Metabolic interactions between glucose and fatty acids in humans

Robert R Wolfe

ABSTRACT In vivo energy production results largely from the oxidative metabolism of either glucose or fatty acids. Under diverse physiologic and nutritional conditions, the oxidation of either glucose or fatty acids may predominate. The nature of the control of the availability and oxidation of each substrate has been studied extensively for ≥30 y. The most popular and enduring hypothesis was proposed by Randle et al in 1963 and is termed the glucose–fatty acid cycle. This proposal places great significance on the regulation of lipolysis as a factor controlling substrate metabolism. Our work has led to an opposite perspective, which could be called the glucose–fatty acid cycle reversed. According to our hypothesis, the rate of glycolysis, determined by the intracellular availability of glucose-6-phosphate, is the predominant factor determining the rate of glucose oxidation. Whereas the rate of lipolysis may have some effect on the availability of glucose, both via a fatty acid–mediated inhibition of plasma glucose uptake and also by supplying glycerol for gluconeogenesis, there is little evidence for a direct inhibitory effect of fatty acid oxidation on the intracellular oxidation of glucose. In contrast, increased glucose oxidation limits oxidation of long-chain fatty acids directly by inhibiting their transport into the mitochondria. Consequently, whereas there is a close coupling between glucose availability and oxidation, fatty acids are generally available in greater quantities than are required for oxidation. We propose that fatty acid oxidation is largely controlled at the site of oxidation, which is in turn determined by the availability of glucose, rather than by its availability via lipolysis. Am J Clin Nutr 1998;67(suppl):519S–26S.

KEY WORDS Glucose–fatty acid cycle, substrate oxidation, lipolysis, glucose production, glucose oxidation, fatty acid oxidation, glycolysis

INTRODUCTION

There is a constant demand for ATP production to provide energy for the various chemical reactions in the body, such as protein turnover and muscle contraction. ATP is produced largely as a consequence of the oxidative metabolism of glucose and fatty acids. The relation between plasma fatty acids and glucose metabolism has been studied by numerous investigators over the past 30 y. Whereas it is agreed that in normal physiologic circumstances there is generally an inverse relation between the availability of fatty acids and the rate of glucose oxidation, the controlling mechanism of that relation is still unclear.

The plasma concentration of glucose is tightly regulated in relation to its clearance from the blood and, consequently, changes in glucose concentration are normally minimal. The liver is primarily responsible for the release of glucose into the blood, either as a consequence of glycogenolysis or gluconeogenesis. The process of hepatic production and release of glucose is determined largely by concentrations of glucagon and insulin. When the blood glucose concentration decreases, insulin release is diminished and glucagon concentrations increase, thereby stimulating glucose production sufficiently to restore the normal plasma concentration. The reverse happens when glucose concentrations increase, for example, after a meal. Insulin concentrations rise, glucagon concentrations fall, and as a result, hepatic glucose output is suppressed to lower the plasma glucose concentration back toward the basal concentration.

Glucose is phosphorylated immediately on entry into cells, and thus there is a tight linkage between glucose uptake and glucose metabolism. Glucose taken up peripherally can be either stored as muscle glycogen or metabolized via glycolysis to pyruvate. Some of the pyruvate will then be decarboxylated via the pyruvate dehydrogenase enzyme system and enter the tricarboxylic acid cycle as acetyl-CoA for complete oxidation; the remainder will be reduced to lactate and released into the blood, where the liver will clear the lactate and the carbons will be recycled via gluconeogenesis. Pyruvate carbons can also return to the liver via alanine.

The breakdown of intramuscular glycogen is even more closely regulated in relation to the requirement for energy substrate metabolism. Although there may always be some turnover of muscle glycogen (1), in a net sense muscle glycogen breakdown occurs to a significant extent only during strenuous exercise. In this circumstance, glycogen breakdown is coupled to the increased energy requirement caused by muscle contraction (2).

In contrast with the tightly regulated glucose system, the release of fatty acids into the plasma is not regulated in relation to substrate requirements. Furthermore, the plasma fatty acid concentration is unregulated and may vary over a range of five-
fold or more. The release of fatty acids into plasma is largely dictated by the rate of lipolysis of stored triacylglycerol in peripheral fat tissue. Whereas the process of lipolysis is affected by several factors (3), none of these factors are themselves responsive to changes in fatty acid availability. Thus, epinephrine is the most important stimulator of lipolysis, but its release is unrelated to fatty acid concentrations. Rather, it is responsive to drops in blood glucose concentration and blood pressure. Similarly, insulin is the most potent inhibitor of lipolysis, but its release is controlled by the blood glucose concentration. Adenosine is also a potent inhibitor of lipolysis (4), yet the adenosine concentration is highest when the need for fatty acids as energy substrates would seemingly be the highest. Thus, adenosine concentration increases during periods of high turnover of ATP, such as during exercise. It is during periods of high ATP utilization that one would anticipate fatty acid release being stimulated to provide more substrate for energy metabolism, yet it is precisely in this circumstance that adenosine inhibits lipolysis.

