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Bioenergetics and Type 2 Diabetes

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Abstract

Hyperglycemia of type 2 diabetes mellitus (T2DM) develops when pancreatic β-cells damaged by chronic exposure to elevated blood glucose and lipids (glucolipotoxicity) fail to synthesize and secrete sufficient quantities of insulin for maintaining plasma glucose level. Despite intensive studies in this field, the molecular mechanism by which fatty acids (FA) cause β-cell impairment is not well understood. It still remains unknown what are the lipid- or glucose-derived molecules directly responsible for the impairment of β-cell function? Our studies showed that in addition to impaired insulin secretion and loss of biphasicity, T2D islets exhibited altered cell bioenergetics as evidenced by decreased oxygen consumption rate as compared to those of the control islets. We also discovered that fuel overload (high level of FA and glucose leads to incomplete FA oxidation and results in accumulation of "toxic" long-chain 3-OH-fatty acids that could induce oxidative stress and disrupt mitochondrial function. Time-dependent impairments of bioenergetics due to chronic exposure to elevated blood glucose and lipids would be the consequence leading to pancreatic β-cell failure.

Keywords: Bioenergetics; Pancreatic islets; Fatty acids; Glucolipotoxicity; Type 2 diabetes; Insulin secretion

Glucolipotoxicity and Diabetes

Overconsumption of calorie rich diets increases the incidence of type 2 diabetes mellitus (T2DM) in genetically predisposed individuals, which has resulted in the worldwide epidemic of T2DM now afflicting about 350 million people. Hyperglycemia of T2DM develops when pancreatic β-cells damaged by chronic exposure to elevated blood glucose and lipids fail to synthesize and secrete sufficient quantities of insulin for maintaining plasma glucose level at a critical level of 5 mM. “Glucolipotoxicity”, the operationally defined condition resulting from caloric overload, is proposed to worsen or cause β-cell damage which eventually leads to T2D. The term "glucolipotoxicity" implies that repeated or continued exposure to high blood glucose and lipid levels are required for β-cell damage and functional dysfunction to occur. However, a compelling mechanistic molecular explanation of “glucolipotoxicity” affecting pancreatic β-cells is still lacking. In an attempt to model "glucolipotoxicity" *in vitro*, pancreatic islets are usually cultured for several days in high glucose and fatty acids (FA) concentrations. Studies have described multiple cellular processes involved in the pathogenesis of β-cell dysfunction, including changes in gene expression [1,2] intermediary metabolism [3], mitochondrial function [4], ion channel activity [5-7], insulin synthesis and exocytosis [8]. Different molecular mechanisms of FA-induced β-cell dysfunction have been proposed including accumulation of ceramide [9], apoptosis of β-cells due to oxidative [10-11] and endoplasmic reticulum (ER) stress [12,13] as well as others mechanisms [14,15]. Many of these mechanisms remain controversial. For example, the exposure of human islets for 24 hours to elevated FA and glucose conditions was found in one study to initiate apoptosis [16], but other studies have failed to find evidence of any significant apoptosis following long-term exposure. Olofsson et al. reported that inhibition of glucose-stimulated insulin secretion (GSIS) by long-term exposure to the FAs oleate and palmitate was not related to any signs of increased β-cell death, reduced insulin synthesis, impaired glucose metabolism, KATP channel regulation, or Ca^{2+} signaling. These discrepancies could be due to differences in acute or chronic islet responses [17,18]. Albumin/FA ratios in *in vitro* studies are often suboptimal (i.e., ≤3:1), glucose concentrations are often excessive to be meaningful (i.e., >16 mM), there are significant limitations inherent in animal models, and there is a lack of a clear definition of the "glucolipotoxicity" phenomenon [19]. While various molecular and cellular mechanisms of glucolipotoxicity and their roles in obesity and diabetes have been described in animal models [19-22], it is unclear whether these models recapitulate the pathogenesis of human T2D.

Pancreatic Islet Bioenergetics and Diabetes

A faulty bioenergetic process is a plausible explanation for defective insulin secretion in T2D. Normally the ATP, generated in glycolysis and oxidative phosphorylation by catabolism of glucose, amino acids, and FAs, serves as coupling factor in fuel stimulated insulin secretion [23]. The unique role of ATP as a critical messenger in the stimulus-secretion coupling was clearly shown in our previous studies with mouse, rat and human islets where oxygen consumption, glycolysis, glucose oxidation were related to insulin secretion [24]. Such measurements allowed us to calculate the ATP production rate in pancreatic β-cells as a function of the glucose concentration and insulin secretion. Our calculation was based on a reasonable assumption that islet glycogen stores are negligible [25] and that coupling of oxidative phosphorylation is intact. Despite major differences in insulin profiles (Figure 1A), the ATP-Production/Insulin-Secretion curves were similar for mouse, rat and human islets. The data for all species fitted a single sigmoidal curve (Figure 1B), indicating a clear relationship between ATP production rate and insulin secretion [24].

