Perspectives in Diabetes

Are the β-Cell Signaling Molecules Malonyl-CoA and Cytosolic Long-Chain Acyl-CoA Implicated in Multiple Tissue Defects of Obesity and NIDDM?

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Widely held theories of the pathogenesis of obesity-associated NIDDM have implicated apparently incompatible events as seminal: 1) insulin resistance in muscle, 2) abnormal secretion of insulin, and 3) increases in intra-abdominal fat. Altered circulating or tissue lipids are characteristic features of obesity and NIDDM. The etiology of these defects is not known. In this perspective, we propose that the same metabolic events, elevated malonyl-CoA and long-chain acyl-CoA (LC-CoA), in various tissues mediate, in part, the pleiotropic alterations characteristic of obesity and NIDDM. We review the evidence in support of the emerging concept that malonyl-CoA and LC-CoA act as metabolic coupling factors in β-cell signal transduction, linking fuel metabolism to insulin secretion. We suggest that acetyl-CoA carboxylase, which synthesizes malonyl-CoA, a "signal of plenty," and carnitine palmitoyl transferase 1, which is regulated by it, may perform as fuel sensors in the β-cell, integrating the concentrations of all circulating fuel stimuli in the β-cell as well as in muscle, liver, and adipose tissue. The target effectors of LC-CoA may include protein kinase C subtypes, complex lipid formation, genes encoding metabolic enzymes or transduction factors, and protein acylation. We support the concept that only under conditions in which both glucose and lipids are plentiful will the metabolic abnormality, which may be termed glucolipoxia, become apparent. If our hypothesis is correct that common signaling abnormalities in the metabolism of malonyl-CoA and LC-CoA contribute to altered insulin release and sensitivity, it offers a novel explanation for the presence of variable combinations of these defects in individuals with differing genetic backgrounds and for the fact that it has been difficult to determine whether one or the other is the primary event. Diabetes 45:273-283, 1996

A PROBLEM AND A CONTROVERSY

A problem of major significance. NIDDM and obesity are common diseases with high morbidity in affluent societies. They share two major features. First, insulin resistance is characteristic of almost all individuals with obesity, including those with NIDDM. In most of these subjects, insulin levels are either normal or greatly elevated compared with those in lean control subjects. Note that a minority of lean subjects with NIDDM do not exhibit early insulin resistance and may represent a different genetic abnormality (1-3). Obesity, with accompanying insulin resistance, is found in people at increased risk for developing NIDDM, suggesting that NIDDM and obesity may share common pathological factors and early events in their development. Second, obesity and NIDDM are often associated with hypertriglyceridemia, increased tissue triglycerides, or elevated circulating levels of free fatty acids (FFAs) (4-6). NIDDM may therefore be considered a lipid disorder as well as a disease of glucose tolerance (6,7), and it is possible that increased lipid levels explain, at least in part, not only insulin resistance but also β-cell dysfunction in NIDDM.

The main focus of this review is on the role played by lipids in the regulation of insulin secretion, with a subsidiary focus on the role of lipids in insulin action and on the pituitary adrenal axis. We will present evidence supporting a role for metabolic signals derived from glucose and fatty acids in modulating these processes. Finally, these concepts will be integrated into a hypothesis in which a common etiology is expected to have tissue-specific consequences. An unsettled controversy. Widely held theories of the pathogenesis of the insulin resistance syndrome (and secondarily NIDDM) have implicated apparently incompatible events as seminal: 1) hypersecretion of insulin by the pancreatic β-cell, 2) increases in intra-abdominal fat and consequent to this, local release of FFAs, and 3) insulin resistance in muscle. If our hypothesis is correct, that common signaling abnormalities produce all of these changes, it offers a novel explanation both for the presence of all these alterations together in some individuals and for the fact that it has been difficult to determine whether one or the other is the primary event. Indeed, individuals may exhibit dissimilar sensitivity to the same metabolic signaling alterations in different tissues.

