

Effect of lipid oxidation on glucose utilization in humans^{1,2}

Eric Jéquier

ABSTRACT The mechanisms responsible for the competition between glucose and fatty acids as oxidative fuels are not yet completely understood in humans. Maintenance of plasma fatty acid concentrations by means of lipid and heparin infusion during hyperinsulinemic, euglycemic clamps in humans first suppresses glucose oxidation and only later decreases nonoxidative glucose disposal; muscle pyruvate dehydrogenase activity is inhibited when plasma fatty acid concentrations are maintained during hyperinsulinemic, euglycemic clamps. The maintenance of plasma fatty acid concentrations impairs insulin-stimulated muscle glucose uptake only if fatty acid uptake by skeletal muscles is increased. The role of hyperglycemia in glucose–fatty acid competition has recently been emphasized. Fatty acid utilization by muscle is impaired in patients with type 2 diabetes mellitus during fasting hyperglycemia: both lipid oxidation and uptake of plasma fatty acids by skeletal muscle are impaired during postabsorptive conditions. Hyperglycemia indirectly activates pyruvate dehydrogenase, the rate-limiting enzyme for glucose oxidation. The ability of increased glucose availability to stimulate glucose oxidation and reduce lipid oxidation by skeletal muscle can be considered a corollary of the Randle glucose–fatty acid cycle. It can be concluded that within a reasonable range of carbohydrate-to-fat ratios, the addition of fat to a meal does not decrease postprandial carbohydrate oxidation. Furthermore, high-fat meals do not promote fat oxidation leading to fat storage in adipose tissue. *Am J Clin Nutr* 1998; 67(suppl):527S–30S.

KEY WORDS Insulin resistance, non-insulin-dependent diabetes mellitus, type 2 diabetes mellitus, obesity, skeletal muscle, dietary fat, glucose, fatty acids, substrate oxidation, pyruvate dehydrogenase, lipid oxidation

INTRODUCTION

The effect of lipid oxidation on glucose utilization has raised considerable interest since Randle et al's (1) publication of the glucose–fatty acid cycle in 1963. These authors reported a competition between glucose and fatty acids as oxidative fuel sources in rat heart and diaphragm. When concentrations of plasma fatty acids increase, muscle fatty acid uptake is favored and fatty acids compete with glucose for oxidation. The enhanced fatty acid oxidation produces an increased ratio of acetyl-CoA to CoA-SH and an augmentation of cytoplasmic citrate concentration. The elevated acetyl-CoA concentration activates pyruvate dehydrogenase kinase, which phosphorylates and inhibits pyruvate dehydrogenase. Glucose metabolism is inhibited at two important

steps. First, the increase in cytoplasmic citrate concentration inhibits phosphofructokinase, which results in an increased glucose-6-phosphate concentration; as a consequence, hexokinase is inhibited and, finally, glucose uptake is impaired. Second, inhibition of pyruvate dehydrogenase impairs the entry of pyruvate into oxidative metabolism and thus contributes to inhibiting glucose oxidation.

The relevance of Randle's concept to humans has long been the subject of controversy. Because obesity and type 2 diabetes mellitus are often characterized by postabsorptively increased plasma fatty acid concentrations, it was of great interest to test whether this concept contributes to explaining the mechanisms of insulin resistance in human obesity and type 2 diabetes mellitus.

The aim of this paper is to review recent developments in this field illustrating that the glucose–fatty acid competition for oxidative metabolism can be considered as a two-direction process: 1) increased extracellular fatty acid concentrations inhibit muscle glucose uptake and oxidation, and 2) increased extracellular glucose concentrations inhibit muscle fatty acid uptake and oxidation, as shown in patients with type 2 diabetes mellitus. The resulting substrate oxidation in muscle is in part controlled by the availability of glucose and fatty acids. In addition, plasma insulin concentrations and insulin sensitivity of muscle and adipose tissues also play a role in the regulation of oxidative substrate metabolism.

COMPETITION BETWEEN FATTY ACIDS AND GLUCOSE OXIDATION

Studies in which lipid emulsions with heparin were infused to increase plasma fatty acid concentrations show a dose-dependent inhibition of insulin-stimulated nonoxidative glucose disposal, and, to a lesser extent, an inhibition of muscle glucose oxidation (2). The inhibition of nonoxidative glucose disposal corresponds to a defect in glycogen synthesis. There are two steps in the inhibition of muscle glycogen synthesis induced by fatty acids: the first is observed at plasma fatty acid concentrations of ≈ 550 $\mu\text{mol/L}$ and is associated with a decrease in muscle concentrations of glucose-6-phosphate (2); inhibition of glycogen synthesis is probably due to a reduction in glucose transporters and phosphorylation (3). The second defect occurs later (after 4–5 h of fat infusion) and is observed at higher plasma fatty acid con-

¹ From the Institute of Physiology, Faculty of Medicine, University of Lausanne, Lausanne, Switzerland.

