Glucose–fatty acid interactions in health and disease

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ABSTRACT It is widely held that although obesity and type 2 diabetes are polygenic in origin, the primary defect causing both conditions is insulin resistance, which in turn gives rise to a constellation of other abnormalities, including hyperinsulinemia, dyslipidemia, glucose intolerance, and (in the genetically predisposed) frank hyperglycemia. Explored here is an alternative, albeit speculative, scenario in which hyperinsulinemia and insulin resistance arise either simultaneously or sequentially from some preexisting defect within the leptin signaling pathway. In either case, a central component of the model is that the breakdown of glucose homeostasis that is characteristic of the condition of obesity with type 2 diabetes is secondary to disturbances in lipid dynamics. The possibility is raised that abnormally high concentrations of malonyl-CoA in liver and skeletal muscle suppress the activity of mitochondrial carnitine palmitoyltransferase I and thus fatty acid oxidation in both sites. It is suggested that the buildup of fat within the muscle cell (caused in part by excessive delivery of VLDLs from the liver) interferes with glucose transport or metabolism or both, producing insulin resistance. Elevated circulating concentrations of fatty acids are also implicated in the etiology of type 2 diabetes by virtue of 1) their powerful autoinsulotropic effect, 2) their ability to exacerbate insulin resistance in muscle, and 3) their long-term detrimental action on pancreatic β-cell function. Am J Clin Nutr 1998;67(suppl):500S–4S.

KEY WORDS Diabetes mellitus, NIDDM, type 2 diabetes, hyperinsulinemia, insulin resistance, obesity, lipids, malonyl-CoA, carnitine palmitoyltransferase I, fatty acid oxidation, pancreatic β-cell

INTRODUCTION The early stages of obesity and type 2 diabetes are characterized by a constellation of metabolic and hormonal abnormalities including insulin resistance, hyperinsulinemia, hypertriglyceridemia, glucose intolerance, and, in some instances, hypertension [often referred to as the syndrome X (1)]. Much debated has been the temporal sequence in which these component derangements appear and how they relate to one another. For example, it is widely held that obesity-related type 2 diabetes is polygenic in origin, an early—though not primary—defect is insulin resistance, which in turn leads to glucose intolerance, compensatory hyperinsulinemia, dyslipidemia, and, when the pancreatic β-cell can no longer meet the excessive demand for insulin, frank hyperglycemia (2, 3, and Figure 1A). However, from the vast literature in the field it is difficult to find a study in which two of the key elements in this scenario, namely insulin resistance and hyperinsulinemia, were clearly separated in time. An alternative formulation would be that both hyperinsulinemia and insulin resistance stem simultaneously from a prior lesion, and together pave the way for the other derangements (Figure 1B). Yet a third possibility, and one that we tend to favor for reasons detailed elsewhere (4, 5), is that hyperinsulinemia begets insulin resistance, the latter being a necessary adaptation to prevent hypoglycemia (Figure 1C). A hypothetical model that attempts to explain the basis for the initial hyperinsulinemia and how this might bring about muscle insulin resistance is presented in Figure 2.

The essential features of the model are as follows: 1) An early defect, perhaps within the leptin–central nervous system–pancreatic β-cell axis (6), results in neurally mediated hypersecretion of insulin and amylin from the pancreatic β-cell, possibly accompanied by hyperphagia. 2) The resultant hyperinsulinemia promotes excessive production of VLDLs by the liver through stimulation of fatty acid biosynthesis and reesterification of circulating fatty acids. 3) Over the course of years, the increased delivery of VLDLs to adipose tissue promotes obesity. 4) The concomitant accumulation of triacylglycerols and fatty acyl-CoAs in muscle tissues negatively affects insulin-mediated glucose uptake, glycogen biosynthesis, and glucose oxidation; thus, insulin resistance begins to develop (4, 5). The ensuing glucose intolerance causes even greater postprandial hyperinsulinemia, promoting a vicious cycle. 5) At some point, fat cells become refractory to the antilipolytic effect of insulin and plasma fatty acid concentrations begin to climb, exacerbating the insulin resistance in muscle tissues and providing a further stimulus for insulin secretion (discussed below). The simultaneous elevation of plasma insulin and fatty acid concentrations promotes even greater hepatic VLDL overproduction, resulting in hypertriglyceridemia. 6) In those individuals genetically predisposed to progress from impaired glucose tolerance to frank type 2 diabetes, a critical event appears to be the failure of the β-cells to maintain a high output of insulin in response to glucose.

