Nutrigenomics, β -Cell Function and Type 2 Diabetes

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Abstract: “Nutrigenomics” refers to the ability of nutrients to alter gene expression. Insulin secreting β -cells exhibit genomic and molecular changes that enhance their function when acutely exposed to physiological concentrations of glucose and fatty acids. However, chronic exposure, such as occurs in the hyperlipidemic, hyperglycemic state of obesity/prediabetes can exert deleterious effects on β -cell function through alteration of gene expression. The genomic underpinnings of so-called glucolipotoxicity on the β -cell and its relationship to development of type 2 diabetes will be discussed in this review article. For example, free fatty acids influence β -cell gene expression by direct interaction with transcription factors such as peroxisome proliferator-activated receptors. Glucose responsive genes include the insulin gene as well as genes involved in β -cell survival and other functions. In addition, obesity is now recognized as a condition of chronic, low-level inflammation. The adipose tissue secretes multiple circulating hormones termed adipokines, and the relationship between these and the β -cell has been termed adipotoxicity. The influence of adipokines on regulation of insulin secretion and β -cell survival will be reviewed.

Received on: July 12, 2006 - Revised on: August 12, 2006 - Accepted on: October 13, 2006

Key Words: Insulin, β -cell, glucolipotoxicity, adipotoxicity, nutrigenomics.

INTRODUCTION

The World Health Organization estimates that type 2 diabetes mellitus (T2DM) afflicts ~200 million people worldwide and its prevalence will nearly double within 30 years. The burgeoning global obesity epidemic [1] virtually ensures that T2DM will become a major health issue in all countries and a major drain on health budgets. Being obese increases the risk of developing the disease by at least 10 fold [2,3]. In developing countries, transition from traditional diets to those that include frequent consumption of red meat, refined carbohydrates and saturated fats is associated with obesity [4]. It is therefore of interest to examine molecular determinants of phenomena reported at the population level.

Nutrigenomics, a relatively new scientific field, refers to the ability of nutrients to alter gene expression. Thus, dietary transition, in addition to causing obesity, may be altering fundamental functions of metabolically sensitive cells to cause diseases such as T2DM. The hormone insulin, which is secreted from pancreatic β -cells, is an important controller of both glucose and fat metabolism. Impaired regulation of its secretion is observed in both obesity and T2DM. It has been suggested that diets high in sugar and saturated fatty acids elicit a condition termed “glucolipotoxicity” [5] that negatively impacts the ability of the β -cell to adequately secrete insulin, resulting in hyperglycemia and hyperlipidemia. Many of the effects of sugars and fats are mediated through

transcriptional regulation of β -cell gene expression. Moreover, as the fat mass of obese individuals increases, the concentration of inflammatory mediators produced by adipocytes rises. These mediators, termed adipokines, may also influence insulin secretion directly and *via* genomic changes. Whether many of the adipokines are influenced by dietary factors is not well known. Improving our understanding of how nutrigenomics modifies both adipokine secretion and β -cell function may facilitate prevention or amelioration of diet-related chronic diseases, such as T2DM.

THE PANCREATIC β -CELL

Chronically elevated plasma free fatty acids (FFA) and glucose contribute to the development of insulin resistance and impaired β -cell function, which further reduce the body's ability to control plasma nutrient levels, ultimately resulting in frank T2DM. Although both insulin resistance and pancreatic β -cell dysfunction are present at diagnosis, evidence suggests that β -cell dysfunction precedes insulin resistance in the development of T2DM [6,7]. Moreover, recent evidence shows that insulin resistance alone cannot cause diabetes without β -cell failure [8]. It is thus the purpose of the initial sections of this review to discuss the role of FFA and glucose in the development of β -cell dysfunction and how this relates to the development of T2DM.

The primary role of pancreatic β -cells is to secrete insulin in response to a glucose stimulus, which is essential for maintaining plasma glucose homeostasis. β -cells must respond appropriately or T2DM will ensue. However, chronic exposure to elevated plasma glucose and/or FFA, such as is experienced with overnutrition and obesity, is deleterious to β -cell function and a major contributing factor to the devel-

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opment of T2DM [5]. The exact mechanisms underlying this impairment are currently unclear, but changes in gene expression under control of nutrient-sensitive transcription factors appear to play a major role.

GLUCOLIPOTOXICITY

There is much evidence for a causal link between elevated plasma FFA, impaired insulin secretion and T2DM. Male Zucker diabetic fatty (ZDF) rats have elevated plasma FFA prior to the development of diabetes [9] and long-term exposure (>48h) to FFA impairs glucose-stimulated insulin secretion (GSIS) both *in vitro* and *in vivo* in animals [10] and humans [11-15]. Furthermore, reducing plasma FFA improves insulin secretion in T2DM patients [11-16] and their first degree relatives [17].