It has been proposed that in obesity and in NIDDM with accompanying obesity, muscle becomes resistant before adipose tissue and probably before liver (8). There is some
disagreement about whether adipose tissue ever becomes resistant in NIDDM (9). Delayed insulin resistance in adipose tissue could be a key to the development of obesity and NIDDM because the fat cell may store fat and generate signals, as a consequence of its excess stores, that alter fuel handling and signal generation by other cell types. We propose that a cellular metabolite derived from dietary or stored excess lipid provides a unique signal to susceptible tissues. A prime candidate for this signal molecule is cytosolic long-chain acyl-CoA (LC-CoA) or one of its immediate products, such as phosphatidic acid (PA) or diacylglycerol (DAG). Cytosolic LC-CoA esters presumably increase in the presence of high-saturated fat, high-sucrose diets because glucose forms malonyl-CoA, which inhibits the mitochondrial oxidation of cytosolic LC-CoA formed from the fat (10,11).

A key question is whether signaling abnormalities occur in β-cells, insulin target tissues, and possibly the hypothalamo-pituitary adrenal (HPA) axis concurrently or sequentially in response to increased circulating lipids or whether FFAs may produce insulin resistance and obesity even when they do not produce hyperinsulinemia or altered patterns of insulin secretion. It should be noted that the altered responsiveness to FFAs refers mainly to studies in which either palmitate or oleate, the most prevalent FFAs in the circulation and in the LC-CoA pools (12,13), were used. The influence of polyunsaturated, trans, or other less prevalent fatty acids has not been extensively evaluated and may differ from the more common FFAs (14,15). Animal studies have documented a strong correlation between LC-CoA content in liver and skeletal muscle and plasma insulin levels in rats fed a diet high in saturated fat (16). In the same study, a positive correlation between tissue LC-CoA content and body weight or weight gain was also found (16). Also noteworthy is the observation that exposure of pancreatic islets to palmitate or oleate for several days leads to basal hypersecretion of insulin (17) with diminished glucose responsiveness (18) and that FFA-treated β-cells have increased LC-CoA content (19). Thus, we will present evidence to support the concept that altered cell content of LC-CoA (Fig. 1) is an early common feature shared by several cell types exposed to elevated FFAs.

MECHANISM OF NUTRIENT REGULATION OF INSULIN RELEASE
Role of metabolism in β-cell stimulus-secretion coupling. In seeking to identify defects in the β-cell, it is necessary to focus on glucose metabolism because nonfuel secretagogue-induced secretion either is not affected or is less affected than glucose-induced secretion in NIDDM (20) or rat models of NIDDM (21). The molecular mechanism by which glucose and other fuels stimulate insulin release is still uncertain, β-cells possess a unique stimulus-response coupling system that requires that the fuel stimulus be metabolized to initiate membrane electrical events and then secretion (22,23). Only fuels that stimulate insulin secretion stimulate electrical change. In addition, inhibition of fuel metabolism inhibits both secretion and electrical activity (22,24). Metabolism of glucose generates signals that modulate the activities of enzymes and ion channels to provoke modifications in the levels of intracellular messengers (25-28). These metabolic coupling factors are probably high-energy intermediates and may include adenine nucleotides (29-31), pyridine nucleotides (32,33), and CoA derivatives (19,28,94). Exposure of pancreatic β-cells to stimulatory concentrations of glucose decreases the activity of the ATP-sensitive K⁺ (KATP) channels (23,35). This results in depolarization of the membrane potential, Ca²⁺-dependent bursting electrical activity (36), and insulin secretion. We have recently suggested that K⁺-channel regulation is not by ATP alone (present at millimolar concentrations, relative to a half-maximal inhibitory concentration of ATP of 12 μmol/l) but that a decrease in free Mg-ADP, which acts as an activator at a separate site, plays a major role in regulation of the channel (37). It is clear that fuel-induced secretion, like other secretory processes, is mediated in part by elevations in cytosolic free Ca²⁺ (25).

The pattern, rather than the quantity, of insulin secretion may also be important in regulating blood glucose levels (38). Oscillatory insulin secretion is observed in humans and animals in vivo and from the perfused pancreas and perfused islets in vitro (31,39-42). The physiological importance of the oscillatory mode is suggested by its loss in patients with NIDDM and their near relatives (40,43-45). We have suggested (30,31) (Fig. 2) that oscillations characterize most steps of stimulus-secretion coupling, starting with oscillatory glucose metabolism and associated rises in the ATP/ADP ratio, causing closure of KATP channels and thus leading to the oscillations in membrane potential and intracellular free Ca²⁺ that have been observed in glucose-stimulated single β-cells and islets. Regulation by oscillations has the advantage of an improved signal-to-noise ratio (large variations in effectors occur between peaks and troughs), economy of energy expenditure (excess ATP is only produced transiently), and greater sensitivity to changes in external signal (the oscillations in coupling factors and insulin release are rapidly turned on or off when fuel use changes). Nevertheless, the absolute peak and trough values reached, not just the oscillatory behavior, may also play an important role in generating appropriate signals.

