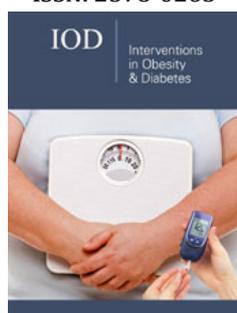# The Role of Obesity-Induced Inflammation in Pancreatic β-Cell Dysfunction and Death

Danielle Melloul*

Department of Endocrinology, Hadassah University Hospital, Israel

*Corresponding author: Danielle Melloul, Department of Endocrinology, Hadassah University Hospital, Jerusalem, Israel

Abstract

Type 2 diabetes (T2DM) is frequently associated with elevated levels of lipids, in particular plasma free fatty acids and toxic lipid metabolites in muscle, liver, adipocytes, pancreatic islets and arterial tissues, contributing to insulin resistance and pancreatic islet β-cell dysfunction. The pathophysiology of T2DM is increasingly being linked with inflammatory mediators such as cytokines and chemokines as well as with changes in the number and activation state of macrophages/monocytes leading to β-cell dysfunction and subsequently to insulin insufficiency. The prevalent product of the cyclooxygenase 2 (COX-2) enzyme PGE2, controls numerous physiological functions through a family of cognate G protein-coupled receptors (EP1-EP4). The EP3 receptor which is selectively upregulated in islets of T2DM individuals, is upregulated under lipotoxic conditions and is involved in β-cell dysfunction and demise. This EP3 target presents a new approach to delay the progression of T2DM disease by preserving the pancreatic β-cells.

Keywords: Diabetes mellitus; Obesity; Pancreatic islet β-cell; Inflammation; Palmitate; Apoptosis;

Introduction

Obesity is a growing and serious epidemic in the modern society leading to the development of multiple disorders including Type 2 diabetes mellitus (T2DM). The progression from obesity-related insulin resistance to T2DM implicates a failure of pancreatic β-cells to compensate for insulin resistance, leading to chronic hyperglycaemia. In early stages, β-cells adapt to changes in insulin sensitivity by varying insulin secretion. However, in susceptible subjects, when β-cells fail to compensate for insulin resistance, T2DM ensues [1]. As nutrient excess persists, hyperglycemia (glucotoxicity) and elevated free fatty acids (FFAs, lipotoxicity) contribute to β-cell failure and subsequent apoptosis [2,3]. It has been reported that most individuals with T2DM, whether obese or lean, show a decrease in β-cell mass [4,5]. Since pancreatic β-cell dysfunction and destruction are the key events in the onset and progression of the disease, this review will focus on the contribution of obesity-related inflammatory mediators to these processes. T2DM is associated with increased plasma free fatty acid (FFA) levels, accumulation of toxic lipid metabolites in muscle, liver, adipocytes, β-cells and arterial tissues contributes to insulin resistance and β-cell dysfunction [6-8]. While fatty acids acutely enhance glucose-induced insulin secretion [9], chronic exposure to mainly saturated FFAs causes β-cell failure and contributes to diabetes development in genetically predisposed individuals. Subjects with high fasting levels of plasma FFAs have an elevated risk of developing T2DM [10,11]. Furthermore, lipid infusion in individuals who are genetically predisposed to T2DM induces hepatic insulin resistance and impairs β-cell function [11].

Cumulative evidence indicates that FFAs can induce β-cell dysfunction and death through multiple mechanisms, including oxidative stress, ceramide formation, ER stress and inflammation (reviewed) [12-14]. Systemic low-grade inflammation is a hallmark feature of obesity and was suggested to play a role in T2DM. Inflammatory mediators have been shown to be involved in the pathogenesis of obesity-related insulin resistance, the development of the disease and its complications with insulin-sensitive peripheral tissues being themselves sites of inflammation in presence of obesity [15,16]. Immune cells and mainly macrophages infiltrate these tissues and produce pro-inflammatory cytokines, which act in an autocrine and paracrine manner to interfere with insulin signaling [16-18]. In fact, activation of inflammatory pathways in adipocytes impairs triglyceride storage and increases release of free fatty acids, exacerbating insulin resistance in muscle and liver [19]. Thus, chronic inflammation appears to be a clinically important change that occurs in adipose tissue when it becomes obese [20].

