

Fatty acids and glucolipotoxicity in the pathogenesis of Type 2 diabetes

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Abstract

The prevalence of Type 2 diabetes is increasing dramatically as a result of the obesity epidemic, and poses a major health and socio-economic burden. Type 2 diabetes develops in individuals who fail to compensate for insulin resistance by increasing pancreatic insulin secretion. This insulin deficiency results from pancreatic β -cell dysfunction and death. Western diets rich in saturated fats cause obesity and insulin resistance, and increase levels of circulating NEFAs [non-esterified ('free') fatty acids]. In addition, they contribute to β -cell failure in genetically predisposed individuals. NEFAs cause β -cell apoptosis and may thus contribute to progressive β -cell loss in Type 2 diabetes. The molecular pathways and regulators involved in NEFA-mediated β -cell dysfunction and apoptosis are beginning to be understood. We have identified ER (endoplasmic reticulum) stress as one of the molecular mechanisms implicated in NEFA-induced β -cell apoptosis. ER stress was also proposed as a mechanism linking high-fat-diet-induced obesity with insulin resistance. This cellular stress response may thus be a common molecular pathway for the two main causes of Type 2 diabetes, namely insulin resistance and β -cell loss. A better understanding of the molecular mechanisms contributing to pancreatic β -cell loss will pave the way for the development of novel and targeted approaches to prevent Type 2 diabetes.

Pathogenesis of Type 2 diabetes

In parallel with the increase in life expectancy of the last two centuries, lifestyles have changed considerably. Western diets are rich in energy and saturated fats [1], and physical exercise is taken infrequently. The increased lifespan and the obesity epidemic have caused a dramatic increase in the prevalence of Type 2 diabetes [2]. Diabetes poses a major and growing health and socio-economic burden on society. Obesity is nearly invariably associated with insulin resistance, but this is not sufficient to cause diabetes [3]. Diabetes develops in a subset of genetically predisposed individuals whose pancreatic insulin secretion fails to meet the insulin requirements set by the individual's insulin sensitivity [3]. In a longitudinal study of first-degree relatives of Type 2 diabetic patients, pancreatic β -cell insulin secretory function declined over time, while insulin sensitivity did not [4]. In the relatives who progressed from normal to impaired glucose tolerance, β -cell function deteriorated (36% decrease over 7 years), whereas those who did not progress had only minor changes in β -cell function (14% decrease) (Figure 1) [4]. Over the 7-year follow-up period, the first-degree relatives gained weight and increased their waist circumference. This

increase in abdominal obesity was inversely correlated with the evolution of insulin secretion and β -cell function [4]. These observations and those from other groups [5,6] raise the possibility that increased abdominal adiposity is deleterious to β -cells. The accumulation of pancreatic ectopic fat seen with high-fat feeding and obesity [7] may contribute to β -cell dysfunction [8], or it may be due to cross-talk between the visceral (and subcutaneous) fat compartments and β -cells. A model for the interplay between adipocytes and β -cells is presented in Figure 2. Similar interactions have been described between other tissues, such as muscle, and β -cells [9].

In addition to functional defects, β -cell mass seems to be decreased in Type 2 diabetes. Post-mortem studies reported a 30–60% decrease in β -cell mass in Type 2 diabetic patients [10–13] as a result of increased apoptosis [10]. It is not yet understood how obesity and gene–environment interactions contribute to β -cell dysfunction and apoptosis in Type 2 diabetes. The *FTO* gene was shown to increase diabetes risk by increasing body fatness, probably through hypothalamic effects [14]. Many of the other recently discovered Type 2 diabetes genes are expressed in β -cells [15] and may alter resistance of the β -cell to environmental stresses or insults.

Key words: apoptosis, diabetes mellitus, lipoprotein, lipotoxicity, non-esterified fatty acid, pancreatic β -cell.

Abbreviations used: ER, endoplasmic reticulum; iNOS, inducible nitric oxide synthase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NEFA, non-esterified ('free') fatty acid; NF- κ B, nuclear factor- κ B; ROS, reactive oxygen species; UPR, unfolded protein response; VLDL, very-low-density lipoprotein.

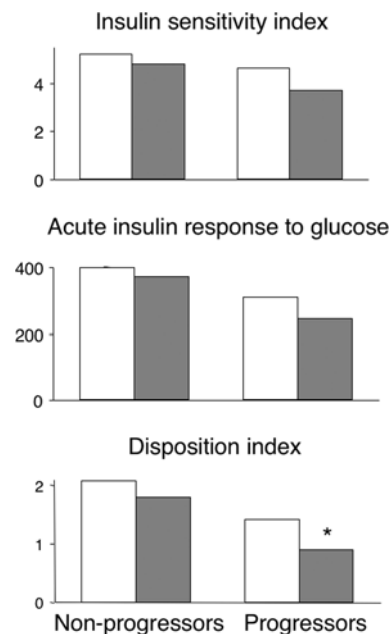
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Mechanisms of β -cell failure in Type 2 diabetes

Cross-talk between adipocytes and β -cells is mediated by NEFAs [non-esterified ('free') fatty acids] and adipocyte-secreted adipokines. High levels of circulating NEFAs (in