![Cytosolic LC-CoA Production](image)
Although an increase in cytosolic free Ca\(^{2+}\) is necessary for insulin secretion (46,47), it is not sufficient, because the concentration dependence of glucose-induced insulin release remains intact under conditions in which Ca\(^{2+}\) is maximally elevated (in the presence of 30 mmol/l K\(^+\)) and when K\(_{\text{ATP}}\) channels are bypassed (in the presence of diazoxide) (46,47). Thus, the concept is emerging that glucose also controls insulin release independently from its action on K\(_{\text{ATP}}\) channels (48–50) and that Ca\(^{2+}\) plays only a permissive role in glucose-induced insulin secretion (51,52). Thus, metabolic coupling factors besides adenine nucleotides are likely to play an essential signaling role to trigger insulin secretion (53,54).

**Lipid metabolism in the β-cell provides a central role for cytosolic LC-CoA.** Glucose-induced insulin secretion is associated with inhibition of FFA oxidation, increased FFA esterification, and complex lipid formation by pancreatic β-cells (34,55–57). Significant increases occur in the total mass of DAG (58), triglyceride (56), and PA (26,59) in glucose-stimulated β-cells. Indeed, islets contain high levels of triglyceride similar to liver (34,60). Glucose and endogenous LC-CoA are the main sources of glycerol and lipid acyl groups for LC-CoA formation or complex lipid synthesis (Fig. 1).

Methods are not yet available to measure cytosolic levels of LC-CoA esters, however, such measurements are likely to be difficult because the CoA pool is localized mainly in the mitochondria and LC-CoA esters readily bind to proteins and phospholipids. Evidence that a rise in cytosolic LC-CoA plays a role in signaling is indirect and based on the following findings. First, addition of FFA increases total LC-CoA (19). Second, although glucose acutely lowers total LC-CoA, because of inhibition of mitochondrial levels as FFA oxidation is inhibited (19,62), it must increase the cytosolic pool because complex lipid synthesis, which is regulated by LC-CoA availability, is stimulated (19). Third, 30 min stimulation of islets with glucose increases total LC-CoA (62). Fourth, pharmacological inhibition of mitochondrial LC-CoA oxidation, which should elevate cytosolic LC-CoA, enhances glucose-induced secretion (57,63). Fifth, inhibition of malonyl-CoA production from glucose, which should prevent the rise in cytosolic LC-CoA, blocks glucose-induced insulin secretion (63).

Fatty acids appear to be a major source of energy for islets (60). Glucose stimulation of islets diminishes fatty acid oxidation and increases total respiration (56,57,64). Thus, one of the metabolic events induced by glucose stimulation appears to be a relative shift from fatty acids to glucose as an oxidative fuel. In other tissues, this occurs through glucose conversion to the “switch” compound, malonyl-CoA, which in turn inhibits carnitine palmitoyl transferase 1 (CPT-1) and thus blocks LC-CoA transport into the mitochondria where LC-CoA esters are oxidized (Fig. 1) (65,66). We have demonstrated that glucose causes marked alterations in the acyl-CoA profile of clonal pancreatic β-cells, with the largest (fivefold) and earliest (by 2 min) change occurring in malonyl-CoA (19,34). However, there is not a good correlation between secretion and malonyl-CoA levels, but there is between secretion and LC-CoA levels (19). Inhibition of mitochondrial FFA (LC-CoA) oxidation presumably causes an elevation of LC-CoA in the cytosol and could explain the observed increases in de novo synthesis of DAG and phospholipids in islet tissue (34,56,58,67–70).

Only nutrients or combinations of nutrients that can both increase the production of energy, through their conversion to acetyl-CoA, and provide anaplerotic input, i.e., directly increase the level of citric acid cycle intermediates, cause insulin release (Figs. 1 and 2) (19,71). Anaplerosis is essential for the production of the malonyl-CoA needed to elevate cytosolic LC-CoA because efflux of the mitochondrial precursor, citrate, will not occur unless there has been compensatory input into the citric acid cycle. In this light, it should be noted that pyruvate is decarboxylated by pyruvate dehydrogenase and carbonylated by pyruvate carboxylase at high rates in pancreatic islets (72).

