2</sub>, inhibit insulin secretion and promote pancreatic  $\beta$ -cell destruction.
- Lipoxygenase (LOX) products, specifically 12-HETE, promotes  $\beta$ -cell dysfunction and  $\beta$ -cell destruction.
- Increasing the levels of cytochrome P450-derived EETs by suppressing soluble epoxide hydrolase (sEH) improves  $\beta$ -cell function and reduces  $\beta$ -cell destruction.
- $\omega$ -3 PUFAs are  $\beta$ -cell protective.

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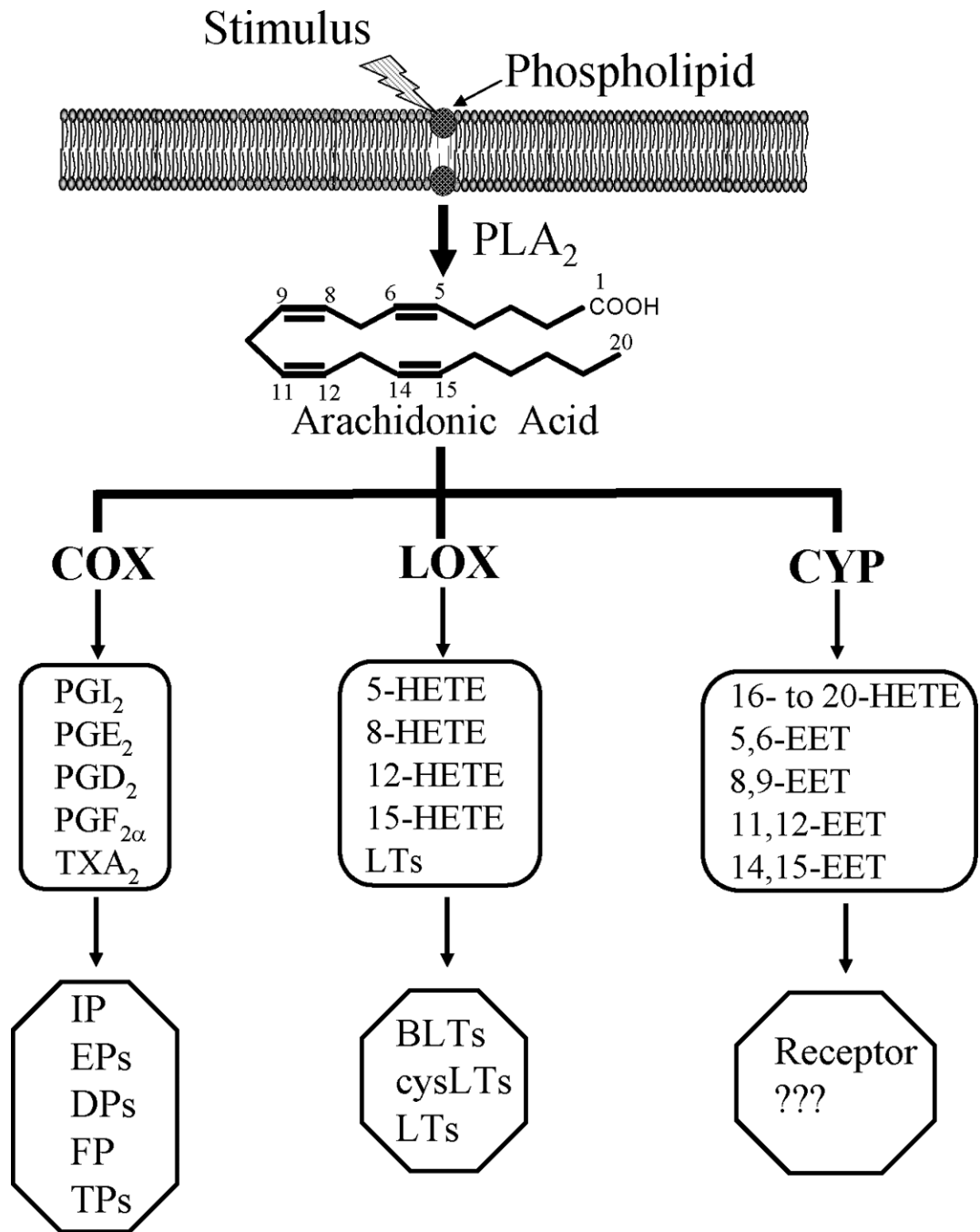


