Alterations in carbohydrate metabolism in response to short-term dietary carbohydrate restriction

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ALTERATIONS IN DIETARY MACRONUTRIENT CONTENT can exert a profound influence on lipid and carbohydrate metabolism. More specifically, dietary carbohydrate restriction presents a challenge in maintaining systemic glucose availability because of the limited carbohydrate storage capacity in the human body. Despite the well-known sensitivity of the human body to carbohydrate availability, the metabolic influence of dietary carbohydrate restriction is not well understood. It has been postulated that a reduction in carbohydrate availability primarily mediates the metabolic responses to fasting (15), indicating that low carbohydrate availability may be a stronger metabolic regulator than a negative energy balance per se. However, little is known about the metabolic effects of carbohydrate restriction without the confounding influence of weight loss or negative energy balance.

Carbohydrate restriction has been found to elicit an adaptive increase in fat oxidation within about 7 days (27). This adaptation in fat oxidation may help delay the development of hypoglycemia when carbohydrate availability is very low by reducing the reliance on glucose for energy. However, blood glucose concentration is determined by the balance between glucose uptake and glucose production, and unfortunately, the effect of carbohydrate restriction on endogenous glucose production is poorly understood. Previous studies examining the influence of eucaloric dietary carbohydrate restriction on endogenous glucose availability have produced equivocal findings. For example, Koutsari and Sidossis (16) found that 14 days of a weight-maintaining, low-carbohydrate diet did not alter endogenous glucose production, whereas Bisschop et al. (2) reported that endogenous glucose production was reduced ~15% after 11 days of a weight-maintaining, low-carbohydrate diet. Additionally, because alterations in fat (27) and carbohydrate (22) metabolism are occurring in the initial days of dietary carbohydrate restriction, it is likely that endogenous glucose production is altered in the early phase of the adaptation to a low-carbohydrate diet. To our knowledge, alterations in endogenous glucose production during the first few days of dietary carbohydrate restriction have not been examined. Therefore, the main purpose of this study was to examine the influence of short-term eucaloric dietary carbohydrate restriction on endogenous glucose production and uptake and whole body oxidation.

METHODS

Eight healthy subjects (4 men and 4 women) participated in this study (means ± SE; age = 29 ± 4 yr; weight = 71 ± 4 kg; BMI = 24.2 ± 1.1 kg/m²). Subjects had no evidence of metabolic or cardiovascular disease, and none were taking any prescription medications. All women were premenopausal and were studied during the first 2 wk of their menstrual cycle. All subjects were sedentary (i.e., performed <1 h of exercise/wk). All subjects were fully informed of the possible risks associated with the study and signed an informed consent form approved by the University of Michigan Institutional Review Board.

Experimental Design

Figure 1 outlines the general experimental design of this study. Subjects reported to the General Clinical Research Center (GCRC) at the University of Michigan Hospital at 1200, 2 days before beginning...
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Fig. 1. General experimental design and timeline. Subjects were admitted to hospital 2 days before beginning the carbohydrate-restricted diet (day −2) and remained in the hospital throughout the 9-day study. Bx, muscle biopsy.

Analytical Methods

Stable isotope analysis. Plasma samples (250 μl) were deproteinized with 3 ml of ice-cold acetone and incubated at −20°C for 15 min, followed by centrifugation for 20 min at 4,000 rpm. The supernatant was transferred to a new tube and added to 3 ml of hexane and 3 ml of distilled H2O, mixed gently for 15 min on a platform shaker, and centrifuged for 15 min at 4,000 rpm. The upper (hexane) layer was then discarded and the lower (aqueous) layer dried down overnight under vacuum. Hydroxyxylamine-pyridine solution (100 μl) was added to dried samples and heated at 100°C for 30 min. Acetic anhydride (75 μl) was then added, and samples were incubated at 100°C for 1 h and then dried down under vacuum. Samples were then resuspended in ethyl acetate (100 μl) and analyzed via electron impact ionization using a gas chromatograph-mass spectrometer (Agilent 6890 gas chromatograph with 5973 mass selective detector). The masses of 187 and 189 of the pentaacetate derivative of glucose were assessed using selective ion monitoring.

Plasma substrate and insulin concentration. Plasma insulin concentration was measured by radioimmunoassay kit (Linco Research, St. Charles, MO). Plasma glucose (ThermoDMA, Arlington, TX), fatty acid (Wako Chemicals, Neuss, Germany), 3-hydroxybutyrate (Ranbuk, UK), and triacylglycerol (Sigma Chemicals, St. Louis, MO) concentrations were measured using commercially available colorimetric assay kits. Plasma glycerol concentration was determined by gas chromatography-mass spectrometry using [2,1-13C]glycerol as an internal standard. Plasma lactate concentration was measured spectrophotometrically (12).

Muscle glycogen concentration. Muscle glycogen was determined from the measurement of glucose after acid hydrolysis (20). Briefly, muscle samples were homogenized and then hydrolyzed in 2 N HCl and heated at 100°C for 2 h. Samples were then neutralized using 1 N NaOH to pH 6.5–7.5, and the free glucose concentration was determined by colorimetric assay.

Calculations

Energy expenditure. Resting metabolic rate was calculated from resting VO2 and VCO2 measurements using the Weir equation (33).