² Reprints not available. Address correspondence to E Jéquier, Institut de Physiologie, 7 rue du Bugnon, 1005 Lausanne, Switzerland.

centrations ($\approx 750 \mu\text{mol/L}$). In contrast with the first step, in this step muscle concentrations of glucose-6-phosphate are increased, reflecting an inhibition of glycogen synthase activity. The latter is due to an increase in long-chain acetyl-CoA or a rise in muscle glycogen concentrations. Thus, elevated plasma fatty acid concentrations inhibit glycogen synthesis, first by interfering with glucose transport and phosphorylation and second by inhibiting glycogen synthase.

The concept of fatty acid-induced inhibition of glucose oxidation in skeletal muscles requires that fatty acid uptake and subsequent oxidation are increased over baseline. Maintenance of plasma fatty acid concentrations by means of lipid and heparin infusion during hyperinsulinemic, euglycemic clamps inhibits insulin-stimulated glucose uptake; it first suppresses glucose oxidation and only later (after ≈ 4 h) decreases nonoxidative glucose disposal (2). Kelley et al (4) reported that the fractional extraction of fatty acids increases during hyperinsulinemia, a result that may be due to the increase in leg blood flow during hyperinsulinemia (5). Insulin also inhibits intramuscular lipolysis and stimulates reesterification of fatty acids, which may result in an increased uptake of plasma fatty acids by skeletal muscle.

Women with visceral obesity have a diminished capacity for fatty acid utilization by skeletal muscles in postabsorptive conditions (6). The activity of muscle carnitine palmitoyl transferase is negatively correlated with visceral fat content. Inhibition of the carnitine palmitoyl transferase mitochondrial enzyme complex impairs fatty acid utilization because carnitine palmitoyl transferase has a rate-limiting role in the transfer of long-chain acetyl-CoA esters into mitochondria. Visceral obesity is clearly associated with insulin resistance of skeletal muscle, but this condition is not explained by glucose-fatty acid substrate competition. There is also a link between insulin sensitivity and the capacity of muscle for lipid utilization; this is supported by the positive relation between the activity of muscle lipoprotein lipase during fasting and insulin sensitivity (7). Thus, part of the regulation of muscle fatty acid utilization seems to be dependent on insulin sensitivity.

COMPETITION BETWEEN GLUCOSE AND FATTY ACID OXIDATION: THE ROLE OF HYPERGLYCEMIA

When euglycemia is maintained during hyperinsulinemic clamps, increasing the extracellular fatty acid concentration by infusing lipid emulsions clearly inhibits muscle glucose uptake and oxidation (2). Under conditions of everyday life, however, carbohydrate balance must be obtained within 24 or 48 h (8), even in obese subjects with elevated plasma fatty acid concentrations. Because skeletal muscle is a tissue that contributes to the regulation of 24-h carbohydrate utilization, how can carbohydrate balance be obtained in subjects with insulin resistance or type 2 diabetes mellitus? Both have elevated fasting plasma fatty acid concentrations due to increased rates of lipolysis (9, 10) and resistance to the antilipolytic effect of insulin. Euglycemic, hyperinsulinemic clamps result in a marked reduction in muscle glucose uptake and oxidation in these patients with a concomitantly higher lipid oxidation rate than in control subjects (10). Yet, these patients also have to oxidize the amount of carbohydrate in their daily diet (8). Hyperglycemia is a powerful factor that stimulates muscle glucose uptake and oxidation (11). In addition, hyperglycemia inhibits muscle fatty acid uptake and oxidation postabsorptively in patients with type 2 diabetes mellitus (9).

In lean control subjects, Mandarino et al (11) reported that hyperglycemia (without hyperinsulinemia, ie, with somatostatin infusion to inhibit insulin secretion and basal insulin replacement) induced increased carbohydrate and decreased lipid oxidation in muscle, with a concomitant activation of pyruvate dehydrogenase in skeletal muscle cells. Because pyruvate dehydrogenase is an important rate-limiting enzyme for glucose oxidation, the indirect activation of this enzyme by hyperglycemia explains the stimulation of carbohydrate oxidation and the reduced lipid oxidation by skeletal muscle in patients with type 2 diabetes mellitus. The increased glucose oxidation resulting from hyperglycemia can be considered a corollary of the Randle glucose-fatty acid fuel competition hypothesis (1, 11).

Hyperglycemia in type 2 diabetes mellitus patients and in nondiabetic subjects with insulin resistance can compensate for the defect in insulin-stimulated glucose disposal (12, 13). The mechanism that explains this compensation is probably the mass action of glucose, which increases the net flux of glucose into skeletal muscle cells. Fasting and postprandial hyperglycemia in patients with type 2 diabetes mellitus can be considered to be adaptive responses to normalize muscle glucose uptake and oxidation. Postabsorptive hyperglycemia in patients with type 2 diabetes mellitus was described by Kelley and Mandarino (14) as the equilibrium point at which glucose production by the liver normalizes the rate of muscle glucose uptake.

Because hyperglycemia impairs muscle fatty acid uptake and oxidation in patients with type 2 diabetes mellitus, it is not possible to explain insulin resistance in these patients by glucose-fatty acid substrate competition (9). Even if hyperglycemia normalizes the rates of systemic and muscle glucose uptake in these patients, insulin resistance is not completely eliminated by hyperglycemia. The decreased insulin sensitivity is illustrated by a reduced glucose clearance, systemically and across the leg. Mechanisms other than glucose-fatty acid substrate competition may involve adverse effects of fatty acids on glucose transporters or on glucose phosphorylation (3). More research is needed in this area to better understand the mechanisms of insulin resistance in muscle.