Hyperglycemia is also linked to the development of β -cell dysfunction and T2DM. Chronically elevated plasma glucose can lead to β -cell exhaustion, a condition in which the β -cells are unable to produce sufficient insulin to meet demands. This can eventually progress to glucotoxicity, where irreversible damage occurs [18]. Interestingly, the combination of elevated glucose and elevated FFA appears to be more detrimental to β -cell function than either condition alone. The authors refer to a recent review by Prentki *et al.* for a detailed review of the mechanisms responsible for this synergistic effect [5], commonly referred to as glucolipotoxicity.

GLUCOLIPOTOXICITY IS TRANSCRIPTIONALLY MEDIATED

Gene expression is tightly regulated by transcription factors, some of which are activated directly or indirectly by dietary nutrients, including glucose and lipids. Subsequently, expression of enzymes involved in β -cell signalling and insulin expression may be altered. Furthermore, genes involved in cell survival, proliferation and apoptosis are regulated by nutrients through various transcription factors.

Glucose and FFA may directly or indirectly activate numerous transcription factors (Fig. 1). In general, upon activation a transcription factor translocates to the nucleus where it

promotes the transcription of its target genes. Typically, lipids and lipid metabolites activate transcription factors that upregulate genes involved in lipid metabolism while glucose and glucose metabolites promote upregulation of genes involved in carbohydrate metabolism. In the next sections, we will focus on nutrient-sensitive transcription factors regulating genes important to β -cell function. In particular, we will focus primarily on those involved in nutrient metabolism as well as those involved in insulin expression and secretion.

FFA ALTER GENE EXPRESSION IN PANCREATIC β -CELLS

Acutely, increased plasma levels of FFA potentiate GSIS [5], whereas long-term exposure increases basal insulin release [19-21] while impairing GSIS [22,23]. The increased secretion at low plasma glucose concentrations may be a compensatory mechanism to cope with increased insulin resistance [22-24]. Nevertheless, the eventual development of suppressed GSIS hinders proper regulation of plasma glucose, ultimately leading to overt T2DM. Many of the effects of FFA on pancreatic β -cell function are transcriptionally mediated (Fig. 1).

Peroxisome Proliferator-Activated Receptors

One well-studied mechanism whereby FFA control gene expression is by increasing both the expression [25] and activity (reviewed in [26]) of peroxisome proliferator-activated receptor (PPAR) transcription factors. Of these, the α and γ subtypes appear to play the most significant role in controlling β -cell function.

PPAR α overexpression and activation impairs GSIS *in vitro* [26,27]. By upregulating genes involved in lipid oxidation [28,29], PPAR α activation reduces lipid intermediates important for the potentiation of GSIS [30]. PPAR α activation also upregulates uncoupling protein 2 (UCP2) in a β -cell line [27] and in hepatocytes [31]. In β -cells, an inverse relationship between UCP2 expression and insulin release has been well documented [32-34]. Thus, activation of PPAR α in β -cells could blunt GSIS by upregulating UCP2. Furthermore, PPAR α activation inhibits amino acid catabolism in hepatocytes [35]. Due to the stimulatory role of certain

Fig. (1). Glucolipotoxicity is partly mediated by gene transcription. Glucose and FFA alter the activity of various transcription factors (see text for details) to reduce β -cell mass, insulin gene expression and insulin secretion.

amino acids such as glutamate on insulin secretion [36], inhibition of protein breakdown is another potential mechanism whereby PPAR α activation negatively affects GSIS *in vivo*.

In adipocytes, PPAR γ promotes FFA uptake and storage [29,37]. However, in β -cells, the effects of PPAR γ appear to mimic those of PPAR α . Indeed, PPAR γ overexpression and activation in isolated islets induces the expression of numerous genes involved in lipid oxidation [38] and PPAR γ overexpression suppresses GSIS *in vitro* [38,39]. The fact that PPAR γ ^{+/−} mice on a high-fat diet develop elevated intra-islet triglyceride levels [40] further supports a lipolytic effect of PPAR γ in β -cells. Furthermore, PPAR γ activation increases UCP2 expression in skeletal muscle and adipocyte cell lines [41]. If a similar situation exists in pancreatic β -cells, this could be another mechanism whereby elevated FFA impair insulin secretion. Contrary to this finding, addition of a thiazolidinedione (troglitazone), a PPAR γ agonist, directly to culture medium of rat islets improves GSIS [42]. However, this effect may be due to alternate actions of troglitazone. For example, thiazolidinediones may directly close potassium channels [43] or activate cell surface receptors in β -cell lines [44], which may account for these effects.

