3. Fat and glucose homeostasis in pancreatic beta cell

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Introduction

Free fatty acids: Nutrient adjustment of insulin secretion

Pancreatic beta cells are responsive to dietary nutrients, under the modulation of neurohormonal signals, resulting in production of stimulus-secretion coupling signals that promote insulin biosynthesis and release. The main stimulus for insulin secretion is an elevation in blood glucose concentration and occurs in the presence of vital biomolecules: amino acids (such as arginine, leucine and glutamine) and fatty acids (such as octanoate (C8:0), linoleate (C18:2) (McGarry and Dobbins, 1999) and butirate (Li et al., 2013). Thus, the presence of these nutrients regulates the beta cells capacity to secrete insulin to keep glucose in the physiological range (Torres et al., 2009). Diets rich in saturated fatty acids (lard) reduce the
responsiveness of islets to glucose, whereas diets rich in monounsaturated AG (olive oil) and polyunsaturated (soybean oil) increase this response (Stein et al., 1997, Hosokawa et al., 1997). Specifically regarding the effect of fatty acids, the response appears to vary greatly, increasing insulin secretion with increasing chain length and decreasing insulin secretion with the degree of unsaturation (McGarry and Dobbins, 1999). The metabolism of linolenic acid at 3.2-8 g/day improves insulin sensitivity, increases GLUT4 (glucose transporter 4) expression in skeletal muscle, reduces IL-6 (interleukin 6) and TNFα (tumor necrosis factor α) expression, increases adiponectin levels, decreases adipose tissue mass and increases lean mass (Figueras et al., 2011, Norris et al., 2009, Whigham et al., 2007). The harm effects of the lipotoxicity can be studied using palmitate, that, when combined with hyperinsulinemia, can activate proinflammatory cytokines and chronic inflammatory state, that are typical of insulin resistance (Bunn et al., 2010). Other study showed that palmitate treatment reduced CaMKII (calcium/calmodulin dependent protein kinase II) and ERK (extracellular signal-regulated kinase) expression in mouse beta cell lineage; both molecules are involved in insulin secretion (Watson et al., 2011).

Many years ago Randle and collaborators (Randle et al., 1963) observed that dysfunctions in the carbohydrate metabolism, that were frequently observed in endocrine and nutritional disorders, like starvation, diabetes, and Cushing’s syndrome, were associated with a high concentration of fatty acids in the plasma. They observed that an increase in plasma free fat acids (FFA) diminished carbohydrate oxidation and glucose uptake in rat heart and diaphragm (Randle et al., 1963). Previous studies have shown that apolipoprotein CIII transgenic mice, that are hypertriglyceridemic, with elevated FFA induced by heparin, exhibited impaired beta cell response to glucose in the ipGTT (intraperitoneal glucose tolerance test) and reduced insulin secretion in isolated islets (Amaral et al., 2002).

Loss in the control of food intake or excessive consumption of food that are rich in fats can lead to increased circulating FFA, a condition known as hyperlipidemia, and metabolic abnormalities associated with insulin resistance in humans and animals. Chronic increase of plasma FFA promotes the lipotoxicity in beta cell. The mechanisms of lipotoxicity include accumulation of malonyl–CoA and long-chain fatty-acyl-CoA. It was established that malonyl-CoA controls long-chain fatty acid (LCFA) entry and oxidation in the mitochondria by inhibiting carnitine palmitoyltransferase-I (CPT-I), thus blocking the transport of long chain acyl-CoA into the mitochondria (Prentki et al., 2002). Increase and accumulation of long chain acyl-CoA in the cytosol promotes increase in intracellular Ca²⁺ levels and changes in the acylation state of proteins. Then,
long-chain acyl-CoA can improve the fusion of insulin secretory vesicles with the plasma membrane and insulin release (Deeney et al., 2000).