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Although the underlying mechanism is unclear, one factor might be the deposition of amyloid-like material (derived from amylin) in and around the β-cell (7). Another could be the detrimental effect of chronically high fatty acid concentrations on β-cell function (8).

To be sure, this is a speculative proposal that runs counter to prevailing views, and whether it is valid remains to be seen. Assuming that it is, the question arises as to how the dysregulation of glucose–fatty acid interactions at various body sites, a central element of the model, might be explained in biochemical terms. Explored briefly below is the potential involvement of one such interaction, ie, that between the simple molecule malonyl-CoA and mitochondrial carnitine palmitoyltransferase I (CPT I).

**ROLE OF THE MALONYL-CoA–CPT I INTERACTION IN THE LIVER**

In the mid-1970s it became clear that the process of hepatic ketogenesis is governed largely by the relative concentrations of two hormones: insulin and glucagon. The picture emerging was that a drop in insulin concentrations during ketotic states triggers adipose tissue lipolysis and provides the liver with an increased supply of fatty acids. The concomitant rise in the ratio of glucagon to insulin endows the liver with an enhanced capacity to oxidize the fatty acids, with the result that ketone body production is accelerated.

It transpired that primary control over the liver’s ability to oxidize long-chain fatty acids is vested in the opposing pathway of fatty acid biosynthesis, such that when the latter is active the former is suppressed, and vice-versa (9). The linking molecule turned out to be malonyl-CoA, the product of the first committed step in fatty acid biosynthesis (ie, the acetyl-CoA–carboxylase reaction). Malonyl-CoA proved to be a potent inhibitor of CPT I, which is essential to the first step specific to the oxidative pathway (10). Thus, in the well-fed (high insulin, low glucagon) state carbon flow through the lipogenic pathway is efficient, the malonyl-CoA concentration is high, and CPT I is suppressed. This ensures a unidirectional carbon flow from glucose to fatty acyl-CoA to triacylglycerol to VLDL, which is then exported from the liver for use in adipose and muscle tissues. Conversely, in ketotic (low insulin, high glucagon) states, malonyl-CoA concentrations fall [because of inhibition of glycolysis and acetyl-CoA carboxylase mediated by adenosene 5’-monophosphate (AMP) and cyclic AMP], fatty acid biosynthesis ceases, CPT I becomes dere-
pressed, and fatty acids delivered to the liver from fat depots are efficiently oxidized with the production of ketone bodies (10) (Figure 3). Under these conditions there is, in addition, a reduced sensitivity of CPT I to the inhibitory effect of malonyl-CoA, thus amplifying the stimulus to fatty acid oxidation caused by the reduction in malonyl-CoA concentrations (10).

Returning to the model of Figure 2, a predictable effect of hyperinsulinemia is that liver metabolism would be set in a hyperanabolic mode that favors glycogen accumulation, high rates of malonyl-CoA and fatty acid biosynthesis, increased efficiency of fatty acid esterification at the expense of a reduced capacity for fatty acid oxidation, accelerated production of VLDL, and hypertriglyceridemia. All of these features were found to apply to genetic rodent models of obesity.

ROLE OF THE MALONYL-COA–CPT I INTERACTION IN MUSCLE TISSUES

In the years since the malonyl-CoA–CPT I interaction was first recognized (Figure 3), it has become clear that this phenomenon is not restricted to the liver. On theoretical grounds, its potential role as an element in fuel “crosstalk” in nonlipogenic tissues such as heart and skeletal muscle gained support from three observations made in rats. First, both heart and skeletal muscle tissues are known to contain malonyl-CoA and in each case the concentration of the malonyl-CoA ester shows the same directional changes with feeding and fasting as in the liver (10). Second, in both tissues malonyl-CoA appears to be synthesized by an isoform of acetyl-CoA carboxylase (≈280 kDa) that is distinct from the liver enzyme (≈265 kDa) (11). Third, both tissues express a muscle type CPT I that differs from liver CPT I not only in its structure but in its Michaelis constant ($K_m$) for carnitine (≈20 times higher) and sensitivity to malonyl-CoA (≈100 times greater) (12).