The above discussion leads to the conclusion that glucose metabolism is regulated primarily by changes in appearance, whereas fat metabolism is regulated primarily by changes in rate of oxidation. Expressed differently, availability of glucose largely determines the rate of glucose oxidation, but the availability of fatty acids does not determine the rate of fat oxidation. The logical extrapolation from this perspective is that fatty acid oxidation is regulated by the rate of intracellular metabolism of glucose. However, this perspective is in contrast with the traditional view of the normal interaction between glucose and fatty acids.

THE GLUCOSE–FATTY ACID CYCLE: THE TRADITIONAL VIEW

The notion expressed above that the intracellular metabolism of glucose controls substrate metabolism is diametrically opposed to certain aspects of the traditional view of glucose–fatty acid interactions first expressed by Randle et al (5) in 1963. Randle et al termed their hypothesis the glucose–fatty acid cycle. The two essential features of the glucose–fatty acid cycle cited in their seminal paper were 1) the limitation on glucose metabolism imposed by the release of fatty acids from muscle or adipose tissue acylglycerols and 2) the inhibition of release of fatty acids by uptake of glucose. In subsequent years, the cycle was expanded to include hypothesized mechanisms (6). Thus, the inhibitory effects of fatty acids on glucose oxidation have been proposed to be mediated by inhibition of pyruvate dehydrogenase, phosphofructokinase, and hexokinase. The inhibition of pyruvate dehydrogenase has been proposed to be mediated by an increased ratio of acetyl-CoA to CoA, the inhibition of phosphofructokinase has been proposed to be mediated by an increase in citrate, and hexokinase has been proposed to be mediated by glucose-6-phosphate (6).

The glucose–fatty acid cycle provides a potential explanation for substrate interactions in a variety of circumstances. For example, high plasma fatty acid concentrations occur in many insulin-resistant states, such as obesity, type 2 diabetes, or severe trauma and sepsis. The glucose–fatty acid cycle potentially provides a link between high fatty acid concentrations and insulin resistance, because the high fatty acid concentrations should inhibit glucose oxidation and thus uptake by virtue of increased fatty acid oxidation.

The original glucose–fatty acid cycle was based entirely on in vitro results from experiments on rat heart and diaphragm muscle metabolism (5). Several in vitro studies have been done since that time, with conflicting results. Whereas some studies showed an inhibitory effect of fatty acids on glucose oxidation in rat skeletal muscle (7), others found no such effect (8, 9). Maizels et al (10) proposed that a fatty acid effect on glucose oxidation may occur only in red muscle under some circumstances, such as when the rate of glycolysis is increased. Thus, it appears that under certain circumstances, the glucose–fatty acid cycle functions in specific tissues. However, the focus of this review is the in vivo response of human subjects, and it is not clear how these in vitro results relate to the situation in vivo.

Direct support is lacking for control of glucose metabolism by fatty acids in human subjects by the mechanisms originally proposed by Randle et al (5). In studies in which fatty acid concentrations were altered, corresponding changes were not observed in concentrations of either muscle citrate or glucose-6-phosphate (11–14). Nonetheless, the glucose–fatty acid cycle has received widespread acceptance as an explanation for substrate interactions in human subjects (15–17) because in certain circumstances elevating the fatty acid concentration causes a decrease in glucose oxidation. Most evidence in this regard comes from experiments in which the euglycemic-hyperinsulinemic clamp procedure was used in human subjects. With this procedure, the effect of fatty acids on glucose oxidation has been assessed in human subjects by acutely elevating the plasma fatty acid concentration by the infusion of a lipid emulsion plus heparin in the setting of euglycemia-hyperinsulinemia. In this experimental setting, it has generally, but not always, been found that the amount of glucose infusion necessary to maintain euglycemia at any particular insulin concentration is less when the fatty acid concentration is high (17). Furthermore, in this circumstance, glucose oxidation also generally decreases (17), leading to the conclusion that fatty acids inhibit glucose oxidation, ie, a validation of a central component of the glucose–fatty acid cycle.

However, these data can be interpreted differently. There is little doubt that decreased uptake of glucose at any concentration of insulin with increasing fatty acid concentrations indicates an inhibitory effect of fatty acids on glucose transport. This is consistent with the observation of an inhibitory effect of fatty acids on insulin-mediated glucose transport in vitro in soleus muscle (18). On the other hand, in the same study there was no effect of fatty acid concentrations on basal glucose transport in either soleus or epimysial muscle, and fatty acids did not affect insulin-mediated glucose transport in the epimysial muscle (18). Furthermore, fatty acids actually stimulated glucose uptake in adipose tissue (18).