The energy sensor AMPK (AMP-activated protein kinase) which is activated by reduction in the ATP/AMP ratio, may provide a mechanism to allow beta cells to oxidize fatty acid when glucose oxidation (and ATP synthesis) is low, while allowing fatty acid and cholesterol synthesis to proceed when glucose oxidation (and ATP synthesis) is higher (Newsholme et al., 2007). Activation of AMPK favors fatty acid oxidation by decreasing malonyl-CoA as a result of ACC (acetyl-CoA carboxylase) inactivation (Hue and Taegtmeyer, 2009). AMPK can regulate beta cell function preferentially through two transcription factors that control lipogenic and glycolytic enzymes, namely sterol-regulatory-element-binding protein 1c (SREBP1c) and hepatocyte nuclear factor 4α (HNF-4α) (Newsholme et al., 2007). On the other hand, increased fatty acid oxidation and esterification accelerated ceramide synthesis, fatty acid-induced apoptosis and activation of endoplasmic reticulum stress (Lupi, and Del Prato, 2008; Newsholme et al., 2007).

An increase in ceramide and diacylglycerol (DAG) levels was observed in beta cells of diabetic rodent models. Accumulation of ceramide, a sphingolipid that can be produced from saturated fatty acids, like palmitate via the serine palmitoyl transferase (SPT) pathway, has been a concern in cell apoptosis, insulin resistance, beta cell dysfunction (Kelpe et al., 2003) and death (Shimabukuro et al., 1998). p38-MAPK kinases and JNK (c-Jun N-terminal kinase) are signaling molecules present in higher levels in damaged cell. In islets and beta cells they are correlated with excessive ceramide depots, TNF-alpha signaling and reactive oxygen species (ROS) production (Kaneto et al., 2005, Paraskevas et al., 2001). These pathways are associated with type 2 diabetes (T2D) and insulin resistance. Previous studies showed that 12(S)-HETE (hydroxyeicosatetraenoic acid, an eicosanoid and a metabolite of arachidonic acid produced by the action of the enzyme lipoxygenase) induced beta cell death in beta TC3 cells. There are evidences that JNK and p38-MAPK kinase pathways deregulations are involved in that cell damage (Chen et al., 2005). Finally, counteracting the apoptotic effects and accumulation of fat acids and their metabolic products in the beta cell is the challenge for the development of therapeutic tools and treatment of T2D and metabolic syndrome.

**Glucose effects on beta cell function**

The beneficial effects of glucose and other nutrients on beta cell function are dependent on their concentration and extent of stimulation. In mammals,
the beta cells of the pancreatic islets sense changes in the nutritional state of the organism and respond by modulating synthesis and secretion of insulin (German, 1993). Early studies reinforced the central role of glucose in beta cell metabolic sensing, showing that intermediates of glycolysis are essential for glucose sensing and the glucose-specific enzyme glucokinase to catalyze the rate-limiting step of glucose catabolism, controlling the sensitivity of the beta cell to glucose (German, 1993; Sener and Malaisse, 1992; McCornack et al., 1990).

Moreover, glucose exerts complex effects on beta cell survivor and gene expression, maintaining the cellular differentiated state by stimulating proinsulin and proteins involved in the extrusion machinery gene expression (Grimaldi et al., 1987; Schuit et al., 1988). The acute, or short-term, exposure of nutrients, within minutes to a few hours, produces changes in the expression of proteins that are mediated by a post-transcriptional mechanism, increasing or decreasing the rate of translation from pre-existing transcripts (Greenman et al., 2007). Noteworthy, it has been supported that glucose also exerts insulin gene regulation in a long-term fashion, or chronic glucose exposure (over 12h), to regulate insulin gene expression and to maintain the beta cell features (Nielsen et al., 1985). The effect of glucose exposure on isolated islets beta cells was observed in rat and human islets. In a study using rat islet beta cells it was found that chronic exposure elevated glucose levels induced a prolonged state of beta cell activation and glucose hypersensitivity, rather than glucotoxicity or glucose desensitization (Ling et al., 1996).

