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Review

Obesity and Type 2 diabetes: Slow down!—Can metabolic deceleration protect the islet beta cell from excess nutrient-induced damage?

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ABSTRACT

Islet β-cell dysfunction is a characteristic and the main cause of hyperglycaemia of Type 2 diabetes. Understanding the mechanisms that cause β-cell dysfunction will lead to better therapeutic outcomes for patients with Type 2 diabetes. Chronic fatty acid exposure of susceptible islet β-cells causes dysfunction and death and this is associated with increased reactive oxygen species production leading to oxidative stress and increased endoplasmic reticulum stress. We present the hypothesis that metabolic deceleration can reduce both oxidative and endoplasmic reticulum stress and lead to improved β-cell function and viability when exposed to a deleterious fat milieu. This is illustrated by the C57BL/6J mouse which is characterised by reduced insulin secretion and glucose intolerance associated with a mutation in nicotinamide nucleotide transhydrogenase (Nnt) but is resistant to obesity induced diabetes. On the other hand the DBA/2 mouse has comparatively higher insulin secretion and better glucose tolerance associated with increased Nnt activity but is susceptible to obesity-induced diabetes, possibly as a result of increased oxidative stress. We therefore suggest that in states of excess nutrient load, a reduced ability to metabolise this load may protect both the function and viability of β-cells. Strategies that reduce metabolic flux when β-cells are exposed to nutrient excess need to be considered when treating Type 2 diabetes.

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1. Introduction

Type 2 diabetes is characterised by hyperglycemia which is contributed to by both insulin resistance and islet β-cell dysfunction. While insulin resistance may be present well before the development of any clinical symptoms, it is the decline in β-cell function that is responsible for the transition of an individual from impaired glucose tolerance to diabetes (Kahn et al., 2006). This is well-demonstrated when one considers the hyperbolic relationship between β-cell function and insulin resistance in pathological conditions such as impaired glucose tolerance and Type 2 diabetes (Kahn, 2003). It is clear from Fig. 1 that individuals with Type 2

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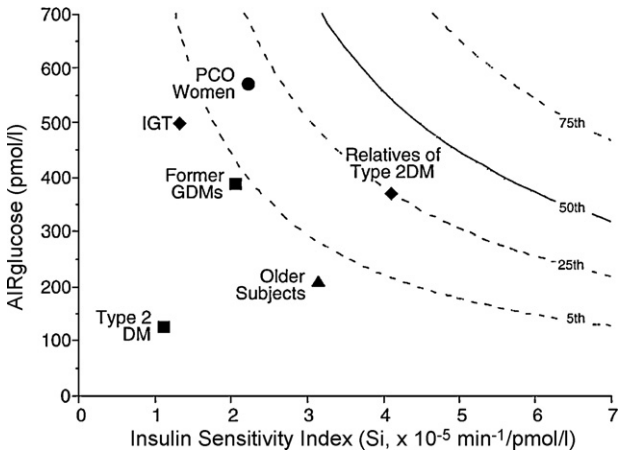

Fig. 1. The relationship between insulin sensitivity (S_I) and the first-phase insulin response (AIRglucose) showing subjects with Type 2 diabetes (Type 2 DM), healthy older subjects, women with a history of gestational diabetes (GDM), women with polycystic ovarian disease and a family history of Type 2 DM (PCO), subjects with impaired glucose tolerance (IGT) and in first-degree relatives with Type 2 DM. The reduction in β-cell function in these latter three groups is compatible with their high risk of subsequently developing Type 2 DM. It is evident that the progression from IGT to Type 2 DM is mostly due to a 4-fold reduction in AIRglucose. Adapted from Kahn (2003).

diabetes have a similar degree of insulin sensitivity to individuals with impaired glucose tolerance. However there is a much greater reduction in β-cell function in individuals with Type 2 diabetes compared with impaired glucose tolerance. Thus, understanding the mechanisms of β-cell dysfunction is critical in providing better therapeutic interventions for individuals with Type 2 diabetes.