Regardless of whether there is an in vivo effect of fatty acids on glucose transport at the whole-body level, this is not part of the glucose–fatty acid cycle. The glucose–fatty acid cycle proposes that the inhibitory effect of fatty acids is exerted intracellularly on oxidation. This distinction is significant, because if the fatty acid effect is on transport, then a higher concentration of glucose will overcome this limitation and enable a normal rate of glucose oxidation. However, there is no evidence that once glucose is in the cell, there is any impairment of glucose oxidation by fatty acids. For example, data from a representative experiment in which high fatty acid concentrations inhibited glucose uptake during the clamp procedure are summarized in Table 1 (from reference 17). In this study, glucose uptake and oxidation were both reduced when the fatty acid concentration was high. However, the percentage of glucose uptake oxidized, an index not expressed by the
authors, showed no indication of impairment at higher fatty acid concentrations. To consider this point in simplistic terms, what isn’t there, can’t be oxidized. If glucose uptake is reduced, glucose oxidation will be reduced simply because there is less glucose available. These results provide no support for an inhibitory effect of fatty acids on glucose oxidation, and thus do not support the notion that impaired glucose uptake is the result of an intracellular inhibition of glucose oxidation. Nonetheless, this and similar studies have repeatedly been cited as validating the traditional glucose–fatty acid cycle (6).

The failure to show that fatty acids inhibit glucose uptake by inhibiting glucose oxidation is not surprising when it is considered that there are no studies in human subjects showing a role of glucose oxidation in controlling glucose uptake. For example, the data in Table 2 (from reference 19) show the results when burned patients were given dichloroacetate to stimulate pyruvate dehydrogenase activity. Glucose oxidation was significantly stimulated by dichloroacetate, but this did not affect the rate of glucose uptake. Rather, plasma concentrations of lactate and alanine decreased. These results indicate that pyruvate dehydrogenase activity does not regulate the rate of glucose uptake, as proposed in the glucose–fatty acid cycle, but rather determines the fraction of pyruvate production that is oxidized as opposed to being converted to lactate or alanine and released back into the blood.

The euglycemic-hyperinsulinemic clamp procedure is not the best means by which to assess the role of changes of fatty acid concentrations in glucose oxidation. This is because although two potentially important variables are controlled (plasma glucose and insulin concentrations), the most important factor in relation to glucose oxidation (the rate of glucose uptake) is uncontrolled. Because, as pointed out above, changes in glucose oxidation during the clamp procedure are normally directly related to the rate of glucose uptake [and thus glucose infusion (21)], it is impossible to assess the intracellular regulation of glucose oxidation when the rate of glucose infusion is variable. This can best be appreciated by considering the extreme case of no glucose infusion compared with a glucose infusion of 10 mg·kg⁻¹·min⁻¹. Obviously, the rate of glucose oxidation could not be as high in the absence of glucose infusion as during high-dose glucose infusion, simply because there is not as much glucose available.

Because of the limitations in interpreting the results of traditional glucose clamp experiments, we tested the effect of an increase in fatty acid availability on glucose oxidation in the setting of constant glucose uptake (21). To maximize the chances of observing a fatty acid effect on glucose oxidation, a high glucose infusion rate was used to stimulate glycolysis and ensure that virtually all tissues were using glucose as an energy substrate. If some tissues were using fat as an energy substrate already, then it would not be possible for an increase in plasma fatty acids to cause any further increase in fat oxidation in those tissues. To maintain glucose uptake constant at a high rate, normal young adults were preloaded with carbohydrate the evening before the experiment with a high-carbohydrate meal, and then glucose was infused intravenously until the start of the experiment the next day. The respiratory quotient was 0.97 ± 0.07 at the start of the experiment, indicating that essentially all tissues were using glucose as an energy substrate. The experiment consisted of two periods. Glucose was infused at a rate of 8 mg·kg⁻¹·min⁻¹ throughout both periods. In the second period, a lipid emulsion (Intralipid; Kabi Vitrum, Clayton, NC) was given with heparin to raise the plasma fatty acid concentration from 0.04 ± 0.016 to a high of 0.922 ± 0.48 mmol/L. Thus, glucose uptake, dictated by the rate of glucose infusion, remained constant, whereas the plasma fatty acid concentration was increased more than 20-fold.