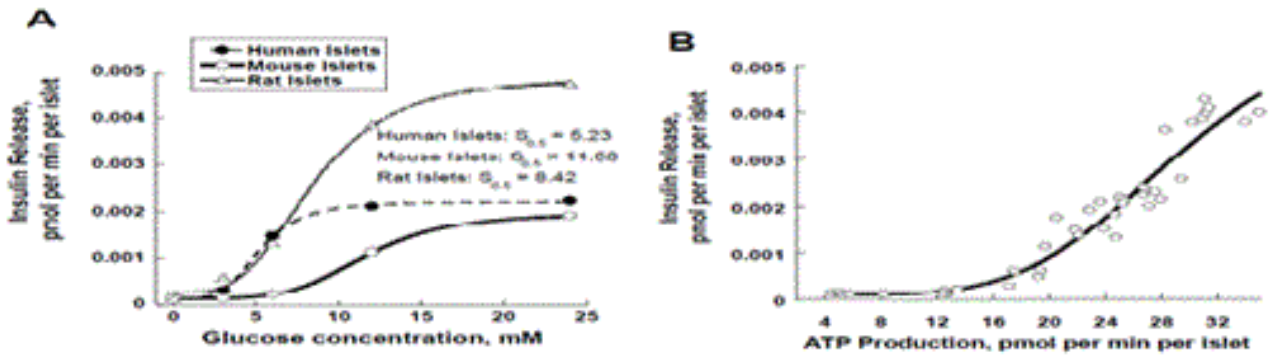

Figure 1: Fusion of mouse, rat and human islets ATP-production/insulin-secretion diagrams. Panel A: Secretion profiles of mouse, rat, and human islets as function of the glucose concentration. Panel B: Combined energy production/insulin-secretion curve with data on ATP production and insulin release from all 3 types of islets projected on 1 single continuous sigmoidal curve. ATP production was calculated based on oxygen consumption and glucose usage data.

The ATP-Production/Insulin-Secretion curve has a threshold for glucose stimulated insulin secretion at about 16 pmole/islet/min and a Hill coefficient of about 11. This data indicate a highly cooperative coupling mechanism between ATP production and insulin secretion with half-maximal effective rate (ER50) of 22 pmole/islet/min. We speculate that the "ATP-Production/Insulin-Secretion" curve has clinical significance comparable to that of the classical "Frank/Starling" curve of the heart. We also showed that ATP-Production/Insulin-Secretion curve is modified by GLP-1 and a glucokinase activator piragliatin [24]. We speculate that the "ATP-Production/Insulin-Secretion" curve is modified in T2D islets.

The literature proposes various ways by which mitochondrial energy metabolism can be altered due to fuel overload. FAs may act as uncouplers and inhibitors of mitochondrial respiration and oxidative phosphorylation [26], operating as protonophors and by inhibiting the electron transport [27-29]. In addition, FAs increase the expression of Uncoupling Protein (UCP2) in pancreatic islets [14,30-31]. FAs may inhibit complex I [32] and can also inhibit ATP and ADP exchanges [33]. FAs may promote opening of the permeability transition pore [34-37].

FAs also increase the expression of PGC-1α which may alter bioenergetics in pancreatic β-cells [38]. PGC-1α is elevated in islets from different animal models of diabetes and in human studies [38-41]. PGC-1α promotes mitochondrial biogenesis in brown tissue [42], however adenovirus-mediated expression of PGC-1α led to a marked inhibition of glucose-stimulated insulin secretion [38], by suppressing glucose oxidation or decreasing the cell's ability to drive ATP production. PGC-1α increases the transcription of UCP2 [43] by PGC-1-mediated upregulation of β-cell sterol element binding protein (SREBP) gene expression. The higher expression of UCP2 may result in a decreased efficiency of ATP production [44] by translocation of protons across the mitochondrial membrane. The latest effect should lead to changes in oxygen consumption and oxidative ATP synthesis. However, such data are limited and related to insulinoma cells [45] and only measurements of total ATP reported in islets exposed to FA [8]. Because in pancreatic islets ATP is co-secreted with insulin, it is difficult to dissociate between the effects of FA on ATP syntheses and changes of ATP content in insulin granules. In fact, the insulin content is decreased in islets chronically exposed to FFA [8].