At a functional level, studies by several groups (13), which will not be elaborated on in this article, point to an important role for glucose-derived malonyl-CoA in the regulation of fatty acid oxidation in heart tissue. More relevant to the present discussion is the likelihood that the same is true in skeletal muscle. Thus, it is known that the malonyl-CoA content of skeletal muscle decreases during exercise, a condition characterized by enhanced fatty acid oxidation (11). Conversely, in the KKA$^+$ mouse, an animal model of obesity and insulin resistance with marked hyperglycemia, hypertriglyceridemia, and hyperinsulinemia, there is a striking elevation in the muscle (and liver) malonyl-CoA concentration during exercise (14). Interestingly, treatment of the animals with pioglitazone, an antidiabetic agent, reduced the circulating concentrations of glucose, insulin, and triacylglycerols, and restored muscle malonyl-CoA concentrations to normal (14). In addition, denervation of normal rats, a manipulation that brings about insulin resistance, caused a striking elevation in their muscle malonyl-CoA content (15). Simple exposure of the isolated rat soleus muscle to high insulin concentrations (in the presence of glucose) had the same effect (15). From such observations it appears that malonyl-CoA is a component of the muscle cell’s fuel-sensing mechanism through which glucose and fatty acid dynamics are kept in balance. The possibility is raised that in hyperinsulinemic states a rise of malonyl-CoA concentrations in muscles causes suppression of fatty acid oxidation and a concomitant elevation of cytosolic fatty acyl-CoA concentrations, the latter negatively affecting indexes of glucose metabolism such as transport, conversion into glycogen, and oxidation (14).

It was observed that obese women who had lost weight by dieting exhibited a significantly lower capacity for whole-body fatty acid oxidation than control nonobese subjects (16). It is tempting to speculate that in the preobese state a higher than normal content of malonyl-CoA in liver and muscle, possibly caused by hyperinsulinemia, predisposes to a reduced capacity for fatty acid oxidation and accumulation of fatty acyl-CoA. The latter would favor excessive hepatic VLDL production and might interfere with insulin-stimulated glucose disposal in muscle tissues by the mechanisms discussed above. The derangements at both sites would, of course, be compounded by an inappropriate elevation of plasma fatty acid concentrations.

ROLE OF THE MALONYL-COA–CPT I INTERACTION IN THE Pancreatic β-CELL

Evidence is now mounting that CPT I inhibition by malonyl-CoA is crucially important to pancreatic β-cell function. In attempting to elucidate which aspects of glucose metabolism are responsible for eliciting insulin secretion from this cell type, Corkey et al (17) measured the time course of changes in various metabolites when hamster insulinoma cells were exposed to a stimulatory concentration of glucose. They noted that malonyl-CoA concentrations rose before insulin release. When Chen et al (18) perfused pancreases from normal rats with hydroxyacetate, an inhibitor of ATP-citrate lyase (which catalyzes the penultimate reaction in the metabolism of glucose to malonyl-CoA), glucose-stimulated insulin secretion (GSIS) was greatly reduced. However, the simple addition of palmitate to the perfusion medium restored high rates of GSIS despite the continued presence of the inhibitor (18). These studies suggest that a key metabolite generated from glucose in the β-cell is malonyl-CoA, which, by block-
ing the activity of mitochondrial CPT I, causes acute elevation of the cytosolic concentration of fatty acyl-CoAs and that these in turn act as important signals for insulin secretion (Figure 4). As discussed in detail elsewhere (18, 19) and indicated schematically in Figure 4, possible mechanisms by which fatty acyl-CoAs could stimulate insulin release include 1) the formation of esterified products, such as phospholipids or diacylglycerols or both, 2) enhancement of insulin granule movement to the cell surface, and 3) modulation of β-cell channel activity.