The steps involved in the glucose-induced increase in LC-CoA are shown in Fig. 1. In this schema, possible sites that could cause defective LC-CoA production include: 1) glucose conversion to pyruvate, 2) pyruvate conversion to acetyl-CoA via pyruvate dehydrogenase, 3) pyruvate conversion to oxaloacetate via pyruvate carboxylase, 4) citrate production via citrate synthase, 5) citrate conversion to acetyl-CoA via citrate lyase, 6) acetyl-CoA conversion to malonyl-CoA via acetyl-CoA carboxylase (ACC), and 7) malonyl-CoA inhibition of CPT-1 and elevated endogenous or exogenous sources of FFAs. Note that ACC in β-cells appears to act as a regulatory signal generator rather than as a step in FFA biosynthesis because fatty acid synthase is very
pressed at appreciable levels (71). The reason why FFAs alone do not stimulate secretion in the absence of glucose (19) is probably their rapid entry into the mitochondria when malonyl-CoA levels are low. Noteworthy is the fact that ACC protein and activity is expressed at appreciable levels (71). The reason why FFAs alone do not stimulate secretion in the absence of glucose (19) is probably their rapid entry into the mitochondria when malonyl-CoA levels are low. Noteworthy is the fact that malonyl-CoA is abundant in islets (73) and that an enzyme of the fatty acid oxidation pathway, β-hydroxyacyl-CoA dehydrogenase, is expressed in the islet at a level among the highest in all tissues (74).

The identification of LC-CoA rather than malonyl-CoA as the effector signal is based on the finding that pharmacological inhibition of CPT-1, which bypasses malonyl-CoA, enhances glucose-induced secretion as does exogenous FFA (Fig. 1 and 2) (19,63). This, however, does not diminish the physiological importance of malonyl-CoA, which by regulating CPT-1 and the level of cytosolic LC-CoA, determines fuel partitioning (the relative rates of glucose and FFA oxidation in the β-cell) and the fate of LC-CoA (oxidation, esterification, or acylation). Hence, malonyl-CoA can be considered a regulatory signaling molecule in insulin secretion, whereas LC-CoA acts as an effector signal. ACC, which controls the synthesis of malonyl-CoA, the “signal of plenty,” and CPT-1, which is regulated by it, should be considered integrators of the concentrations of all circulating fuel stimuli. Indeed, the metabolism of various classes of nutrient stimuli (carbohydrate, fatty acids, and amino acids) converges to form malonyl-CoA and increase LC-CoA esters. Thus, we propose that ACC and CPT-1 are fuel sensors in the β-cell, in comparison with the glucose sensor, glucokinase, which senses only glucose, and that the acute insulinotropic response to glucose is due to an increase in both cytosolic LC-CoA and the ATP/ADP ratio via a fall in Mg-ADP (Fig. 2).

Target effectors of LC-CoA esters. LC-CoA esters and products formed from them are potent regulators of enzymes and channels. High circulating FFAs and certain drugs or steroids have the potential to increase this pool over a period of hours to days (12,13,16,75). It is hypothesized that the elevations in LC-CoA, PA, and DAG resulting from glucose stimulation (67) could directly modulate the activity of enzymes including PKC isoforms (76,77) or modify the acylation state of key proteins involved in regulation of ion channel activity and exocytosis (78–80). Figure 3 illustrates several potential sites of action of LC-CoA as key regulators of enzymes, genes, and various β-cell functions. They inhibit the activities of glucokinase (73,81,82), glucose-6-phosphatase (83), ACC (73), and certain protein kinase C (PKC) isoforms (53,84,85). They stimulate the activities of other PKC isoforms (53,86) and the endoplasmic reticulum Ca2+ ATPase (87), activate peroxisome proliferation (88), and also overcome malonyl-CoA inhibition of CPT-1 activity (89). LC-CoA esters accelerate the transfer of proteins from the cis to the trans Golgi by increasing the budding of vesicles from the cis-Golgi and their fusion to the trans-Golgi compartment (78). Our current work shows LC-CoA stimulation of exocytosis from permeabilized clonal β-cells (J.T. Deeney, P.-O. Berggren, B.E.C., unpublished observations) and potent stimulation of the KATP channel (O. Larsson, J.T. Deeney, P.-O. Berggren, B.E.C., unpublished observations). Not shown is the LC-CoA inhibition of adenine nucleotide translocase (90), which plays an important role in controlling the cytosolic ATP/ADP ratio, and the sodium pump, which is stimulated by LC-CoA in some cells (91–93).