The widespread tissue distribution of PPARs means that direct effect of thiazolidinediones, which are commonly used in the treatment of T2DM patients, on β -cells may be overshadowed by effects on adipose or muscle *in vivo*. Thus, activation of either PPAR α or PPAR γ in a diabetic mouse model (*db/db* mice) restores β -cell function [45]. These effects on insulin secretion are likely secondary to improved peripheral insulin sensitivity and subsequent reduction of plasma hyperglycemia and hypertriglyceridemia.

Sterol Regulatory Element Binding Protein-1c

Elevated FFA also exert effects on gene expression *via* activation of the sterol regulatory element binding protein-1c (SREBP-1c) transcription factor, which controls the expression of many lipogenic genes [46]. Short-term exposure has been shown to increase both insulin expression [47] and secretion [48]. However, long-term exposure could contribute to β -cell failure by increasing triglyceride stores.

SREBP-1c upregulation is observed in islets of diabetic animal models [49–53] and adenovirus-mediated overexpression of SREBP-1c in a β -cell line results in impaired GSIS [54]. β -cell specific overexpression of SREBP-1c is also shown to impair GSIS and reduce islet mass [51]. This reduction in islet mass may be due to direct inhibition of insulin-receptor substrate 2 (IRS2) expression because SREBP-1c has been shown to bind to the IRS2 promoter and suppress IRS2 expression in rodent hepatocytes [55]. Given the important role of IRS2 in β -cell growth and survival [56], this mechanism could at least partially account for the reduction in β -cell mass typical of T2DM. In another study, transfection of a nuclear form of SREBP-1c (nSREBP-1c) in INS-1 cells downregulated glucokinase and insulin gene expression, which impaired glucose signalling and reduced insulin stores, thus impairing insulin secretion [57]. Growth arrest and apoptosis were also noted. Furthermore, SREBP-1c has been implicated in the induction of UCP2 by fatty acids [43].

It is important to note that not all FFA affect SREBP-1c equally. In fact, treatment of pancreatic β -cells with polyunsaturated fatty acids significantly decreases SREBP-1c mRNA expression and transcriptional activity [58]. This may be partially responsible for the beneficial effects of polyunsaturated fatty acids on insulin resistance and β -cell function.

FFA Downregulate Insulin Gene Expression

Chronic exposure to elevated FFA decreases β -cell insulin content by up to 85% [20]. These effects are mediated through changing the activation of numerous transcription factors. The transcription factors islet/duodenum homeobox-1 (IDX-1) and pancreas duodenum homeobox-1 (PDX-1) are important in the regulation of insulin gene expression. Mammalian homologue of avian MafA/L-Maf (MafA) binds to the insulin promoter and its overexpression enhances insulin gene expression [59]. However, recent evidence suggests that this transcription factor may primarily affect the insulin secretory process [60]. In either case, by altering the activity of these transcription factors, FFA would be expected to reduce insulin stores and, in the case of MafA, insulin exocytosis as well.

The long-chain saturated fatty acid, palmitate downregulates preproinsulin mRNA and insulin stores in the presence of high glucose but not low glucose [61], suggesting that palmitate inhibits glucose-stimulated preproinsulin gene upregulation. Of note, palmitate decreases IDX-1 mRNA and protein levels in isolated islets in the presence of 5.6mM and 30mM glucose, but not 2.8mM glucose [20]. Furthermore, palmitate treatment limits the binding of IDX-1 to regulatory elements of the insulin gene promoter [20].

Glucose-induced upregulation of PDX-1 [20] and MafA [59] expression are also blocked by palmitate. Exposure to palmitate for 24h reduces the nuclear localization of PDX-1 prior to changes in expression levels [59] by increasing ceramide synthesis [62], which then activates the c-Jun-NH(2)-terminal kinase (JNK) transcription factor [63,64]. JNK is implicated in the inhibition of both PDX-1 nuclear localization [65] and insulin gene transcription [66–68]. SREBP-1c may also be involved, based on the observations that palmitate activates SREBP-1c, which downregulates PDX-1 expression [57]. In addition, neither oleate nor linoleate affect preproinsulin expression [61], indicating that the effects are specific to saturated fatty acids.

Effects of FFA on other transcription factors regulating insulin gene expression have also been observed. High FFA and high glucose individually increase expression of cAMP response element modulator-17X (CREM-17X) and inducible cAMP early repressor-1 (ICER-1), both repressors of insulin transcription, and reduce GSIS in treated islets. Notably, decreasing the concentration of either FFA or glucose from the medium restores CREM-17X and ICER-1 expression as well as GSIS [69]. This illustrates a possible mechanism whereby glucose and FFA act synergistically to hinder β -cell function.