Studies on incubated skeletal muscle preparations from morbidly obese and obese persons with diabetes show that all pathways of insulin-stimulated glucose disposal are inhibited (15). However, simulating hyperglycemia in the incubation medium increases basal glucose transport and the insulin responsiveness of glucose disposal in these incubated muscle preparations. These *in vitro* results also show that hyperglycemia can compensate for the defect in insulin-mediated glucose disposal.

Whole-body lipid oxidation measured by indirect calorimetry is usually found to be elevated postabsorptively in patients with type 2 diabetes mellitus (10) despite the reduced fatty acid utilization by muscles (9). This elevated lipid oxidation probably results from a stimulation of hepatic fatty acid oxidation, which can in turn lead to increased gluconeogenesis and glucose production (16).

The relation between fatty acid and glucose utilization in human skeletal muscle of patients with type 2 diabetes mellitus has also been studied by using a long-acting antilipolytic drug (17). Acipimox (5-methyl-pyrazime carboxylic acid L-oxide; Farmitalia Carbo Erba, Milan, Italy) was used to reduce plasma fatty acid concentrations in the basal state and during insulin stimulation (17). Insulin action in patients with type 2 diabetes mellitus was improved in the short term by acipimox: both glu-

cose oxidation and nonoxidative glucose disposal increased. The beneficial effect of acipimox on insulin action may be due to its antilipolytic effect or to a direct effect on the activity of glycogen synthase in skeletal muscles.


INTERACTIONS BETWEEN DIETARY FAT AND GLUCOSE UTILIZATION

After the ingestion of a meal, the rise in glycemia stimulates insulin secretion, which inhibits the release of fatty acids from adipose tissue. As a result, there is a suppression of lipid oxidation by insulin that is essentially mediated by the decrease in plasma fatty acid concentrations (18). Insulin stimulates glucose oxidation by enhancing glucose transport in insulin-sensitive cells, by stimulating glycolysis at several steps, and by activating pyruvate dehydrogenase. The question that has been extensively studied is whether a high-fat meal stimulates lipid oxidation and inhibits carbohydrate oxidation in healthy control subjects. We reported that the addition of 41 g fat to a low-fat breakfast did not promote fat oxidation over a period of 9 h after the meal and did not influence the amounts of nutrients oxidized (19). In this study, the postprandial decrease in plasma fatty acid concentrations was not suppressed by the addition of fat to the meal. The implication was that the fat added to the meal was primarily stored. In another study, we tested whether a more delayed effect on metabolic fuel oxidation of a high fat intake (a supplement of 106 g fat divided in four meals over 24 h and given to healthy subjects) could occur (20). The fat supplement did not stimulate fat oxidation measured over 24 h with a respiration chamber; thus, it was concluded that the excess fat intake was stored.

However, when a very-high-fat load (80 g) was compared with a very-low-fat meal (1 g) otherwise closely matched for carbohydrate and protein, there was a modest rise in fat oxidation by 10 g over the 6-h postprandial period, with a sparing of 20 g carbohydrate (21). It is likely that when lipoprotein lipase is activated by the rise in insulinemia after a very-high-fat meal, some of the fatty acids released from chylomicron triacylglycerols escape storage in adipose cells and pass into the plasma. The enhanced availability of fatty acids for oxidation by muscle will increase fat oxidation somewhat. The overall conclusion of these studies is that within a reasonable range of carbohydrate-to-fat energy ratios, the addition of fat to a meal does not substantially increase fat oxidation.

CONCLUSION

The competition between fatty acids and glucose as oxidative fuel sources is shown clearly in healthy humans when plasma fatty acid concentrations are increased by the infusion of lipid emulsions. There is evidence that the Randle glucose–fatty acid fuel competition model, with an inhibition of muscle pyruvate dehydrogenase activity, explains in part the dose-dependent inhibition of insulin-stimulated glucose uptake and oxidation. A decrease in muscle glycogen synthesis due to a reduction in glucose transporters or phosphorylation, and later to an inhibition of glycogen synthase activity, is also involved. However, in women with visceral obesity (6) and in patients with type 2 diabetes mellitus (12, 13), muscle fatty acid utilization is impaired by fasting hyperglycemia despite elevated plasma fatty acid concentrations. As a result, muscle carbohydrate oxidation increases and lipid

oxidation decreases. The increased glucose availability stimulating glucose oxidation can be considered a corollary of the Randle glucose–fatty acid cycle. By contrast, the competition between fatty acids and glucose is less apparent when fat is given orally. With fat added to a meal, the stimulation of fat oxidation is weak or absent, indicating that dietary fat does not promote fat oxidation in healthy subjects. Further studies are needed to gain insight into the mechanisms involved in the regulation of fat oxidation in obese persons and in those with type 2 diabetes mellitus and the influence of these mechanisms on glucose utilization. 

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