Protein acylation appears to be essential for the process of signaling through trimeric GTP-binding proteins (G-proteins), possibly as a means of targeting these proteins to appropriate membrane sites (94). All α-subunits are modified by saturated fatty acyl chains, by either a myristoyl or a palmitoyl moiety (79,80). Mutation in palmitoylation sites of α-subunits impairs their regulatory function (79,80). Note in this regard that several G-proteins have been implicated in exocytosis (95–97). Thus, LC-CoA is proposed to exert multiple potent effects on diverse β-cell functions from glycolysis to energy metabolism, signal transduction, exocytosis, and gene expression.

A model of glucose-induced insulin secretion. In the model outlined in Fig. 2, both glycolytic and mitochondrial-derived signals play essential roles in glucose-induced insulin secretion. After the rapid entry of glucose into the β-cell via its high-Km transporter GLUT2, glucose phosphorylation by glucokinase initially uses ATP and produces ADP, causing a small lowering of the ATP/ADP ratio (98,99). The fall in this ratio would stimulate flux through phosphofructokinase and pyruvate dehydrogenase, increase citric acid cycle activity and respiration, and result in a large overshoot in the ATP/ADP ratio, particularly where glucokinase or hexokinase is localized. The peak in cytosolic ATP/ADP, which corresponds to a fall in Mg-ADP, would lead to closure of the ATP channel, depolarization, and entry of Ca2+ through voltage-sensitive Ca2+ channels. Although the increase in cytosolic free Ca2+ is necessary for secretion, it is clearly not sufficient (46–50). The further metabolism of glucose leads to production of malonyl-CoA, which blocks LC-CoA transport into the mitochondria and inhibits FFA oxidation, indirectly stimulating glucose oxidation and increasing the cytosolic pool of LC-CoA, which may modulate signal transducing proteins directly or through the production of complex lipids such as PA or DAG. We propose that the increase in cytosolic LC-CoA provides the missing signal that is responsible for the concentration dependence of glucose-induced insulin secretion. Note that only fuels or fuel com-
The combination of high glucose and free fatty acids (FFAs) inhibits fatty acid oxidation in adipose tissue (19). High glucose inhibits fatty acid oxidation directly by stimulating the ACC enzyme, whereas FFAs inhibit the action of the ACC enzyme indirectly by stimulating the ACC enzyme. The inhibitory effect of FFAs is greater than that of glucose, resulting in a stronger inhibition of fatty acid oxidation (19). This inhibition is further exacerbated by the increased production of malonyl-CoA, which is a potent inhibitor of fatty acid oxidation. The increased production of malonyl-CoA is mediated by the ACC enzyme, which is activated by FFAs and inhibited by glucose. The increased production of malonyl-CoA results in a decrease in the ATP/ADP ratio and other metabolites, which further inhibits fatty acid oxidation (20).

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lated PKC isoforms that are regulated by FFA and LC-CoA (84–86,124). This raises the tantalizing prospect that glucose and fatty acids modulate insulin action, insulin secretion, and glucose homeostasis through effects on the expression of genes encoding metabolic enzymes implicated in glycolysis, lipid metabolism, fuel partitioning, and glucose sensing in many tissues.

The identification of the adaptive changes in the β-cell caused by elevated glucose and FFAs is important to our understanding of the pathogenesis of obesity and NIDDM. Besides its action on the insulin gene, glucose has pronounced effects on the expression of genes encoding enzymes implicated in glucose metabolism in the β-cell. Glucose induces the transporter GLUT2 (125), the l-pyruvate kinase (126), and the ACC (110) genes in pancreatic islets and INS-1 cells. It also increases the abundance of islet pyruvate carboxylase and Ela pyruvate dehydrogenase mRNAs in vitro (112) and decreases the expression of the branched-chain 2-ketoacid dehydrogenase transcript (113). The mechanism by which glucose induces ACC is entirely different from its effect on insulin release because it does not require metabolism of the hexose beyond the glucokinase step (since 2-deoxyglucose, which is phosphorylated but not metabolized further, also induces ACC mRNA) and is not mediated by the Ca2+, PKC, or cAMP-dependent protein kinase transduction systems (110). The action of glucose on the GLUT2, l-pyruvate kinase, and ACC genes is apparently transcriptional (110,125,126). It should be noted that the predominant islet pyruvate kinase activity is not t- but rather m-type (127).