2. Free fatty acids and insulin secretion

An important contributor to this impairment in β-cell function in a genetically permissive environment is obesity and the subsequent increase in circulating fatty acid and triglyceride (TG) levels (Prentki and Nolan, 2006). It is essential to highlight that this effect of fatty acids is time-dependent (Zraika et al., 2002). Indeed, fatty acids are required for the normal functioning of β-cells and are essential for both glucose and non-glucose induced secretion (Stein et al., 1997; Dobbins et al., 1998). The intracellular lipid signaling events that lead to this insulin secretory response have recently been reviewed by Nolan and Prentki (Prentki and Nolan, 2006; Nolan and Prentki, 2008). Furthermore, the role of fatty acids in insulin secretion has been exemplified by the use of genetically engineered mice with deletion of the fatty acid receptor GPR40 displaying an approximately 50% reduction in insulin secretion (Lan et al., 2008; Kebede et al., 2008a). Conversely, overexpression of GPR40 in islet β-cell caused an increased insulin secretory response to both glucose and fat (Nagasumi et al., 2009). While this has not been a consistent finding (Steneberg et al., 2005) it does suggest that this receptor and indeed fatty acids are required for an appropriate insulin secretory response to nutrients. Moreover, in the normal setting the islet compensates for obesity and the higher fatty acid levels by increasing islet β-cell mass and insulin secretion. Specifically, insulin hypersecretion is a characteristic of obesity, glucose intolerance and fat infusion in humans (Ferrannini et al., 1997; Weyer et al., 2000; Boden et al., 1995) and in mice (Andrikopoulos et al., 2008, 2005) and this is associated with increased β-cell mass (Andrikopoulos et al., 2005; Hull et al., 2005; Butler et al., 2003). It therefore seems that obesity and increased fatty acid and TG levels are detrimental to genetically susceptible individuals.

3. Free fatty acids and β-cell dysfunction

Chronic exposure of β-cells to fatty acids has been shown to be detrimental both *in vivo* (Sako and Grill, 1990; Paolisso et al., 1995) and *in vitro* (Zhou and Grill, 1994, 1995) in the presence of a permissive genetic setting. This is characterised by an increased basal and a reduction in stimulated insulin secretion and in some circumstances reduced insulin content (Busch et al., 2002; Wang et al., 2004; Zraika et al., 2004).

To understand the mechanisms associated with fatty acid induced β-cell dysfunction, gene expression profiling studies have been conducted in both transformed β-cell lines and in human islets using both the saturated fatty acid palmitate and the monounsaturated oleate (Busch et al., 2002; Wang et al., 2004; Xiao et al., 2001; Martinez et al., 2008; Bikopoulos et al., 2008). The results from these studies were consistent—there was an increase in genes associated with fat oxidation (including cartinitine palmitoyl transferase-1, long chain acyl CoA dehydrogenase, mitochondrial carnitine acylcarnitine translocase, and acetyl-CoA acyltransferase 2), while genes associated with glucose transport and glycolysis were reduced (including glucose transporter 2, phosphofructokinase-1, ATP-citrate lyase, mitochondrial glycerol 3-phosphate dehydrogenase).

In fact, studies in which these processes have been measured following fat exposure support the idea that fat oxidation is increased while glycolytic flux is reduced. Specifically, a 48-h intralipid infusion in rats caused a 49% inhibition in glucose-induced insulin release associated with decreased glucose oxidation which is likely dependent on increased fatty acid oxidation (Sako and Grill, 1990). Similarly, Capito et al. (1992) studied insulin secretion and islet glucose oxidation in pancreatic islets isolated from fat-fed diabetic mice. Glucose-induced insulin secretion was impaired in islets from fat-fed mice and this was associated with a 50% reduction in islet glucose oxidation. Grill and co-workers have performed studies in both human and rat pancreatic islets that showed elevated FFA levels caused increased FFA oxidation and decreased glucose oxidation via the glucose-FFA cycle. They have associated this reduction in glucose oxidation with the inhibition of pyruvate dehydrogenase (PDH) activity (Zhou and Grill, 1995; Zhou et al., 1995; Randle et al., 1994). Conversely as suggested by the gene profiling studies, cartinitine palmitoyl transferase-1 mRNA levels have been shown to be increased by fatty acids (palmitate, oleate, and linoleate) in INS-1 cells (Assimacopoulos-Jeannet et al., 1997) and in human islet cultures (Dubois et al., 2004), accompanied by increased fatty acid oxidation and a reduction in glucose oxidation (Assimacopoulos-Jeannet et al., 1997). Similarly, a 2–3-fold downregulation of acetylCoA carboxylase mRNA by prolonged FFAs resulted in elevated fatty acid oxidation (Brun et al., 1997). While this has not been a universal finding (Liang et al., 1997) it does suggest that in response to chronic fat exposure enhancement of FFA oxidation may reduce glucose oxidation and therefore insulin secretion.

The results from the expression profiling also suggested a reduction in the transcription factor PDX-1 (Busch et al., 2002; Wang et al., 2004). Several groups have investigated the effects of FFAs on insulin biosynthesis. Studies in isolated rat islets and MIN6 cells showed that a 24 h exposure to palmitate or oleate decreased preproinsulin mRNA levels in the presence of high glucose (Bollheimer et al., 1998; Ritz-Laser et al., 1999). Additionally, Jacqueminet et al. found that palmitate decreased insulin gene expression in the presence of 16.7 mmol/L glucose, partly through inhibition of insulin gene promoter activity in rat islets (Jacqueminet et al., 2000; Kelpe et al., 2003). In a recent study, Leahy and co-workers showed that the impairment in β-cell function and moderate hyperglycemia following a 60% pancreatectomy in Zucker fatty rats was associated with reduced insulin stores (Delghingaro-Augusto et al., 2009).