Experiments with human islets demonstrated that 1 week cultured islets have not shown considerable losses in the number and functions of the beta cells (Ling and Pipeleers, 1996). In that study, Ling and Pipeleers reported that after the period of 1 week culture, approximately 80% of the beta cell number present before the experiment was recovered with comparable insulin content as at start. They observed that the presence of lower (3 mmol/liter) or higher (10 and 20 mmol/liter) glucose levels were capable to lead to lower cellular insulin content. This reduction was attributed to a decreased rate of insulin production at low glucose levels, and an imbalance between the increased rates of insulin production and release at high glucose levels (Ling and Pipeleers, 1996). However, when exposed to 6 mmol/liter glucose human islets showed a potent functional responsiveness to glucose, as pointed by approximately five- to six-fold increase in proinsulin synthesis. Moreover, the authors observed that human pancreatic beta cell population is composed of cells that differ in their individual sensitivity to glucose, which determines the shape of their dose-response curves to acute glucose stimulation. Then, prolonged exposure to high glucose could result in a loss of the beta cells
heterogeneity and thus impair the dose-dependent cellular activation as a mechanism to adjust functional responses to acute variations in glucose concentrations within the physiologic range (Ling and Pipeleers, 1996). Noteworthy, glucose is one of the most important stimuli for the maintenance of beta cell mass, stimulating cellular proliferation-neogenesis, hypertrophy and inhibiting apoptosis (Bonner-Weir et al., 1989; Liu et al., 2009; Maedler et al., 2006; Van de Casteele et al., 2003). Since insulin secretion is altered in non-insulin-dependent diabetes mellitus (NIDDM) subjects, in whom the insulin response to glucose is lost (Lerner and Porte, 1972), Leahy and collaborators decided to use rat models with diminished beta cell mass to elucidate whether a reduction in beta cell mass also leads to an alteration of the glucose effect on the beta cell response to non-glucose secretagogues. In this study, rats that received streptozotocin as neonates and those with a partial pancreatectomy, have mild, nonketotic hyperglycemia, loss of glucose-stimulated insulin secretion, and preserved arginine-stimulated insulin secretion (Leahy et al., 1984). As impaired ability of glucose to potentiate nonglucose-stimulated insulin secretion have been described in human subjects with NIDDM, similarly to the observed in the partial pancreatectomy model, the authors suggest that abnormalities in insulin secretion found in NIDDM result from the chronic exposure of a reduced beta cell mass to supra-physiological glucose concentrations (Leahy et al., 1984).

Jonas and collaborators have show that the expression of glucose-induced stress genes, such as Myc and Hmox1, represent early signs of beta cell glucotoxicity (Jonas et al., 2001; Jonas et al., 2003). Those and more evidences showed that high glucose exposure of human and rat islets, and rat insulinoma cells for long periods of time affects glucose stimulated insulin secretion and leads to beta cell demise (Maedler et al., 2001).

Besides direct effects of high glucose concentrations in beta cells and islets, indirect effects resulting from insulin resistance and secreted factors, for example those released by insulin-resistant muscle, can induce beta cell proliferation (Bouzakri et al., 2011). Despite proliferation was observed in the indirect effect of hyperglycemia, noteworthy, evidences of IL-1β production by beta cells stimulated by high glucose concentrations were associated with autocrine activation of the Fas pathway and beta cell apoptosis (Maedler et al., 2001; Maedler et al., 2002; Bouzakri et al., 2011). These observations strongly suggest that glycemic fluctuations in subjects with impaired glucose tolerance may exert glucotoxic effects that, in turn, contribute to the loss of functional beta cell and, consequently, progression to T2D.
As shown, supra-physiological glucose stimulation is involved with deleterious processes in beta cell function, that, despite of deep investigations, the mechanisms and their contributions to the pathology of T2D are not fully elucidated. Thus, understanding the precise mechanisms of the glucotoxicity in the beta cell is imperative for the development of therapeutic tools and treatment of the syndrome.

**Conclusion**

In summary, our review aimed at the pancreatic beta cell, where it is becoming clear that lipid and glucose are vital molecules that have both physiological and pathophysiological roles, depending upon the circumstances. It is mainly depend on our consciousness to feed ourselves with healthy food. Unfortunately, the day-to-day forces us to a poor quality food. Nevertheless, understanding the biological mechanisms by which glucose and fatty acids change the insulin secretion and cell integrity can provide important information toward the development of novel drugs and implementation of new therapies for T2D treatment.

**References**