While in healthy individuals, the M2 macrophages population is present at high levels, in obesity, it switches to pro-inflammatory M1 macrophages leading to high expression levels of cytokines and chemokines [21]. Serum pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 [22] as well as chemokines [23] were found elevated in obese and T2DM individuals.

Inflammation and pancreatic islet β-cells

Pancreatic β-cells are known to be particularly sensitive to damage induced by the immune system compared with the surrounding non β-cells, due in part to their low expression levels of cytoprotective enzymes [24]. While functional impairments in the β-cell are induced shortly after exposure to cytokines, apoptosis is detected after chronic exposure to the inflammatory mediators indicating that an active process is taking place, a race between deleterious and protective mechanisms where ultimately the deleterious prevails, leading to β-cell death. Therefore, β-cells play an active role in their own destruction by expressing high levels of cytokines, chemokines, proinflammatory mediators such as NF-kB, iNOS in response to diabetogenic agents [25]. In fact, increased evidence has emerged that supports a role for islet inflammation in the development of T2DM and not only in T1DM. In the islets of T2DM individuals, a higher number of infiltrated macrophages has been detected [26,27] and increased levels of cytokines and chemokines in obesity dependent diabetes were also reported [22,23,28,29]. Saturated fatty acids can induce β-cell death by apoptosis, whereas unsaturated fatty acids are usually protective [30]. Palmitate is the most common saturated FFA in man and has been used in in vitro studies to elucidate the mechanisms of lipotoxicity and has been implicated in palmitate-induced β-cell dysfunction and death [31-33].

Several mechanisms have been proposed to link inflammation and lipotoxicity with β-cells. Eguchi et al. [34] showed that exposure of β-cells to palmitate causes the production of chemokines such as CCL2/MCP1 and CXCL1/GRO1 that recruit M1-type proinflammatory macrophages to the islets by activation of the TLR4/MyD88 pathway. Depletion of M1-type cells using clodronate protected mice from palmitate-induced β-cell dysfunction and inhibited the downregulation of β-cell specific genes in islets. Therefore, and as mentioned for the adipose tissue, a shift from M2 to M1 macrophages appears to occur. Laser capture microdissection was performed to isolate β-cells from pancreas sections of type 2 diabetic and of non-diabetic donors. Higher expression of the chemokines mainly CCL2/MCP-1 and CCL13/ MCP-4 was detected in T2DM islets [35]. A similar study was performed where the cytokines IL-1β and IL-8 were found to be also upregulated in T2DM islets compared to controls [36]. Altogether, these reports emphasize the active role the β-cell is playing in the activated inflammatory process leading to its loss of function and ultimately to its demise.