Glucose oxidation was measured with [U-¹³C]glucose. The results are presented in Table 3. Even such a large increase in plasma fatty acid concentration had a minimal effect on glucose metabolism when glucose uptake was held constant through the

### Table 1

Effect of increasing the fatty acid concentration on glucose uptake and oxidation in normal volunteers

<table>
<thead>
<tr>
<th>Fatty acid concentration (μmol/L)</th>
<th>Insulin concentration</th>
<th>Glucose uptake</th>
<th>Glucose oxidation</th>
<th>Percentage glucose uptake oxidized</th>
</tr>
</thead>
<tbody>
<tr>
<td>161 ± 5 (n = 9)</td>
<td>372 ± 24</td>
<td>5.9 ± 0.4</td>
<td>2.4 ± 0.1</td>
<td>40</td>
</tr>
<tr>
<td>342 ± 13 (n = 6)</td>
<td>372 ± 12</td>
<td>4.5 ± 0.2</td>
<td>1.7 ± 0.1²</td>
<td>38</td>
</tr>
<tr>
<td>650 ± 10 (n = 11)</td>
<td>378 ± 24</td>
<td>3.5 ± 0.2</td>
<td>1.6 ± 0.1</td>
<td>46</td>
</tr>
</tbody>
</table>

1. x ± SEM. Data are from reference 17.
2. Significantly different from the low fatty acid group, P < 0.001.

### Table 2

Response to pyruvate dehydrogenase stimulation during a glucose clamp procedure

<table>
<thead>
<tr>
<th>Insulin and dichloroacetate concentration</th>
<th>Insulin concentration</th>
<th>Glucose uptake</th>
<th>Glucose oxidation</th>
<th>Lactate concentration</th>
<th>Alanine concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>mmol/L</td>
<td>mg·kg⁻¹·min⁻¹</td>
<td>mg·kg⁻¹·min⁻¹</td>
<td>mmol/ml</td>
<td>mmol/ml</td>
<td>mmol/ml</td>
</tr>
<tr>
<td>6.79 ± 0.85</td>
<td>4.60 ± 0.62</td>
<td>9.7 ± 1.2</td>
<td>3.09 ± 0.91</td>
<td>171 ± 23</td>
<td></td>
</tr>
<tr>
<td>3.99 ± 1.17</td>
<td>5.70 ± 1.0</td>
<td>9.6 ± 0.8</td>
<td>0.91 ± 0.08</td>
<td>71 ± 6</td>
<td></td>
</tr>
</tbody>
</table>

1. x ± SEM. Subjects were patients with burn injury. From reference 19.
2. Glucose uptake was estimated to be equal to the glucose infusion rate.
3. Significantly different from insulin alone, P < 0.05.
Effect of plasma fatty acids on glucose oxidation during constant glucose infusion

<table>
<thead>
<tr>
<th>Plasma fatty acid concentration</th>
<th>Glucose uptake</th>
<th>$^{13}$CO₂ excretion</th>
<th>Percentage glucose uptake oxidized</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu$mol · kg⁻¹ · min⁻¹</td>
<td>mg · kg⁻¹ · min⁻¹</td>
<td>$\mu$mol · kg⁻¹ · min⁻¹</td>
<td>%</td>
</tr>
<tr>
<td>Period 1</td>
<td>0.04 ± 0.02</td>
<td>8.64 ± 0.60</td>
<td>0.065 ± 0.009</td>
</tr>
<tr>
<td>Period 2</td>
<td>0.92 ± 0.48</td>
<td>8.65 ± 0.65</td>
<td>0.067 ± 0.008</td>
</tr>
</tbody>
</table>

$\bar{x}$ ± SEM. Glucose was infused at a rate of 8 mg · kg⁻¹ · min⁻¹. Intralipid (Kabi Vitrum, Clayton, NC) and heparin were infused in period 2 to raise the plasma fatty acid concentration. Volumes are the average of the last 30 min of each 2-h period. Glucose kinetics and oxidation were determined by means of [U-¹³C]glucose. From reference 21.

There was no significant effect of fatty acids on glucose concentration, but, interestingly, the indirect calorimetry data indicated a modest increase in fat oxidation and a decrease in total carbohydrate oxidation. The small difference between the isotopic and indirect calorimetry data could be attributed to a change in the extent to which label cycled into and out of glycogen. Regardless of the slight discrepancy between the isotopic and indirect calorimetry data, plasma fatty acids had minimal effects on both plasma glucose uptake and oxidation as determined by either technique.

The conclusion from the study described above, which involved a prolonged glucose infusion and a brief (2 h) increase in fatty acid concentration, may have reflected to some extent an adaptation to the glucose infusion, which does not occur over the normal time course of a euglycemic-hyperinsulinemic clamp procedure. Even so, our findings are consistent with some studies in which the traditional euglycemic-hyperinsulinemic clamp approach was used. For example, Bevilacqua et al (22) found no effect of fatty acids on glucose uptake during a euglycemic clamp study in obese subjects.

The effect of changing the plasma fatty acid concentration on substrate oxidation has also been investigated during exercise. In the absence of any nutrient intake, the utilization of plasma fatty acids as an energy substrate decreases as a proportion of total energy requirements as exercise intensity increases (23). Conversely, the proportionate contribution of energy derived from carbohydrate oxidation increases (23). During high-intensity exercise, the relation between lipolysis and the oxidation of fatty acids is different from the situation at rest. Whereas at rest the fatty acids are normally released into plasma at least twice as fast as they are oxidized (24), during high-intensity exercise the rate of fat oxidation actually exceeds the rate of peripheral lipolysis (23). This is possible because of concurrent intramuscular triacylglycerol lipolysis.