In order to access β-cell bioenergetics and its relationship to insulin secretion, we performed two sets of experiments: (i) The bioenergetics, ionic and secretion profiles of pancreatic islets isolated from healthy and T2D organ donors were examined; (ii) Isolated normal human islets were exposed to a glucolipotoxicity condition (high glucose and FFAs) in organ culture and the bioenergetics and insulin secretion were studied in perifusion experiments. Diabetic islets exposed to a "staircase" increase in glucose concentration in the perifusion setup showed a significant decrease in insulin secretion profile (Figure 2A) and oxygen consumption (Figure 2C) as compared to those of the control islets. The baselines for both parameters are comparable. The difference in insulin secretion profile is most pronounced at the 6 and 12 mM glucose stimulation (Figure 2B) indicating decreased rates of insulin secretion and loss of biphasicity. The glucose-dependency curve of the OCR of the diabetic islets was right shifted and reduced by 50% (Figure 2C).

The uncoupler of respiration and oxidative phosphorylation FCCP (5 μM) stopped insulin secretion instantly and transiently increased respiration in control and diabetic islets to the same extent indicating a strong coupling between islets respiration and oxidative phosphorylation in both types of islets (Figure 2C). Glucose dependency of oxygen consumption (VO2) was sigmoidal for both type of islets (Figure 2D). However, islets from T2D exhibited a right shift and lower maximal stimulation of respiration (V_{max}) by glucose. The S0.5 in T2D islets rose from 4.39 ± 0.01 in control to 5.43 ± 0.13 mM (Figure 2D). Panel E of Figure 2 presents changes in intracellular [Ca^{2+}] of human islets. Low glucose (3 mM) produced a transient and high glucose (9 mM) produced a biphasic and a sustained increase in [Ca^{2+}] of control islets. Diabetic islets did not respond to 3 mM glucose and the responses to 9 mM glucose were delayed and lower than in controls.

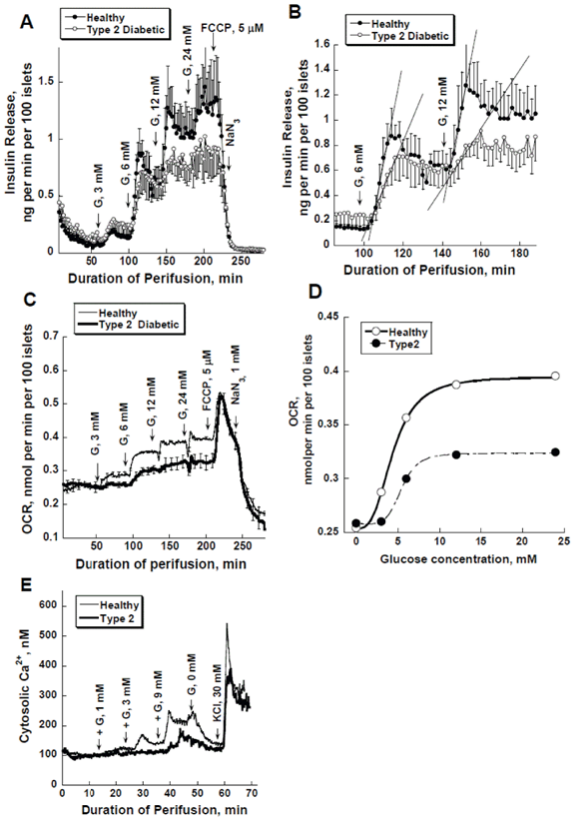

Figure 2: Impaired insulin release (A and B), oxygen consumption (C and D) and intracellular calcium (E) of isolated islets from control and type 2 diabetic organ donors. Panel A: shows the insulin release patterns with glucose stimulation using stepwise increases of glucose from zero to 3, 6, 12 and 24 mM. Panel B: magnified view of selected section (85-190 min) of the experiment presented in A to show the loss of first phase of insulin release in type 2 diabetic islets. Panel C: islet respiration during stepwise of glucose concentration followed by treatment with 5 μM of the uncoupler of Ox/Phos FCCP and 1 mM Na-azide. O2 consumption was determined with a method based on phosphorescence quenching of metalloporphyrins by oxygen [46]. Panel D: oxygen consumption rate as function of glucose concentration. Panel E: represents corresponding changes in intracellular Ca^{2+} of human islets due to stepwise increases of glucose from zero to 1, 3 and 9 mM. The Fura-2 method was employed. Typical experiments are presented (n of the series=3). Hb-A1c levels for the pancreas donors with T2DM were 9.3, 11.0 and 7.4%. Results are presented as means ± SE (SE when applicable) of 3 experiments.