Figure 1 | Evolution of insulin sensitivity, insulin secretion and β -cell function in subjects with or without worsening glucose tolerance

Results are geometric means for the insulin sensitivity index ($\times 10^{-5} \text{ min}^{-1}/\text{pmol per l}$), the acute insulin secretion in response to glucose (pmol/l), and the disposition index ($\times 10^{-2} \text{ min}^{-1}$), a measure of β -cell function adjusted for the prevailing insulin sensitivity. Results are derived from intravenous glucose tolerance tests performed at initial assessment (open bars) and at follow up 7 years later (grey bars) in subjects who did (progressors) or did not progress (non-progressors) from normal to impaired glucose tolerance. * $P < 0.05$ for comparison between progressors and non-progressors at follow up. Data taken from [4].

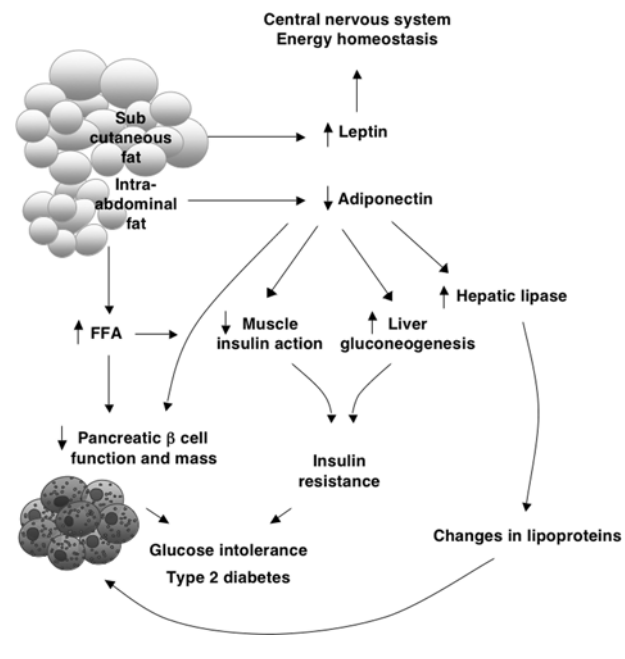


particular of saturated NEFAs) and low adiponectin levels are predictive of diabetes development [16–19]. It is conceivable that NEFAs and adipokines play a direct role in pancreatic β -cell failure in Type 2 diabetes. It remains to be investigated whether the decrease in adiponectinaemia contributes to pancreatic β -cell dysfunction. We have shown that pancreatic β -cells abundantly express adiponectin receptors [20], but the long-term effects of adiponectin on β -cells have not been elucidated.

High-fat feeding impairs β -cell compensation for insulin resistance and obesity [21,22]. Similarly, prolonged elevation of circulating NEFAs by lipid infusion impairs pancreatic β -cell function *in vivo* [23–26], particularly in individuals with a genetic predisposition to Type 2 diabetes [24]. It will be interesting to re-evaluate these findings in the light of the recently discovered diabetes-risk genes [15]. Prolonged exposure (2 days) of β -cells to high levels of NEFAs *in vitro* reduces glucose-stimulated insulin secretion, at least in part by inhibition of glucose oxidation and proinsulin transcription and translation [27–30]. In addition to β -cell dysfunction, NEFAs can induce β -cell death. The saturated

Figure 2 | Model for the effects of adipocytes on pancreatic β -cell function/mass and insulin sensitivity in the pathogenesis of Type 2 diabetes

The intra-abdominal fat compartment is the main fat depot determining plasma adiponectin levels and insulin sensitivity, while leptin levels are determined by the subcutaneous fat mass [61,62]. An increase in the intra-abdominal fat depot will decrease adiponectin and increase NEFA ('FFA') levels, which will antagonize insulin effects in liver and muscle, leading to increased gluconeogenesis and less efficient glucose uptake respectively. In the presence of increased intra-abdominal adiposity, low adiponectin levels and resultant hepatic insulin resistance, hepatic lipase activity will increase, leading to a reduction in HDL cholesterol and an increase in small dense LDL particles [63], as seen in the metabolic syndrome. The insulin resistance associated with intra-abdominal fat accumulation will also favour the development of glucose intolerance. It is, however, the worsening of pancreatic β -cell function that is the main determinant of the development of impaired glucose tolerance. This loss in β -cell function and mass may also result from exposure to NEFAs, lipoproteins and adipokines.



NEFA palmitate and, to a lesser extent, the unsaturated oleate induce apoptosis in FACS-purified primary rat β -cells and the insulin-producing cell line INS-1E [31,32]. Interestingly, the equimolar combination of oleate and palmitate is not toxic to pancreatic β -cells. Diet may therefore also have adverse effects through qualitative changes in circulating NEFAs, affecting the balance between saturated and unsaturated NEFAs. As the circulating NEFA composition is rapidly reflected in cellular NEFA content, increased supply of saturated NEFAs may lead to β -cell apoptosis *in vivo*.