Therefore, to determine whether the availability of fatty acids was limiting for the rate of fatty acid oxidation in high-intensity exercise, we infused Intralipid plus heparin to raise fatty acid concentrations during high-intensity exercise (25). The relation between the rate of appearance of plasma fatty acids ($R_{FA}$) and total fat oxidation (from both plasma and intracellular lipolysis) for different exercise intensities and the response to increasing the $R_{FA}$ during exercise at 85% of maximal oxygen uptake ($\dot{VO}_2_{max}$) are shown in Table 4. First, at progressively higher exercise intensities, the rate of peripheral lipolysis did not increase despite the greatly increased demand for energy. This underscores the lack of regulation of lipolysis and the $R_{FA}$ in relation to substrate requirements. In fact, the $R_{FA}$ decreased significantly when exercise intensity increased from 65% to 85% of $\dot{VO}_2_{max}$, which can be explained by a decrease in adipose tissue blood flow (23). Second, when the $R_{FA}$ was increased from 17 ± 3.4 to 61.0 ± 10.6 $\mu$mol · kg⁻¹ · min⁻¹ by the infusion of Intralipid plus heparin, the rate of fat oxidation increased < 5 $\mu$mol · kg⁻¹ · min⁻¹. Although that increase was statistically significant, fat provided only 35% of the total energy expended during the lipid infusion, even though ample fatty acids were provided to meet most of the energy requirements. Similarly, total carbohydrate oxidation during exercise at 85% of $\dot{VO}_2_{max}$ was significantly reduced by the increase in the $R_{FA}$, but the magnitude of change (12%) was of little physiologic significance compared with the 350% increase in the $R_{FA}$.

The minimal effect of changing the $R_{FA}$ on glucose oxidation during exercise at 85% of $\dot{VO}_2_{max}$ is consistent with other observations during exercise. Ravussin et al (26) measured the respiratory exchange ratio (RER) during 2.5 h of exercise at 42–47% of $\dot{VO}_2_{max}$ during control conditions (ie, saline infusion) and also when the plasma fatty acid concentration was raised via intravenous lipid-heparin infusion. Their data indicated that increasing the plasma fatty acid concentration did not increase the rate of fat oxidation. However, close inspection of their data reveals that RER values were significantly higher in the lipid infusion group at some of the time points when plasma fatty acid concentrations were lowered by the ingestion of exogenous glucose. On the other hand, when plasma fatty acid concentrations were > 0.7 mmol/L during the control conditions, the RER was not significantly different from that with lipid-heparin infusion. Consistent with this finding, Hargreaves et al (13) raised plasma fatty acid concentrations from fasting control concentrations of 0.6 mmol/L to > 1 mmol/L via lipid-heparin infusion while measuring metabolism of the knee extensor muscles and arteriovenous differences. Lipid-heparin infusion had no significant effect on muscle glycogen use or respiratory quotient in the exercising leg, although there was a lower rate of blood glucose uptake and whole-body RER during lipid-heparin infusion (13). Thus, whereas there might be an effect of changing fatty acid concentrations on glucose oxidation when fatty acid concentrations are < 0.6 mmol/L, there is no effect of raising fatty acid concentrations > 0.7 mmol/L.

The preponderance of data from in vivo experiments indicate that fatty acids do not directly control the rate of glucose oxidation at a cellular level. Furthermore, evidence indicates that plasma fatty acids affect only glucose clearance, and thus the plasma glucose concentration, in certain specific circumstances. In particular, fatty acids may inhibit glucose transport in the insulin-stimulated state but not in the basal state. Because the inhibitory effect of fatty acids on glucose oxidation is the cornerstone of the glucose–fatty acid cycle (5), we must reject that traditional explanation of glucose–fatty acid kinetics.
There is no doubt that there is a reciprocal relation between fatty acid and glucose oxidation. If from the above discussion we can conclude that this relation is not controlled by the metabolism of fatty acids, it is logical to propose the reverse of the traditional glucose–fatty acid cycle, ie, that the intracellular metabolism of glucose controls the rate of fatty acid oxidation. In the following section, support for this notion will be provided, including evidence for a proposed mechanism whereby this process may be controlled.