Peroxisome Proliferator-Activated Receptor- γ Coactivator 1 α

Peroxisome proliferator-activated receptor- γ coactivator 1 α (PGC-1 α) is not itself a transcription factor, but rather

functions to enhance the effect of transcription factors by mediating functions necessary for the transcription process. One of the transcription factors activated by PGC-1 α is PPAR γ . As noted earlier, PPAR γ activity negates GSIS [39]. However, even when acting through the same transcription factor, promoter specificity is observed [70]. That is, only certain genes regulated by a given transcription factor are upregulated. Nevertheless, many genes important for insulin secretion are regulated by PGC-1 α . For example, PGC-1 α overexpression in isolated islets induces the expression of glucose-6-phosphatase while suppressing the glucose transporter GLUT2 as well as some glycolytic enzymes resulting in suppressed insulin secretion [71].

Much evidence implicates PGC-1 α in the development of β -cell dysfunction. In islets, PGC-1 α overexpression impairs GSIS [71] and inhibition of PGC-1 α by siRNA improves FFA-induced impairment of GSIS [72]. Furthermore, PGC-1 α mRNA and protein are elevated in islets from multiple animal models of diabetes [71]. A direct connection between FFA and PGC-1 α has also been demonstrated. Exposure to elevated FFA (oleate/palmitate) for 72h increases PGC-1 α mRNA in isolated islets and a mouse β -cell line. Interestingly, exposure to hyperglycemic conditions actually reduces PGC-1 α expression [72]. This indicates that the elevated PGC-1 α mRNA and protein levels observed in islets from animal models of diabetes are due primarily to hyperlipidemia.

FFA Induce β -Cell Apoptosis

Loss of β -cell mass is characteristic of T2DM. Furthermore, exposure to elevated levels of FFA can lead to β -cell apoptosis [5]. In islets from ZDF rats ceramide synthesis is implicated as the mediator of FFA-induced apoptosis [73]. Notably, inhibition of ceramide synthesis completely blocked FFA-induced DNA laddering in this study [73]. Effects of FFA on β -cell apoptosis may also be mediated *via* the transcription factors c-fos [74-76] and nur-77 [77-79]. Interestingly, treatment of a β -cell line with physiological concentrations of palmitate or oleate increase c-fos and nur-77 mRNA expression [80].

GLUCOSE ALTERS GENE EXPRESSION IN PANCREATIC β -CELLS

Short-Term Hyperglycemic Conditions

Given the important role of glucose metabolism in regulating insulin secretion, it follows that glucose would have a major role in controlling β -cell physiology (Fig. 1). Elevated glucose induces the expression of many genes directly involved in glucose entry into β -cells and genes involved in glucose metabolism. Phosphofructokinase, glyceraldehyde-3-phosphate dehydrogenase, L-type pyruvate kinase, and GLUT2 [81] are all upregulated by acute hyperglycemic conditions. These changes increase the capacity of the β -cell to import and metabolize glucose. Furthermore, mRNA levels of K_{ATP} channels [82] are upregulated by glucose. These channels play a key metabolism-sensing role in the signaling of insulin release.

Glucose upregulates insulin biosynthesis at both the transcriptional and translational level [83-85]. Previously, it was believed that acute effects of glucose on insulin expression

were *via* increased translation and mRNA stability, but newer research shows that transcription is also enhanced acutely by glucose [85]. Effects on translation are in agreement with the finding that glucose upregulates prohormone convertase-1 [86]. Effects on transcription may be due to glucose-induced PDX-1 and MafA activation [87], two crucial transcription factors regulating insulin expression. This effect may be mediated through a reduction in AMP-activated protein kinase (AMPK) activity because antibodies against a subtype of AMPK fully mimicked the effects of glucose on preproinsulin transcription in a β -cell line [88].

In addition to effects on glucose signalling and insulin secretion, increased plasma glucose levels are associated with enhanced β -cell proliferation [89]. *In vivo* glucose infusion for 4 days increases β -cell mass by 50% [89] thereby increasing total insulin output. Glucose causes activation of the immediate-early response genes c-fos, c-jun, junB, zif-268 and nur-77 [50], which encode transcription factors involved in cell proliferation and differentiation. This effect may be secondary to glucose-induced calcium influx because these immediate-early response genes are induced by calcium agonists [90].

Glucose has also been shown to activate the mitogen-activated protein kinase pathway in [91], which has a pivotal role in regulating cell growth, proliferation and survival [92]. Furthermore, growth hormone-induced β -cell proliferation is glucose dependent [93,94], although the pathways responsible have yet to be elucidated. Because growth hormone causes insulin resistance in insulin-responsive tissues [95, 96], the observed increase in β -cell growth and proliferation is likely a compensatory mechanism to cope with elevated plasma glucose levels resulting from insulin resistance. Conversely, in conditions of low glucose exposure, both whole islets and purified β -cells undergo apoptosis in a caspase-dependent manner [97].