Inducing genes implicated in the glucose sensing process should accelerate glucose metabolism and consequently insulin secretion. Consistent with this view, exposure of pancreatic islets for 2 days to elevated glucose in a partial pancreatectomy model causes a leftward shift in the dose dependence of glucose-induced insulin secretion (109). Basal insulin release is elevated in INS-1 cells preincubated at elevated glucose levels for 24 h, and basal insulin secretion correlates with the ACC protein content of cells preincubated at various glucose concentrations (110).

Our recent work indicates that long-chain FFAs also markedly affect the expression of genes coding for enzymes of intermediary metabolism in the β-cell. Long-term exposure of INS-1 cells to FFAs decreases ACC mRNA and protein at low glucose and antagonizes the inductive effect of the sugar (T. Brun, M.P., unpublished observations). In contrast, FFAs markedly induce the liver type CPT-1 transcript in INS-1 cells (F. Assimacopoulos-Jeannet, D. McGarry, M.P., unpublished observations). Accordingly, it is tempting to propose (Fig. 4) that alterations in the expression of metabolic enzymes by FFAs, in particular ACC and CPT-1, may account at least in part for the β-cell insensitivity to glucose in NIDDM or the alterations in insulin secretion observed in pancreatic islets exposed to elevated FFAs in vitro (17). This proposal is attractive because, as we discussed above, ACC and CPT-1 may act as nutrient sensors, since the metabolism of all classes of fuel secretagogues converges toward these enzymes.

 Peroxisome proliferator–activated receptors (PPARs) are most likely implicated in the processes characterized by excessive fat deposition, insulin resistance, and β-cell insensitivity to glucose caused by FFAs. Noteworthy is the recent observation that the cellular target of the antidiabetic thiazolidinediones is γ-PPAR (128). PPARs are members of the steroid/thyroid/rexinoid hormone receptor superfamily. They mediate the induction by certain long-chain FFAs of a number of genes encoding proteins involved in FFA oxidation and biosynthesis as well as in ketogenesis (88,129,130). A defect in PPAR regulation might therefore be involved in the etiology of obesity and diabetes. The link of the PPAR field with what is discussed in this review is evident, since PPARs are thought to be, like malonyl-CoA (10,11), key factors implicated in the nutrient/metabolism/gene interaction in the context of the substrate competition between glucose and FFAs (Figs. 1 and 3) (88).

**RELATIONSHIP BETWEEN GLUCOSE AND FFA METABOLISM IN OTHER TISSUES**

When lipids are high and glucose is not, excess fat is mainly oxidized in the mitochondria at the expense of glucose, as in starvation. This is achieved by the activation of FFAs to LC-CoA, followed by the transport of cytosolic LC-CoA into the mitochondria, where it is oxidized. Low levels of malonyl-CoA prevent LC-CoA accumulation in the cytosol. When glucose is high and fats are not, small increases in cytosolic LC-CoA derived from the low rate of endogenous lipolysis occur in response to glucose conversion to malonyl-CoA. Although glucose can also be converted to fat via fatty acid oxidation by the liver, this process is unlikely to be as important as the conversion of glucose to acetyl-CoA for fatty acid synthesis because of the energy cost of this reaction and the competing requirement for glucose by anaerobic tissues. However, the potential for glucose to be converted to fat in the liver is increased when fatty acids are present, as occurs in obesity.

**FIG. 4. A mechanism for altered glucose sensing of the pancreatic β-cell in NIDDM.** In the control situation, glycolytic flux is enhanced, malonyl-CoA accumulates, fatty acid oxidation is inhibited by glucose, and LC-CoA accumulates to induce insulin secretion. In NIDDM, LC-CoA is primarily oxidized and secretion is inadequately stimulated because of altered expression of metabolic enzymes, in particular FFA-induced downregulation of ACC and upregulation of the CPT-1 genes. Metab. enz, metabolic enzymes; PA, phosphatidic acid; TG, triglyceride.
proposed that such increased cytosolic LC-CoA esters are resistant states, including those associated with hyperinsulinemia and inactivity (denervation) (131,137). In contrast, rodent muscle have been found in a wide variety of insulin-sensitivity. Also, improved in insulin sensitivity in muscle of obese hyperinsulinemic rodents caused by treatment with a thiazolidinedione is associated with a decrease in the concentration of malonyl-CoA (140). A schema linking changes in the concentration of malonyl-CoA and other events that increase cytosolic LC-CoA to insulin resistance in muscle has recently been proposed by Ruderman and co-workers (131).