THE GLUCOSE-FATTY ACID CYCLE REVERSED

Effect of glucose on lipolysis

A glucose effect on fatty acid metabolism could be controlled by either regulation of lipolysis or control of fatty acid oxidation. There is little doubt that glucose infusion or ingestion inhibits lipolysis and decreases the release of fatty acids into the blood. The response to glucose infusion is dependent on the dose of glucose (27). At a low glucose infusion rate (4 mg · kg\(^{-1} \cdot \) min\(^{-1}\)), which causes glucose and insulin concentrations of 7.2 mmol/L and 120–150 pmol/L, respectively, both lipolysis and the \(R_{FA}\) are suppressed. During glucose infusion at 8 mg · kg\(^{-1} \cdot \) min\(^{-1}\) (glucose = 10.5 mmol/L, insulin = 240 pmol/L), the \(R_{FA}\) was further suppressed but lipolysis was not lower than during the glucose infusion of 4 mg · kg\(^{-1} \cdot \) min\(^{-1}\) (27). The higher glucose uptake stimulated the extent to which fatty acids released into the adipocytes as a consequence of lipolysis were reesterified into triacylglycerol without ever appearing in the blood (27). This presumably reflects the fact that availability of \(\alpha\)-glycerol phosphate, which is the backbone of newly formed triacylglycerol and which, in the adipocyte, is derived from the metabolism of plasma glucose, is rate limiting for the process of reesterification.

The inhibition of lipolysis during glucose infusion is mediated predominantly by insulin. When the plasma glucose concentration is held constant and glucose is infused to maintain euglycemia, the appearance of fatty acids is inhibited in a dose-dependent manner (28). Conversely, when glucose is infused at different rates but the insulin concentration is maintained constant by the infusion of somatostatin to inhibit insulin secretion and the replacement of the basal insulin concentration by a constant infusion, lipolysis is not significantly suppressed by glucose (29, 30).

The inhibitory effect of insulin on lipolysis was a key part of the original glucose–fatty acid cycle (5). The control of lipolysis by insulin was proposed to be the mechanism whereby fatty acid oxidation decreased when carbohydrate availability was high. However, in the preceding sections we documented that the availability of plasma fatty acids is not a primary determinant of the rate of fat oxidation. Rather, different rates of fat oxidation for a particular \(R_{FA}\) are determined by the availability of glucose (discussed below). As a consequence, unmetabolized fatty acids are cleared from the blood and reesterified into triacylglycerol. The liver is a major site of fatty acid clearance. Those fatty acids taken up by the liver that are not oxidized are reesterified into triacylglycerol and secreted into the blood as VLDL triacylglycerol. In general, the rate of VLDL triacylglycerol secretion is related to the availability of fatty acids (31). However, during periods of hyperglycemia and hyperinsulinemia, hepatic oxidation of fatty acids is low, and fatty acids that are taken up by the liver are more efficiently channeled into triacylglycerol.

We found that in normal volunteers given a continuous high-carbohydrate feeding for 4 d, not only was the hepatic secretion of VLDL triacylglycerol derived from newly synthesized fatty acids increased significantly, so too was the rate of secretion of VLDL triacylglycerol derived from reesterified fatty acids (32). Even with the inhibitory effect on lipolysis during prolonged hyperglycemia and hyperinsulinemia, the reesterification of plasma fatty acids was the predominant pathway for the production of VLDL triacylglycerol. This occurred because of an increased fractional reesterification of nonoxidized fatty acids (32). The result was sustained hypertriglyceridemia (Table 5). The channeling of fatty acids in the liver to VLDL triacylglycerol production, as opposed to oxidation, could potentially be explained by an inhibition of hepatic fatty acid oxidation by glucose. This process is discussed below.

Effect of glucose on fatty acid oxidation

We recently tested the effect of the acute elevation of glucose availability and oxidation on fatty acid oxidation in the setting of constant fatty acid concentrations (33). Normal volunteers were studied in the basal state and during a hyperinsulinemic, hyperglycemic clamp procedure (plasma insulin = 1789 ± 119 pmol/L, 25 mmol/L, and insulin = 240 pmol/L, 20–25 \(\mu\)U/mL, respectively).

<table>
<thead>
<tr>
<th>Table 4</th>
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<tbody>
<tr>
<td>Effect of exercise intensity and plasma fatty acid concentration on fat and carbohydrate oxidation</td>
</tr>
</tbody>
</table>

| Exercise intensity (\% of \(V_{O_2\max}\)) | Metabolism during exercise |
| --- | --- | --- | --- | --- |
| Peripheral lipolysis | Plasma RaFA | Total fat oxidation | Carbohydrate oxidation |
| 85 | 9.8 ± 1.6 | 25.8 ± 2.6 | 26.8 ± 1.8 | 15 ± 1.8 |
| 65 | 6.9 ± 0.6 | 22.8 ± 2.7 | 42.8 ± 3.7 | 132 ± 7.9 |
| 85 | 8.5 ± 2.5 | 17.0 ± 4.2 | 29.6 ± 4.3 | 259 ± 8.0 |
| 85 + lipid | — | 61.0 ± 10.6 | 34.0 ± 4.4 | 230 ± 9.1 |

\(\pm\) SEM. \(V_{O_2\max}\), maximal oxygen uptake; RaFA, rate of appearance of fatty acids. From references 23 and 25.
plasma glucose = 7.7 ± 0.2 mmol/L). In this study it was found that increased availability of glucose inhibited fat oxidation, despite the constant availability of fatty acids (Table 6). This result is precisely contrary to that predicted by the traditional glucose–fatty acid cycle, and leads to the conclusion that the intracellular availability of glucose (rather than fatty acids) determines the nature of substrate oxidation in human subjects.