Long-Term Hyperglycemia is Detrimental to β -Cell Function

Despite the beneficial effects of short-term hyperglycemic conditions on β -cell function, long-term exposure to elevated glucose contributes to the development of β -cell failure and T2DM. Indeed, chronic high-glucose treatment results in impaired GSIS, lipid accumulation, and β -cell apoptosis [98,99].

Numerous genes involved in the specialized function of β -cells are downregulated in a mouse model of diabetes (*db/db*) including those involved in the maintenance of β -cell differentiation, glucose metabolism and ion channel pumps involved in the insulin secretion signalling pathway [100]. Notably, expression of ID-1, a protein capable of inhibiting insulin promoter activity [101,102], is increased while expression of PDX-1, a transcription factor regulating insulin expression, is reduced. In their study, Kjørholt *et al.* conclude that hyperglycemia, as opposed to hyperlipidemia, is primarily responsible for these effects [100] because selectively lowering plasma glucose in *db/db* mice restores GSIS and normalizes gene expression while selectively lowering plasma lipids has no effect. This indicates that hyperglycemia, independent of hyperlipidemia, is sufficient to cause β -cell dysfunction.

SREBP-1c

In isolated islets and β -cells, glucose treatment is strongly correlated with SREBP-1c activation [103] mediated through both insulin-dependent [104,105] and insulin-independent [58] mechanisms. Furthermore, insulin has been shown to upregulate SREBP-1c in other cell types [106-108]. Hence, glucose may induce SREBP-1c expression secondary to stimulation of insulin release. As noted previously, SREBP-1c is upregulated in animal models of diabetes [52,109-113] and SREBP-1c negatively affects GSIS and reduces β -cell mass [51,54]. These effects are likely attributable to induction of lipogenic pathways and subsequent β -cell lipid accumulation [54].

β -Cell Membrane Signalling

The expression of leptin and functional leptin receptors are upregulated in isolated islets and β -cells by hyperglycemic conditions [114], leading to increased sensitivity to leptin, which others have shown directly inhibits insulin biosynthesis and secretion [115,116]. In addition, obese individuals often have hyperleptinemia [117], so the effect of enhanced leptin signalling in β -cells may be further exacerbated in obese T2DM individuals.

T2DM patients have a blunted response to glucose-dependent insulinotropic peptide (GIP), an incretin capable of potentiating GSIS. This may partially result from diminished GIP receptor levels because high glucose reduces GIP receptor mRNA levels in β -cells after only 6h exposure [118]. Although β -cells actually have increased function at this time point, this finding indicates that the manifestations of glucotoxicity may actually begin during acute hyperglycemia.

PROTEIN ALTERS GENE EXPRESSION IN PANCREATIC β -CELLS

Rats fed a low-protein diet have impaired GSIS [119-121]. This may result from impaired glucose metabolism [122] and/or reduced GLUT2 expression [122,123], impaired calcium fluxing [124], and reduced expression of protein kinases involved in the insulin secretion process [119,120]. A reduction in β -cell mass is also observed following a low-protein diet [125,126], potentially due to reduced expression of the transcription factors extracellular signal-regulated kinase 1 and 2 [123], which have important roles in regulating cell growth and proliferation. It should be noted, however, that these effects are accompanied by increased insulin sensitivity in peripheral tissues [126-132]. Thus, diminished GSIS may be a compensatory mechanism for reduced insulin requirement.

Islets from rats fed isocaloric low-protein diets for 15 days show a diminished response to forskolin-induced insulin release [121], indicating reduced signalling *via* the cyclic AMP/protein kinase A (cAMP/PKA) pathway. This would reduce the potentiating effects of certain incretins, such as glucagon, glucagon-like peptide-1 and GIP on GSIS. It is likely that reduced PKA is primarily responsible for this effect because the expression of a PKA subtype is downregulated following a low-protein diet [121]. Furthermore, protein kinase C displays reduced expression in response to a

low-protein diet [119], and certain isoforms are implicated in the potentiation of GSIS [133].

One major concern with attributing the effects from protein-altered diet studies is that low-protein diets are inevitably higher in the other macronutrients, typically carbohydrates. However, while high-carbohydrate diets acutely upregulate PDX-1, insulin, and GLUT2, high protein diets have the opposite effect [123].