Prostanoids and pancreatic islet β-cells

The cyclooxygenase-2 (COX2) enzyme and its major product, the prostaglandin E2 (PGE2), have been implicated in the pathogenesis of several inflammatory diseases [37]. Results obtained using knock-out mouse studies, indicate that prostanoids including PGE2 exert both pro-inflammatory and anti-inflammatory responses, through regulation of gene expression in different tissues. In most tissues, Cox1 is predominantly expressed relative to COX2. While the isoenzyme Cox1, is constitutively expressed in most mammalian tissues and is involved in maintaining physiological functions, the inducible COX2, is usually expressed at low levels in most tissues and cells, but is rapidly induced in response to a wide range of inflammatory stimuli [38]. Previous studies reported that COX2 is dominant in the HIT β-cell line and in human islets under basal condition [39,40]. COX2 expression was induced in human islets exposed to high glucose and was elevated in islets of db/db mice, a mouse model of T2DM [12,13]. Importantly, we have recently shown that its expression is strongly upregulated in human islets exposed to the saturated FA palmitate as well as in islets of T2DM diabetic donors as compared to control individuals [41]. Differing results regarding the role of PGE2 on insulin secretion were reported. While a few studies showed that PGE2 inhibited glucose stimulated insulin secretion (GSIS) in HIT cells [42-44], others reported a lack of inhibitory effect on insulin secretion in rat [45,46] and human islets [45,47]. The molecular mechanism of PGE2 effect on β-cell dysfunction in HIT cells, was suggested to be mediated through the activation of the JNK pathway and inhibition of the Akt pathway leading to nuclear accumulation of FoxO1 and defective GSIS [44,48]. An in vitro study reported that treatment with the selective COX2 inhibitor, Celecoxib, increased insulin release in INS-1E cells [49] and in isolated mouse islets concomitant with the reduction in PGE2 production [50]. In vivo studies showed that the inhibitor, improved the impaired insulin secretion in C57BL/6 mice following glucose load [50]. Most importantly, transgenic mice overexpressing COX2 and microsomal PGE synthase 1 (mPGES-1) in β-cells, showed significant reduction in β-cell mass and severe hyperglycemia from 6 weeks of age [51]. The roles of COX2 and PGE2 in β-cell death were recently confirmed in human islets and in MIN6 β-cells [41].

PGE2 acts in an autocrine or paracrine manner and numerous physiological functions via binding to a family of four G-protein-coupled receptors (GPCRs) termed EP1, EP2, EP3, and EP4. The expression of the four subtypes of EPs varies between tissues and cell types and exhibit differences in signal transduction, tissue localization, and regulation of expression. It was suggested that activation of the EP1 receptor mediates Ca2+ mobilization. While the activation of the EP3 receptor usually inhibits adenylate cyclase and subsequently leads to a decrease in cAMP concentrations, that of EP2 and EP4 causes increases in intracellular cAMP levels [52]. Several lines of evidence suggest regulatory roles for PGE2 in islet functions through its receptors. In the HIT-T15 β-cell line, Robertson and associates [53] demonstrated the presence of PGE2 receptors in the cell membrane fraction and which were regulated by inhibitory component of adenylate cyclase. Before the PGE2 receptors subtypes were characterized, studies from the Laychock's group [54] demonstrated that Pertussis toxin (PTx) was able to reverse the PGE2-inhibition of GSIS, indicating the coupling to a PTx-sensitive G-protein (Gi). Stimulatory (Gs) and inhibitory (Gi) classes of heterotrimeric G proteins, in the

modulation of insulin secretion have been described in insulin-secreting cells [55,56]. In particular, PGE2 is suggested to activate the inhibitory class of trimeric G-proteins in insulin secreting cells [57,58]. The hetero-trimeric Gi protein α-subunit, Gαz, was also shown to modulate a signaling pathway that is inhibitory to GSIS in INS1 cells by suppressing cAMP production [59]. Islets of null mice to this subunit showed significantly higher GSIS than those of wild-type mice and higher levels of cAMP even in the absence of exogenous stimulation [60]. Moreover, it was reported that among the EPs receptor, EP3 is the one whose expression is increased in islets from diabetic BTBR mice [61] and human cadaveric T2D donors, and the EP3 antagonists improved GSIS [41,61]. Blockade of EP3 was also shown to enhance β-cell proliferation in young, but not old, mouse islets and to increase human β-cell proliferation. We more recently showed that increased EP3 expression was observed in human islets and in MIN6 β-cells exposed to palmitate [62]. Downregulation of the pathway using pharmacological tools (inhibitor or antagonist) and the RNA interference approach to either COX2 or EP3 significantly decreased the levels of palmitate-induced apoptosis. The data suggest that the involvement of EP3 in PGE2- and palmitate-induced apoptosis is highly important for better understanding the lipotoxicity mechanisms in β-cells [41].

Conclusion

Based on the described inflammatory aspects shown to be associated with T2DM disease, anti-inflammatory therapies could have a place in the development of strategies aimed at preserving adequate β-cell mass and insulin production to limit the progression of the disease.

Acknowledgement

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