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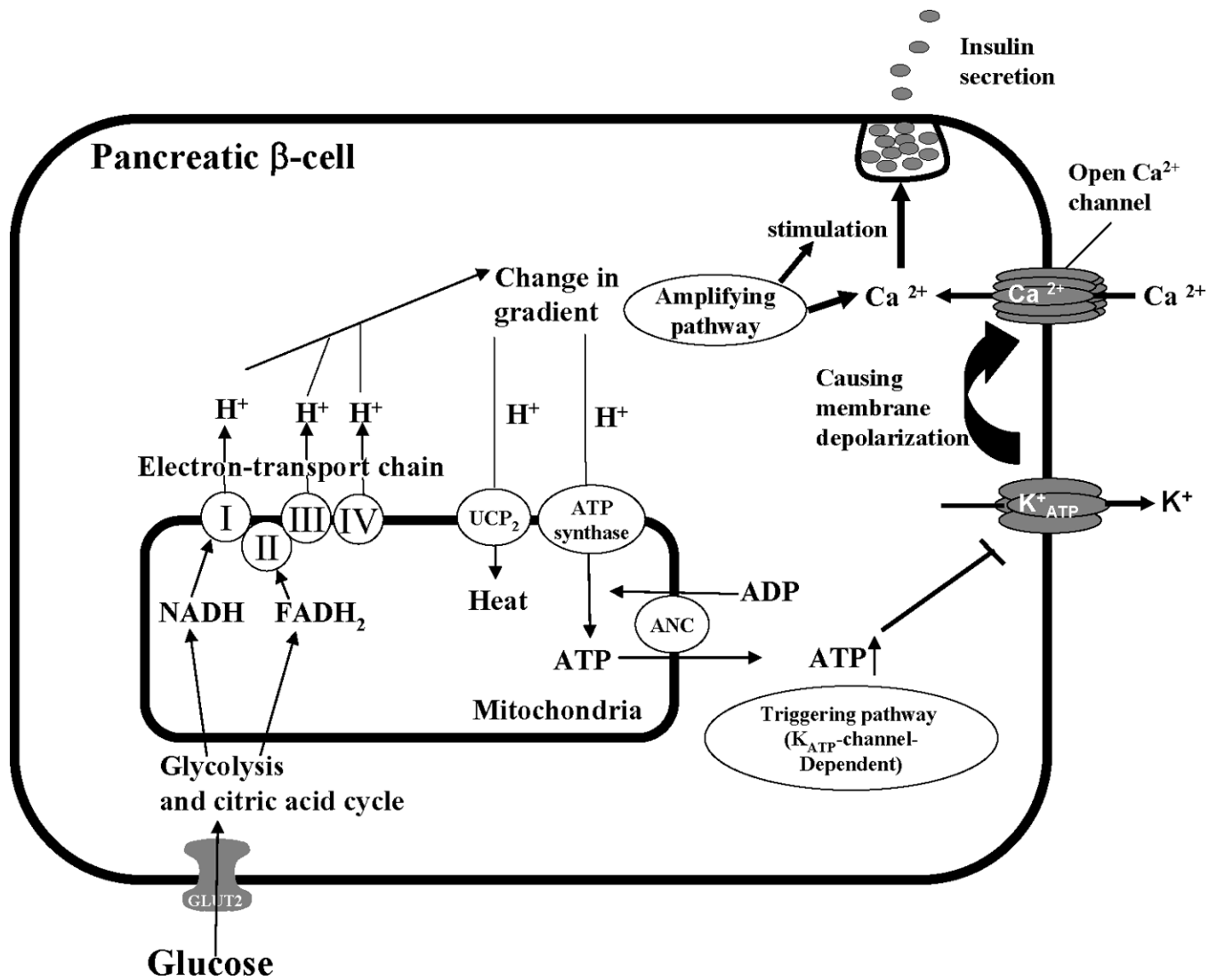
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**Figure 1.**

Bioactive eicosanoids derived from the arachidonic acid (AA) cascade. After triggering by inflammatory conditions such as the presence of cytokines and growth factors, AA-containing phospholipids are hydrolyzed by phospholipase A<sub>2</sub> (PLA<sub>2</sub>) resulting in the release of free AA. AA can be further metabolized by three pathways, i.e., the cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP) pathways. AA cascade generates prostaglandins (PGs), thromboxane A<sub>2</sub> (TXA<sub>2</sub>), and a series of hydroxyeicosatetraenoic acids (HETEs), leukotrienes (LTs), and epoxyeicosatrienoic acids (EETs). The action of these bioactive eicosanoids is mediated through the binding of these substances to their receptors. However, an EET receptor has yet to be identified.



**Figure 2.**

In pancreatic  $\beta$  cells, the uptake of glucose is mediated by glucose transporter, GLUT2. Within  $\beta$ -cells, glucose is further metabolized by the glycolysis and the citric acid cycle to generate NADH and FADH<sub>2</sub>, which donate electrons to the mitochondrial electron-transport chain. Protons are pumped out by complexes I, III, and IV of the electron-transport chain creating a proton electrochemical gradient. Protons reenter the mitochondria via ATP synthase to generate ATP. In pancreatic  $\beta$  cells, increasing ATP inhibits the K<sup>+</sup><sub>ATP</sub> channel, causing plasma membrane depolarization, which opens voltage-gated Ca<sup>2+</sup> channels. Increasing the intracellular Ca<sup>2+</sup> concentration contributes to the release of insulin. UCP2 acts as a negative regulator of GSIS by decreasing ATP levels.