This data indicates that impaired pancreatic islet β-cell bioenergetics resulting in reduced ATP production is a critical factor in the molecular pathogenesis of T2D. Importantly, the glucokinase activator piragliatin was able to correct the defect of respiration and glucose-stimulated insulin secretion [24]. In our second set of experiments, the glucolipotoxicity which is a hallmark of T2D, was mimicked *in vitro* by culturing the islets for 3 or 5 days with 0.5 mM palmitic acid or a mixture of palmitic and oleic acid at 1% albumin, and different concentrations of glucose: 10, 16 and 25, 46. As a result, chronic exposure of mouse islets to glucolipotoxic condition led to bioenergetic failure, as evidenced by decreased OCR and reduced glucose-stimulated insulin secretion. In addition, the islet ATP levels and glucose induced ATP rise were reduced as well as mitochondrial DNA and expression of mitochondrial transcription factor A (Tfam). We also discovered accumulation of carnitine esters of hydroxylated long chain FA [47], that have been shown to uncouple the respiration and oxidative phosphorylation in heart and brain mitochondria [48,49]. We propose that mitochondrial accumulation of unsaturated hydroxylated long-chain FA uncouples and ultimately inhibits pancreatic islet β-cell respiration and that this effect of the toxic FA metabolite causes a slow decline of mitochondrial ATP production resulting in bioenergetic failure as the main cause of impaired insulin secretion and reduced β-cell mass, both hallmarks of T2D.

Effects of Fatty Acids in Humans

FAs play an essential role in the function of pancreatic β-cell in humans [50]. In the fasting state, free FAs support basal insulin secretion and promote efficient nutrient-stimulated insulin secretion when the fast is terminated. Elevated plasma FFA levels lead to chronic hyperinsulinemia in insulin-resistant obese subjects [51]. Removal of this FFA stimulus by overnight reduction of plasma FFAs with nicotinic acid impairs insulin secretion stimulated by glucose [51]. Despite the evidence from *in vivo* studies, the effects of prolonged elevation of FFA on insulin secretion in humans remain controversial. Boden and colleagues demonstrated that 48-h elevation of plasma FFA potentiated glucose-stimulated insulin secretion in healthy subjects at glucose levels clamped at 8.6 mM [52] but insulin secretion was defective in T2D patients [53]. In contrast, Carpentier et al. [54] have reported that acute stimulation of insulin secretion by FA in healthy humans is lost with chronic FA elevation. This loss of hormone secretion was specific to glucose because the response to arginine was normal [55]. It is of interest that obese but not diabetic subjects are more sensitive to the inhibitory effect of lipids on glucose-stimulated insulin secretion [56]. Kashyap et al. [57] have studied both insulin secretion and insulin action in normal subjects with and without a family history of T2D during a 4-day lipid infusion. The most striking finding is that a 4-day intralipid infusion stimulated insulin secretion in normal subjects but inhibits glucose-stimulated insulin secretion in individuals with family history of T2D [57]. These data suggest that β-cell lipotoxicity may play an important role in the progression from normal glucose tolerance to overt hyperglycemia in subjects with a high risk of developing T2D. In support of this data, the antilipolytic agent acipimox improved the first phase of insulin secretion in nondiabetic patients with a family history of type 2 diabetes [58].

Conclusion

To conclude, based on the existing literature it is clear that excessive glucose and fatty acids levels have time-dependent deteriorating effects on pancreatic β-cell pathophysiology in diabetes. These effects are different at the various stages of β-cell dysfunction during development of T2D. When insulin resistance develops the β-cells mount a compensatory response that increases insulin biosynthesis, insulin secretion and β-cell mass. This compensatory β-cell response is genetically determined [57,59-60] and plays an important role in the long-term ability to maintain glucose homeostasis during insulin resistance. In individuals that genetically predisposed to diabetes, β-cell compensation eventually may become insufficient to maintain a

secretory response that meets the demand imposed by insulin resistance.

The failure of β-cells to compensate for insulin resistance is a major component of impaired glucose homeostasis and overt diabetes. This defect is the consequence of a decline of insulin response to glucose due to functional β-cell deficiency. Bioenergetics of β-cell plays an essential role in stimulus-secretion coupling and contributes to molecular pathogenesis of T2D. It is also the consequence of an inability of the endocrine pancreas to adapt the β-cell mass which eventually leads to a decrease in functional β-cells. This idea has resulted in considerable attention being paid to the development of new therapeutic strategies aimed toward preserving or regenerating functional β-cell mass [61]. GLP-1 enhances β-cell survival by activating β-cell proliferation and differentiation, and inhibiting β-cell apoptosis and thus contributing to the long-term regulation of insulin secretion by maintaining a functional β-cell mass. It should be pointed out that any intervention to improve insulin secretion should start early in the disease when the endogenous insulin secretion and presumably the number of functional β-cells has not decreased excessively [62-64].

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