With respect to liver, it is has been established that FFAs enhance gluconeogenesis (141,142), inhibit glycolysis (143), and alter gluconeogenic gene expression (144). FFAs have also been implicated as the possible messengers of insulin-mediated inhibition of hepatic glucose output (145). It was originally and extensively demonstrated by McGarry and Foster and colleagues (10,11,65,66,146) that changes in malonyl-CoA play a key role in the disposition of FFA in liver and in the regulation of ketogenesis and gluconeogenesis, suggesting a role for the effector signal LC-CoA in regulating hepatic glucose production. These seminal studies provided much of the inspiration for our islet studies.

Malonyl-CoA and cytosolic LC-CoA levels have not been reported in adipose tissue, although altered gene expression and fat cell function are associated with elevated FFAs or obesity (119,147–149). We have found that LC-CoA levels increase in isolated rat adipocytes with obesity and in response to insulin (B.E.C., K.L. Kelly, unpublished observations). We suggest that adipose cell mass is, in part, determined by fuel partitioning, which in turn depends on the supply of LC-CoA, the activity of CPT-1, and the capacity of the fatty acid oxidizing pathway, such that control of flux through CPT-1 by malonyl-CoA determines cytosolic LC-CoA and, by mass action, its rate of conversion to triglycerides. LC-CoA may act as a central fat cell size-sensor, since it is the common intermediate linking oxidation, esterification, activation, and lipolysis with high levels favoring esterification.

Thus, it is proposed that altered levels of malonyl-CoA and LC-CoA are causally implicated in insulin resistance (Fig. 5). ACC, which controls the synthesis of malonyl-CoA, the signal of plenty, and CPT-1, which is regulated by it, may perform as integrators of the concentrations of all circulating fuel stimuli in muscle, liver, and adipose tissue, as in the β-cell. The mechanism whereby elevated cytosolic LC-CoA levels may cause insulin resistance remains to be determined. It possibly implicates altered expression of metabolic enzymes and signal transducing effectors, protein acylation, or the modulation of the levels or activity of PKC subtypes.

**THE HPA AXIS**

Steroid production in the HPA axis of rats is modulated by fuels (150,151); steroids in turn are known to alter lipid metabolism (152), insulin sensitivity (153), and insulin secretion (154,155). Obesity, diabetes, and consumption of a high-fat diet are characterized by hyperactivity of the HPA axis (156–159). While glucocorticoids and other catabolic hormones mobilize glucose and fatty acids during times of need, the synthesis and secretion of these hormones is normally under negative feedback control (160). For example, glucocorticoids potently inhibit further secretion of the major adrenal trophic factor, ACTH (161). Elevated glucose inhibits corticotropin-releasing hormone (CRH) secretion from the hypothalamus, closing a negative feedback loop (151). FFAs, on the other hand, activate the HPA axis in normal rats, stimulating an increase in plasma ACTH and corticosterone levels (Fig. 5) (150). The monounsaturated fatty acids oleate and linoleate stimulate corticosterone production from cultured rat adrenocortical cells (150),

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**FIG. 5.** Altered malonyl-CoA and LC-CoA levels as a common mechanism for tissue malfunction in obesity and NIDDM. Elevation in LC-CoA resulting from increased circulating lipids and hyperglycemia is proposed as a common signal that induces altered insulin secretion by the β-cells, increased adipose tissue mass, insulin resistance in muscle, excessive glucose production in liver, vascular contraction, and excessive cortisol production from cultured rat adrenocortical cells.
although it is not known whether this action of FFAs is mediated by LC-CoA. Thus, ACTH and corticosterone may elevate glucose and fatty acids, although via different mechanisms; exacerbate the HPA axis; and contribute to obesity, insulin resistance, and altered insulin secretion (162,163).