To assess the mechanism by which glucose inhibits fatty acid oxidation, we investigated the hypothesis that glucose, insulin, or both inhibit entrance of fatty acids into the mitochondria (34). We gave constant infusions of [1–13C]oleate, a long-chain fatty acid, and [1–14C]octanoate, a medium-chain fatty acid, in the basal state and during a hyperglycemic and hyperinsulinemic state. Plasma oleate enrichment and fatty acid concentration were maintained constant by means of the infusion of Intralipid and heparin. Oleate, but not octanoate, requires carnitine acyltransferase to gain access to the mitochondrial matrix. Thus, if glucose or insulin limit long-chain fatty acid entrance into the mitochondria, then during the clamp procedure, long-chain acylcarnitine formation should be decreased, causing a decrease in oleate but not octanoate oxidation. During the clamp procedure, oleate oxidation decreased from the basal value of 0.9 ± 0.1 to 0.4 ± 0.1 µmol·kg⁻¹·min⁻¹. In contrast, octanoate oxidation remained unchanged in the transition from basal to clamp conditions. The conclusion that glucose or insulin directly limits fatty acid oxidation by restricting long-chain fatty acid entrance into the mitochondria was supported by a decrease in intramuscular acylcarnitine concentration from 843 ± 390 in the basal state to 296 ± 77 nmol/g dry wt during the clamp procedure (34).

**TABLE 5**

<table>
<thead>
<tr>
<th>Triacylglycerol (TG) kinetics during prolonged hyperglycemia and hyperinsulinemia¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>TG concentration (mmol TG/L)</td>
</tr>
<tr>
<td>VLDL-TG secretion (µmol TG·kg⁻¹·min⁻¹)</td>
</tr>
<tr>
<td>VLDL-TG secretion from reesterified FA (µmol TG·kg⁻¹·min⁻¹)</td>
</tr>
<tr>
<td>VLDL-TG secretion from newly synthesized FA (µmol TG·kg⁻¹·min⁻¹)</td>
</tr>
</tbody>
</table>

¹ ± SEM. FA, fatty acid. From reference 32.
²Significantly different from basal value, P < 0.01.

**TABLE 6**

<table>
<thead>
<tr>
<th>Effect of hyperinsulinemia-hyperglycemia on glucose and fatty acid oxidation¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose concentration (mmol/L)</td>
</tr>
<tr>
<td>Glucose oxidation (µmol·kg⁻¹·min⁻¹)</td>
</tr>
<tr>
<td>Fatty acid concentration (mmol/L)</td>
</tr>
<tr>
<td>Fatty acid oxidation (µmol·kg⁻¹·min⁻¹)</td>
</tr>
</tbody>
</table>

¹ Mean ± SEM. From reference 33.
²Significantly different from basal value, P < 0.01.

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**PHYSIOLOGIC ROLE OF GLUCOSE AVAILABILITY IN CONTROLLING METABOLISM**

One of the appealing aspects of the traditional glucose–fatty acid cycle was that it was consistent with certain physiologic and pathologic circumstances. For example, high plasma fatty acid concentrations are associated with many insulin-resistant states, such as obesity (35), type 2 diabetes (36), and severe trauma and sepsis (37). The glucose–fatty acid cycle potentially provides a link between high fatty acid concentrations and insulin resistance, because the high fatty acid concentrations should lead to increased fatty acid oxidation, which in turn should inhibit glucose uptake and oxidation (ie, cause insulin resistance). However, we established in the previous sections that this explanation is not likely. Consequently, it is pertinent to consider the physiologic regulation of substrate metabolism with glucose availability as the controlling factor.

Much of the early work describing metabolic regulation from a physiologic perspective came from the study of responses to fasting (38). With progressive fasting, fatty acid concentrations rise and glucose concentrations decrease, and fat becomes essentially the sole nonprotein energy substrate. According to traditional explanations, high fatty acid concentrations inhibit glucose uptake, which limits gluconeogenesis and therefore serves to spare protein (6). In this case, however, the plasma glucose concentration would have to increase to signal the liver, yet this does not happen. Furthermore, there is no evidence either in vitro or in vivo that high fatty acid concentrations exert an inhibitory effect on basal glucose uptake. We infused enough glucose in normal, fasting volunteers to maintain the normal postabsorptive concentration during fasting (39). Fatty acid concentrations nonetheless increased, but rather than causing a corresponding decrease in glucose clearance, basal glucose clearance actually increased over the 3-d period (39).