ADIPOKINES, OBESITY AND TYPE 2 DIABETES

The Endocrine Adipose Tissue

Storage and release of fatty acids and thermal insulation were formerly recognized as the main functions of adipose tissue (AT). However, AT is now considered to be a major secretory organ responsible not only for releasing FFA but also cholesterol ester transfer protein, prostanoids and steroid hormones [134,135]. Additionally, AT secretes diverse chemical mediators (adipokines) into the surrounding environment, allowing us to define AT as an endocrine organ. The total amount of adipokines strongly affects the body function due to the general distribution by systemic regulation. Multiple functions and increased number of adipokines have been described lately [136,137]. Among the more important are those related to insulin resistance (leptin, adiponectin, resistin, and visfatin) and inflammation, including the interleukins (IL-1- β , IL-6, IL-8, IL-10), tumor necrosis factor- α (TNF- α), and transforming growth factor- β (TGF- β), acute phase response proteins serum amyloid A, plasminogen stimulating protein-1 and acylation stimulating protein.

Recent research shows that obesity is characterized by chronic mild inflammation. The main basis of this view is that there are increased circulating concentrations of several inflammatory markers such as C-reactive protein, TNF- α , IL-6, IL-8, and others [138,139]. The inflammatory state of obesity and particularly the production of inflammatory adipokines are now considered important factors in the development of the diseases associated with high body mass index such as T2DM [140].

Hypoxia may be a critical factor governing development of the chronic inflammatory state, the underlying proposition being that the formation of new AT mass expanding distant from the vasculature may become relatively hypoxic [136]. AT is poorly vascularized and the proportion of blood flow going to the tissue is decreased in obesity. Initiation of hypoxia may lead to stimulation of the release of inflammatory cytokines, chemokines and angiogenic factors [141]. The inflammatory process is a multiple cell-mediator interaction that is highly regulated normally playing an important role in defense against infections and repair of damaged tissue. The deregulation of inflammation may result in a chronic inflammatory condition and substantial damage in involved tissues [142,143].

ADIPOKINES

The expression profile of adipokines has been determined in specific regions of fat tissue, for instance TNF- α , IL-6, visfatin and resistin are predominantly expressed in almost all human AT due to the presence of macrophages [144,145]. This adipokine profile is different in animal models of obe-

sity. Leptin and TNF- α are highly expressed in perigonadal fat tissue as compared with subcutaneous fat tissue in hyperglycemic and hyperinsulinemic obese mice. However, high fat diet and severe obesity modifies the distribution of proinflammatory adipokines [146]. Adiponectin and leptin, among others, are expressed in all fat deposits examined in dogs [147]. Differences in regional adipokine expression identified in obese animal models and obese humans give rise to questions about how to best measure and interpret the role of AT adipokine expression and activity in the pathogenesis of obesity and its related diseases.

NUTRIENT REGULATION OF ADIPOKINE EXPRESSION

Changes in gene expression caused by the ingestion of different kinds of nutrients and food have been intensively researched in recent years but few reports focus on the expression of adipokines. Following is a synopsis of the effects of nutrients on adipokines relevant to obesity, β -cell function and T2DM. The major concepts are summarized in Fig. (2). The mainly deleterious effects of adipokines on β -cell function have been referred as “adipotoxicity” [148,149].

Tumor Necrosis Factor- α

A major step forward in the recognition of the role of AT in obesity occurred with the discovery that the pro-inflammatory cytokine TNF- α is synthesized and released by adipocytes [150]. TNF- α expression increases in obesity and is implicated in impaired insulin signalling, reduced adi-

ponectin synthesis and increased release of FFA by adipocytes [151]. In addition, TNF- α not only acts as an inflammatory cytokine but also as a transcriptional regulator of some adipokines, such as leptin [152] and adiponectin, by the JNK signaling pathway [153]. Furthermore TNF- α exerts an important role in adipocyte differentiation, eliciting a characteristic adipokine mRNA expression profile in mature adipocytes of IL-6, metallothionein, monocyte chemoattractant protein-1, and nerve growth factor [154,155].

TNF- α induces β -cell dysfunction and increases sensitivity of β -cells to glucolipotoxicity *via* increased accumulation of nitric oxide (NO), leading to β -cell apoptosis and reduced GSIS [156,157]. In addition, TNF- α and interferon- γ exert synergistic pathologic effects on β -cells by activating the transcription factor nuclear factor kappa-B and generation of inducible NO synthase [158,159] to induce apoptosis.

In target tissues of insulin, down-regulation of TNF- α expression is a potential target to reduce insulin resistance. Clinical studies in human patients show that oral (n-3) fatty acid supplementation [160] as well as concomitant fish oil and vitamin E reduced TNF- α plasma levels [161]. However, infusion of TNF- α neutralizing antibodies to T2DM patients did not reduce glucose levels or improve insulin sensitivity [162].