A UNIFYING HYPOTHESIS

We propose that a metabolite derived from dietary or stored excess lipid provides a unique signal to susceptible tissues (Fig. 5). A prime candidate for this signal molecule is cytosolic LC-CoA or one of its immediate products such as PA or DAG. Cytosolic LC-CoA esters are expected to increase in the presence of a high-fat, high-sucrose diet because glucose forms malonyl-CoA, which inhibits the mitochondrial oxidation of cytosolic LC-CoA formed from FFAs. Malonyl-CoA is the intracellular signal of abundance that regulates fuel partitioning and the balance between FFA and glucose oxidation. The signaling abnormalities that occur in β-cells in altered lipid environments, due to both short- and long-term elevations of LC-CoA esters, may also be relevant to the development of metabolic and signaling alterations in adipose tissue, muscle, and the HPA axis via the tissue-specific targets of LC-CoA (Fig. 5). Depending on individual genetic background, these alterations may occur in a variable manner. Finally, these concepts may be integrated into an hypothesis in which a common etiology is expected to have tissue-specific consequences, appearing in pancreatic β-cells as altered insulin secretion, in liver as inadequate suppression of glucose production, in adipose tissue as altered fuel partitioning leading to excess fat storage, in vascular tissue as vasoconstriction and resulting elevated blood pressure, in skeletal muscle and liver as insulin resistance, in the adrenal as excessive cortisol production, and in neural tissue as potentiated neurotransmitter release and increased sympathetic nerve activity. Thus, according to this hypothesis, insulin resistance, hyperinsulinemia, obesity, syndrome X, and NIDDM are different clinical components of a more general metabolic disease, which may be termed glucolipoxia.

The hypothesis we have presented here is testable and consistent with the available evidence and provides a resolution to the quandary as to whether insulin resistance, defective insulin secretion, obesity, or alterations in the HPA initiate NIDDM. Our model implies that many tissues participate in the pathogenesis of NIDDM and more importantly that all of these tissues possess tissue-specific fuel-sensing capabilities that respond to malonyl-CoA and LC-CoA. In nutritional environments with excessive caloric intake, this can lead to altered signal generation by some tissues and altered feedback regulation of critical processes in others. Importantly, an altered fuel milieu may have different consequences in different settings. The initial dominant tissue defect may depend on genetically determined tissue-specific effector sensitivity to a change in malonyl-CoA and LC-CoA, leading in some cases to dominant insulin resistance, in certain cases mainly to obesity, and in others chiefly to hyperinsulinemia. For example, excessive intake of both carbohydrate and fat may in one susceptible individual initially alter the malonyl-CoA and LC-CoA content of muscle, causing insulin resistance followed by insulin deficiency. In contrast, in another individual, the acyl-CoA profile may be initially altered in the β-cell, with a resulting hypersecrec-

ATION OF INSULIN BEING INSTRUMENTAL IN CAUSING INSULIN RESISTANCE.

ACKNOWLEDGMENTS

The work from our laboratories was supported by National Institutes of Health Grants DK-35914 and DK-46230 and Juvenile Diabetes Foundation Grant 195014 to B.E.C. and grants from the Medical Research Council of Canada and the Canadian Diabetes Association to M.P.

The authors express appreciation to Drs. Françoise Assimacopoulos-Jeannet, Per-Olof Berggren, Christopher J. Rhodes, Neil B. Ruderman, and Gerald van der Werve for critical reading of the manuscript and for making relevant material available to us prior to publication.

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Biochemical mediators including arachidonic acid, its metabolites, and phospholipids are involved in pancreatic β-cell function. These factors include insulinotropic peptides and other hormones that stimulate insulin secretion. The regulation of insulin secretion by glucose is mediated through a series of intracellular events, including depolarization of the β-cell membrane, activation of voltage-gated calcium channels, and entry of extracellular calcium. This influx of calcium triggers a cascade of events leading to the activation of protein kinases and phospholipases, which in turn lead to the synthesis of second messengers such as diacylglycerol and inositol triphosphate. These second messengers activate protein kinases and phospholipases, leading to the phosphorylation of regulatory proteins and the mobilization of intracellular calcium stores. This process is essential for the regulation of insulin secretion and the control of blood glucose levels.

In summary, the regulation of insulin secretion by glucose is a complex process involving multiple factors and pathways. Understanding these mechanisms is crucial for the development of new therapeutic strategies for the treatment of diabetes.

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