Thus, there are many flaws in the notion that fatty acid availability controls substrate metabolism in fasting. In contrast, invoking glucose availability as the controlling factor in modulating changes in substrate metabolism with fasting makes a more consistent explanation possible. The decreased availability of hepatic glycogen with fasting leads to a decrease in the availability of plasma glucose, causing a decrease in glucose oxidation, thereby inhibiting fat oxidation. Contrary to the notion that the increase in fatty acid concentration stimulates fat oxidation in fasting, we propose that the primary physiologic role of the increased rate of lipolysis in fasting is to provide glycerol as a gluconeogenic precursor (40). After an overnight fast there are already more than enough fatty acids available to easily satisfy energy requirements, and the stimulation of lipolysis in prolonged fasting is unrelated to any demand for excess energy substrates. The controlling role of the plasma glucose availability in determining the rate of fat oxidation in the liver in fasting is indicated by the marked reduction in plasma ketone concentration (reflecting fat oxidation) when the normal postabsorptive plasma glucose concentration is maintained (39).

Another response that can be better explained by glucose, rather than fatty acids, controlling substrate metabolism is the
increase in triacylglycerol concentration with excessive carbohydrate intake (41, 42), yet recent studies indicate a limited capacity for hepatic fatty acid synthesis (43). We propose that high glucose intakes inhibit fatty acid oxidation in the liver, thereby channeling fatty acids into triacylglycerol.

The notion of glucose availability controlling metabolism is also consistent with experimental evidence during exercise. Under normal circumstances, fatty acid oxidation increases as exercise intensity increases from low (25% of $V_{\text{O2 max}}$) to moderate (65% of $V_{\text{O2 max}}$) intensity, but decreases as intensity exceeds 65% (23). This can be explained by stimulation of muscle glycogenolysis during high-intensity exercise, which leads to increased glycolytic flux and thus inhibition of fatty acid oxidation. With endurance training, fat is used to a greater extent than carbohydrate at the same exercise intensity as in the untrained state. This is related to a stimulation of lipolysis in trained individuals, both in the resting state (44) and during exercise (45). Traditionally, it has been thought that the greater availability of fat with training decreased muscle protein glycogen breakdown by inhibiting glycolysis at the phosphofructokinase step (6). However, Coggan et al (46) could not confirm this mechanism. In contrast, they found that muscle glucose-6-phosphate was significantly lower in the trained state, indicating that training-induced reduction in carbohydrate utilization results from attenuation of flux before the phosphofructokinase step in glycolysis (46). It thus seems likely that training results in a reduced rate of glucose breakdown and that fatty acid oxidation is greater because of decreased availability of pyruvate for oxidation.

Providing an explanation of the altered substrate kinetics in diabetes was one of the original reasons for the glucose–fatty acid cycle (5). We propose that in insulin-resistant states such as diabetes, an impaired rate of glucose uptake leads to increased fatty acid oxidation, rather than the reverse. A variety of mechanisms may be responsible for the impaired glucose uptake. A deficiency in glycogen synthesis is a likely possibility.

Although it is clear that the traditional glucose–fatty acid cycle is flawed, it clearly would not have endured so long if it had absolutely no merit. Indeed, in many circumstances, some fatty acid effect on glucose can be shown, even if glucose availability predominates in importance. The modest increase in fatty acid oxidation during exercise when fatty acid concentrations were elevated (Table 4) is a good example. Thus, whereas glucose availability predominates in determining the mix of substrate oxidation, there is a reciprocal relation between glucose and fatty acids in which fatty acid availability also plays a role, albeit a minor one. This is to be expected, considering that the mechanism whereby glucose inhibits fatty acid oxidation is by limiting their entry into mitochondria by inhibiting carnitine acyltransferase. For any given enzyme activity, within some range of substrate concentration, a greater concentration of fatty acids will cause more fatty acyl-CoA to be transferred to the mitochondria. Our studies of octanoate metabolism indicate that once inside the mitochondria, there is no inhibitory effect of glucose on β-oxidation of fatty acids. Consequently, whereas our explanation of the normal relations between glucose and fatty acids places great weight on glucose availability as the controlling factor, the mechanism whereby glucose controls metabolism can be overridden to a modest extent when there are large changes in fatty acid concentrations. Furthermore, a direct effect of fatty acids on glucose clearance may also exert some control over substrate oxidation in certain circumstances, provided that the actual rate of glucose uptake is impaired.

REFERENCES

23. Romijn JA, Coyle EF, Sidossis LS, et al. Regulation of endogenous fat and carbohydrate metabolism in relation to exercise intensity and