Adiponectin

The adiponectin gene is highly expressed in adipocytes and released into the general circulation. Adiponectin pro-

Fig. (2). Possible linkages between nutrition, adipokines and other factors contributing to development of obesity and T2DM. Several adipokines may have a role in the development of β -cell dysfunction and apoptosis, leading subsequently to T2DM.

duces an increase in fatty acid oxidation by AMPK activation in muscle [163] and liver cells [164], and reduces glucose synthesis and increases glucose uptake [165]. These actions are mediated by binding to adipokine receptors, which are highly expressed in muscle and liver. Data suggest that individuals with high adiponectin serum concentrations are less susceptible to developing T2DM than individuals with low concentrations [166]. Adiponectin serum levels are significantly reduced in obesity, perhaps because TNF- α and IL-6 inhibit adiponectin expression and secretion in AT [167]. Therefore, insulin resistance may be due to attenuated adiponectin release mediated by TNF- α and IL-6.

Adiponectin effects on β -cells have not been completely defined. However, adiponectin protects insulinoma cells against cytokine and FFA-induced apoptosis [168] and increases GSIS in isolated islets from mice fed with high fat diet [169].

Although the specific control mechanisms of adiponectin gene expression have not been completely elucidated, weight loss, low calorie diet, and thiazolidinedione treatment all increase adiponectin expression and plasma levels [170-172]. Circulating adiponectin concentrations are decreased by ingestion of a single high-fat meal in both normal and T2DM subjects [173]. Conversely, healthy food intake (e.g., diets high in fresh fruit and low in regular soft drinks and red meat) is associated with high adiponectin levels and substantially reduced incidence of T2DM [174]. Also, increased plasma adiponectin levels and weight loss are observed in diabetic [175] and obese [176] women after cereal fiber intake. Similar results are observed in fatty rats fed with dried plums [177]. Rats fed long-term with a sucrose-rich diet become overweight and have decreased plasma leptin and adiponectin levels without changes in gene expression. Dyslipidemia, increased adiposity, and insulin resistance accompany these modifications. Effects of sucrose-rich diet are reversed by feeding fish oil for 2 months [178]. Combined, these reports suggest that nutrients alter expression of adiponectin gene but the transcriptional regulators have yet to be identified. Recent studies have begun to characterize promoter regions in the adiponectin gene [179-181], which will allow delineation of nutrient effects on its expression.

Leptin

Leptin is a hormone secreted by mature adipocytes that binds to its receptor in the hypothalamus where it stimulates release of anorexic factors such as proopiomelanocortin and cocaine-amphetamine-regulated transcripts. Mutations in the leptin gene receptors result in obesity as observed in several animal models: *ob/ob* mice [182], *db/db* mice [183] and *fa/fa* rats [184]. Rare leptin gene mutations in obese humans have been observed, where recombinant leptin treatment normalizes the body weight [185].

Leptin expression and secretion is induced by several hormones, for example, insulin, TNF- α , glucocorticoids, and estrogens. β -adrenergic activity, androgens, and PPAR- γ inhibit leptin synthesis. The presence of PPAR- γ on the leptin promoter suggests that its expression may be regulated by fatty acids. Feeding a high fat meal decreases plasma leptin independent of fatty acid saturation [186]. Conversely, infusion of FFA in mice elevated plasma leptin, an effect

attributed to direct stimulation of adipocytes by insulin [187]. Likewise, effects of glucose on leptin expression were accounted for by insulin activity [188].

The “adipoinular axis” term is used to describe the relationship between leptin and insulin. Insulin enhances leptin secretion from AT and leptin down regulates insulin secretion. Under these circumstances leptin is an important regulator of insulin secretion [189]. Leptin reduces insulin secretion by several mechanisms including inhibition of the insulin gene promoter [190,191] by increasing the expression of suppressor of cytokine signalling 3, which inhibit janus kinase-signal transducer and activator of transcription (JAK-STAT) signal transduction and transcriptional activity [192]. In addition, acute hyperpolarization of the β -cell membrane is observed [193,194]. However, in obesity conditions, hyperinsulinemia over stimulates AT to synthesize leptin. High levels of leptin fail to reduce insulin synthesis in β -cells (leptin resistance) making them more susceptible to developing T2DM [189]. On the other hand, in ZDF rats, which have a mutated leptin receptor, leptin over-expression improves GSIS by reducing SREBP-1c activity to promote lipolysis and decrease intracellular triglyceride [195].