β -Cell lipotoxicity might also be mediated by lipoproteins (Figure 2). Primary rat and human β -cells express the LDL (low-density lipoprotein) receptor [33], which mediates abundant LDL uptake [34]. The endocytosis of LDL can cause β -cell death as a result of ROS (reactive oxygen

species) formation [35]. Intracellular oxidative modification of the LDL lipid moiety leads to formation of reactive peroxides of cholesterol and NEFAs and propagation of complex radical reactions. β -Cell LDL lipotoxicity could be counteracted by antioxidants and by HDL (high-density lipoprotein), which can enzymatically inactivate reactive fatty acyl species that are generated during LDL oxidation. VLDL (very-low-density lipoprotein) was also protective, probably because it competes for the LDL receptor [35]. In human β -cells, LDL and VLDL receptor-mediated endocytosis contributes to progressive lipid accumulation in large lipid-storing lysosomes [34]. This lipid accumulation may also contribute to the dysfunction and death of pancreatic β -cells due to a worsening of amyloid formation in the islets of Langerhans [36–38].

Mechanisms of β -cell lipotoxicity

Studies in the Zucker diabetic fatty rat, a rodent model for leptin insensitivity and obesity-related diabetes, suggested that high circulating NEFAs induce massive triacylglycerol accumulation in pancreatic islets [39,40]. It should be noted that this triacylglycerol accumulation was observed using triacylglycerol assays only, and not by microscopy. It was suggested that the associated rise in cytoplasmic NEFA levels induced expression of nitric oxide synthase and nitric oxide-mediated β -cell apoptosis [41]. On the other hand, our own findings indicated an inverse correlation between triacylglycerol accumulation and β -cell apoptosis [31], suggesting that NEFA esterification is not necessarily deleterious. The greater toxicity of palmitate, compared with oleate, has been attributed to its less efficient esterification [31] and to the *de novo* synthesis of ceramides, as the ceramide synthetase inhibitor fumonisins partially protected islet cell apoptosis [42]. The desaturation of palmitate by stearoyl-CoA desaturase was shown to protect the MIN6 β -cell line by facilitating NEFA esterification [43]. NEFA-induced β -cell death occurred in the absence of iNOS (inducible nitric oxide synthase) mRNA expression and nitric oxide production [31,32]. Consistent with the absence of iNOS induction, we excluded a role for the transcription factor NF- κ B (nuclear factor- κ B), which is pro-apoptotic in β -cells and regulates iNOS expression [44]. Using electrophoretic mobility-shift assays, immunostaining for the p65 subunit of NF- κ B and an NF- κ B luciferase reporter, we did not observe NF- κ B activation in NEFA-exposed primary rat β -cells or INS-1E cells [32]. By the same means, we also did not observe NF- κ B activation in β -cells exposed to high glucose [45], and did not find evidence for NF- κ B activation in high-glucose-exposed human islets or in islets from Type 2 diabetic donors [46]. These findings differ from observations made in peripheral tissues, in which NEFAs, via binding to Toll-like receptors, activate NF- κ B and thereby contribute to insulin resistance [47].

The deleterious effects of NEFAs have been shown to be augmented in the presence of high glucose concentrations by some [48], but not by others [31]. Glucolipotoxicity was

attributed to glucose-mediated inhibition of mitochondrial NEFA oxidation and increased esterification [48]. Favouring mitochondrial NEFA β -oxidation has been shown to be protective, whereas inhibiting it increased lipotoxicity [48,49]. However, increasing mitochondrial oxidation and oxidative phosphorylation generates more ROS, which have also been implicated in NEFA toxicity. Pancreatic β -cells are particularly susceptible to ROS, given that they express low amounts of scavenging enzymes.

Previously, we have shown that NEFAs induce an ER (endoplasmic reticulum) stress response in β -cells [32]. This adaptive cellular response, also called the UPR (unfolded protein response) regulates protein synthesis physiologically to balance it with ER folding capacity, but, when prolonged or exaggerated, it may trigger β -cell apoptosis [50]. Several recent studies provided evidence for increased expression of ER stress markers in β -cells in pancreatic sections from Type 2 diabetic patients [51–53] and for ER expansion [54]. The importance of ER stress signalling in β -cells and its contribution to human β -cell apoptosis and diabetes is supported by the discovery of neonatal forms of human diabetes due to mutations in UPR transducers [55,56] or in the insulin gene itself [57]. In addition to its putative role in β -cell lipotoxicity, ER stress has also been proposed as one of the cellular/molecular mechanisms linking obesity with insulin resistance [58,59]. For a comprehensive review on the role of ER stress in diabetes, see [60].

Conclusions

Accumulating evidence suggests that prolonged exposure to increased lipid concentrations is detrimental to pancreatic β -cells. These lipotoxic effects result in impaired insulin secretion and β -cell apoptosis, and may contribute to the loss of β -cell function in the pathogenesis of Type 2 diabetes. Although the molecular mechanisms of lipotoxicity remain to be fully elucidated, they probably involve oxidative and ER stress. A better understanding of the molecular mechanisms contributing to pancreatic β -cell loss will pave the way for the development of novel approaches to prevent Type 2 diabetes.

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