The studies cited pointed to a long-overlooked but crucially important interaction between glucose and fatty acids in normal pancreatic β-cell function (17, 18). This principle has since received major support from studies designed to clarify why, when rats are deprived of food for only 18–24 h, GSIS is so profoundly attenuated when measured in isolated pancreas preparations, but not when glucose is administered to the whole animal. The paradox was resolved with the finding that when the high plasma fatty acid concentrations characteristic of fasted rats were lowered by infusion of nicotinic acid, an antilipolytic agent, insulin secretion in response to intravenously fed glucose was ablated, ie, the pancreas behaved the same way in vivo as it had in vitro. However, when fatty acids were maintained at high concentrations in nicotinic acid–treated rats by the simultaneous administration of Intralipid (Kabi Pharmacia, Clayton, NC) and heparin, the rate of GSIS became supranormal (20). Fed animals, on the other hand, showed a robust insulin response to intravenously fed glucose regardless of whether their plasma fatty acid concentrations (which were already low compared with those in rats deprived of food) were further reduced by nicotinic acid treatment. Here again, artificial elevation of the plasma fatty acid concentration dramatically enhanced GSIS (20). Important, all of the in vivo results could be reproduced in the perfused pancreas preparation simply by performing the experiments in the absence or presence of palmitate (20). Thus, although the ability of fatty acids to stimulate insulin secretion has been known for 30 years (21), the studies summarized above bring to light a point that has not been recognized heretofore, namely that in fasted rats an elevated plasma fatty acid concentration is a sine qua non for efficient insulin secretion when the fast is terminated.

As to why starvation shifts the pancreatic β-cells in rats from a fatty acid–independent to a fatty acid–dependent state in terms of GSIS remains an intriguing question. We suspect that it relates to a diminished capacity of the cell to convert glucose into malonyl-CoA, possibly because of a starvation-induced reduction in the activity of pyruvate dehydrogenase or acetyl-CoA carboxylase or both, as well as of glucokinase (20). If so, the suppression of CPT I and elevation of the cytosolic fatty acyl-CoA concentration, as occurs in the fed state, would be impaired. To the extent that fatty acyl-CoAs are important signaling molecules in stimulus-secretion coupling (Figure 4), insulin release could also be dampened. However, GSIS should be reinstated provided that the fatty acyl-CoA deficit can be corrected. We propose that a high plasma fatty acid concentration subserves this role (20).

CONCLUSION

Should circulating fatty acids prove to be as important to β-cell function in humans as they appear to be in rats, the implications could be far reaching. At the physiologic level, it would mean that during periods of starvation the role of fatty acids is not simply to act as a replacement fuel for glucose in most body tissues (thus conserving the hexose for use by the central nervous system). Two additional functions would then have to be considered. One is that the rise in plasma fatty acid concentrations during periods of prolonged food deprivation is self-limiting because of the ability of these substrates (possibly in combination with ketone bodies) to support a basal, albeit low, rate of insulin secretion, which in turn

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**FIGURE 4.** Potential interactions in the pancreatic β-cell. DAG, diacylglycerol; DHAP, dihydroxyacetone phosphate; FA-CoA, fatty acyl-CoA; GLUC, glucose; GLYCERALD, glyceraldehyde; α-GP, glycerol-3-phosphate; INS, insulin; OAA, oxaloacetate.
modulates the extent of adipose tissue lipolysis (a feature that distinguishes the physiologic ketosis of starvation from the pathologic ketosis of uncontrolled type 1 diabetes). The other is that fatty acids can prime the \( \beta \)-cell for efficient insulin secretion when glucose reenters the system, and thus to bring about their own disappearance (because of the antilipolytic effect of the \( \beta \)-cell hormone). On the other hand, because of the powerful stimulus imparted by fatty acids to GSIS, it seems likely that a modest but inappropriate elevation of the plasma fatty acid concentration, as seen in many obese individuals (22), could be a major factor in the hyperinsulinemic response to glucose in these individuals (22). This could be viewed as the body’s attempt to overcome the insensitivity of adipose tissue lipolysis to insulin. However, the coexistence of high insulin and fatty acid concentrations—a clearly abnormal situation—would provide the key elements for excessive hepatic VLDL production (Figure 2). The predicted consequences would be hypertriglyceridemia, hypercholesterolemia, and increased risk of cardiovascular disease.

REFERENCES