Resistin

Resistin is a dimeric protein first described in asthmatic bronchoalveolar fluid and also known as FIZZ1. Two resistin homologues have been found: FIZZ2 in epithelial cells at the base of intestinal crypts and FIZZ3 in adipocytes [196,197]. Genetic variations in the resistin gene are related to insulin resistance and diabetes in humans [198-200]. However, low mRNA expression of resistin in human adipocytes is not related to insulin resistance and obesity [201,202] making the role of resistin in these metabolic disorders controversial. Transcriptional regulation of resistin expression by nutrients includes inhibitory effects of vitamin A/retinoic acid, possibly by reducing CCAAT enhancer binding protein- α activity [203]. In addition, the resistin gene promoter encodes several peroxisome proliferator response elements [201] and is up-regulated by PPAR- α agonists [204]. However, FFA does not affect resistin expression in cultured adipocytes [205].

High concentrations of resistin produce hyperglycemia, hyperinsulinemia, and impair the hypoglycemic response to insulin in obese animal models [206,207]. Similar results are observed in mice after recombinant resistin administration. These resistin effects are reduced after antiresistin antibody treatment in obese mice [198,208]. It is suggested that resistin inhibits the AMPK pathway, which has an important role in regulation of β -oxidation and gluconeogenesis [209].

Visfatin

Visfatin is a protein secreted mainly by AT [210] and released to the general circulation to reach potential target organs including liver and muscle. High concentrations of visfatin are observed in obese humans. Proinflammatory cytokines such as IL-1, IL-6, and TNF- α regulate the expression of visfatin gene [211] and a hypoxia response element has been identified in the visfatin promoter [212]. FFA applied directly to adipocytes enhances visfatin gene expression [213].

Visfatin is implicated in adipocyte differentiation [214] and plays an important role in fat deposition and hypoglycemia due to its insulin-like function. Visfatin stimulates tyrosine phosphorylation of the insulin receptor and IRS1/2, and activation of protein kinase B/Akt [215] in target tissues such as muscle. The role of visfatin in obesity and T2DM needs to be clarified. High concentrations of visfatin may be a response from AT to insulin resistance or could contribute to the deleterious effects of the mild chronic inflammation in obesity [216]. Although elevated visfatin is associated with deterioration of β -cell function in T2DM patients, the nature of the relationship is unresolved [217] and it is unclear whether visfatin directly affects insulin secretion.

CONCLUSION

The increase in obesity and T2DM prevalence globally will only be mitigated by a substantive public health initiative. Research on both the deleterious and beneficial effects of various dietary components and natural health products is required to substantiate public health strategies. The molecular basis for the effects of nutrients, i.e., nutrigenomics is an expanding field that will play a major role in elucidating how nutrients contribute to the pathogenesis of obesity and T2DM.

β -cell secretory defects and loss through apoptosis are two main pancreatic pathologies in T2DM. Much has been learned about the direct effects of nutrients, particularly glucose and FFA, on β -cell gene expression and function but less is known about mitigating the deleterious, chronic effects of glucolipotoxicity. Moreover, although the ability of cytokines produced in AT, including TNF- α , to induce β -cell apoptosis is known, the potential role of circulating novel adipokines such as adiponectin, visfatin and resistin needs to be elucidated.

ACKNOWLEDGEMENTS

Work done in the author's laboratory is supported by the Canadian Institutes of Health Research (MOP 43978). We thank Dr. Zahra Fatehi-Hassanabad and Dr. Blanca Esparza for helpful discussions.

ABBREVIATIONS

AMPK	=	AMP-activated protein kinase
AT	=	Adipose tissue
CREM-17X	=	cAMP responsive element modulator-17X
ERK1/2	=	Extracellular Signal-Regulated Kinase 1 and 2
FFA	=	Free fatty acid
GIP	=	Gastric inhibitory peptide
GLUT	=	Glucose transporter
GSIS	=	Glucose-stimulated insulin secretion
ICER-1	=	Inducible cAMP early repressor-1
ID-1	=	Inhibitor of DNA binding-1
IDX-1	=	Islet/duodenum homeobox-1
IL	=	Interleukin

IRS	=	Insulin receptor substrate
JAK-STAT	=	Janus kinase-signal transducer and activator of transcription
JNK	=	c-Jun-NH(2)-terminal kinase
MafA	=	Mammalian homologue of avian MafA/L-Maf
PDX-1	=	Pancreas duodenum homeobox-1
PGC-1 α	=	PPAR γ coactivator-1
PKA	=	Protein kinase A
PPAR	=	Peroxisome proliferator-activated receptor
SREBP-1c	=	Sterol response element binding protein-1c
T2DM	=	Type 2 diabetes mellitus
TNF	=	Tumor necrosis factor
TZD	=	Thiazolidinedione
UCP	=	Uncoupling protein
ZDF	=	Zucker diabetic fatty

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