Carbohydrate oxidation. Resting carbohydrate oxidation rate was calculated from resting VO2 and VCO2 using the equations of Frayn (9).

Glucose rates of appearance and disappearance. Glucose rate of appearance (Ra) was calculated by using the Steele equation for steady-state conditions (31). Because measurements were made under steady-state conditions, glucose Ra = glucose rate of disappearance (Rd).

Percent glucose Rd oxidized. The relative proportion of glucose uptake that was oxidized was estimated using the following equation:

\[ \text{% glucose } R_d \text{ oxidized} = \frac{\text{glucose } R_d \text{ / carbohydrate oxidation}}{100} \]  

Nonoxidative glucose disposal. The amount of glucose that was taken up and not oxidized (i.e., glucose storage) was estimated using the following equation:

\[ \text{nonoxidative glucose disposal} = \text{glucose } R_d - \text{ carbohydrate oxidation} \]

Statistical Analysis

A one-way analysis of variance (ANOVA) for repeated measures with Tukey post hoc analysis was used to determine differences in

Dietary interventions.

After being admitted to the hospital, subjects ate a standardized diet for 2 days consisting of 60% carbohydrate, 30% fat, and 10% protein and a daily caloric content estimated to maintain body weight (i.e., kcals = 1.3 X REE (28)). During the 1-wk carbohydrate-restricted diet, subjects consumed a weight-maintaining (i.e., kcals = 1.3 X REE), low-carbohydrate diet consisting of 5% carbohydrate, 60% fat, and 35% protein. To maintain energy balance during carbohydrate restriction, total fat and protein intake was increased, thus making the carbohydrate-restricted diet relatively high in fat and protein. On most days, meals were served at 0800, 1300, and 1830. However, on days in which glucose kinetics were measured, the meals were delayed until 1300, 1645, and 1945.

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Nonoxidative glucose disposal. The amount of glucose that was taken up and not oxidized (i.e., glucose storage) was estimated using the following equation:

\[ \text{nonoxidative glucose disposal} = \text{glucose } R_d - \text{ carbohydrate oxidation} \]

Statistical Analysis

A one-way analysis of variance (ANOVA) for repeated measures with Tukey post hoc analysis was used to determine differences in
body weight, fat mass, fat-free mass, glucose Ra and Rd, %glucose Rd oxidized, nonoxidative glucose disposal, muscle glycogen concentration, and plasma concentrations of glucose, glycerol, fatty acids, triacylglycerol, lactate, and 3-hydroxybutyrate. P ≤ 0.05 was considered statistically significant.

RESULTS

Body Weight and Composition

One week of the carbohydrate-restricted diet did not affect body composition. Percent body fat, total fat mass, and fat-free mass were not different before compared with after the diet (Table 1). However, the 2% reduction in total body weight during the 7 day diet (i.e., 1.0 ± 0.5 kg weight loss) was statistically significant (P = 0.01).

Plasma Glucose Concentration, Endogenous Glucose Production, and Glucose Uptake

In the early stages of carbohydrate restriction, postabsorptive plasma glucose concentration decreased and was significantly reduced to below baseline levels (P = 0.01) on the morning of the 3rd day of the diet (Fig. 2A). This reduction in plasma glucose was transient, as fasting plasma glucose concentration returned to baseline levels the next day (day 4) and remained stable throughout the remainder of the dietary intervention (Fig. 2A). In parallel with the early reduction in plasma glucose concentration, postabsorptive glucose Ra was reduced nearly 20% after 2 days of carbohydrate restriction (P < 0.001; Fig. 2B). However, despite the return to euglycemia by the 4th day of the diet, glucose Ra remained suppressed below baseline levels after 7 days of the diet (P < 0.001). Because the postabsorptive measurements were made in steady state (i.e., Ra = Rd), the rate of glucose uptake (glucose Rd) was also suppressed ~20% with carbohydrate restriction (Fig. 2B).

Plasma Insulin Concentrations

Despite dietary carbohydrate restriction, postabsorptive plasma insulin concentration was unaffected throughout the dietary intervention (Fig. 3A). However, 24-h insulin concentration (area under the curve, measured hourly) was more than 50% lower (P < 0.001) after 1 day of carbohydrate restriction and remained suppressed throughout the dietary intervention (Fig. 3B).

Plasma Fatty Acid, Ketone, Glycerol, Triacylglycerol, and Lactate Concentrations

Postabsorptive plasma fatty acid and 3-hydroxybutyrate concentrations were significantly increased above basal levels (P < 0.001) after 1–2 days on the low-carbohydrate diet and remained elevated (P < 0.001) after 7 days on the diet (Fig. 4, A and B). Conversely, carbohydrate restriction did not alter postabsorptive plasma glycerol concentration (Fig. 4C). Post-

Table 1. Body composition before and after 7-day carbohydrate-restricted diet

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
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<tbody>
<tr>
<td>Body weight, kg</td>
<td>70.5 ± 3.7</td>
<td>69.5 ± 3.6*</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>28.7 ± 4.7</td>
<td>28.3 ± 4.9</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>20.2 ± 3.0</td>
<td>19.7 ± 3.2</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>50.3 ± 3.6</td>
<td>49.9 ± 3.6</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SE. *Significantly different from values measured before carbohydrate-restricted diet, P = 0.01.
absorptive plasma triacylglycerol concentration was reduced ($P = 0.01$) to below baseline levels only after 2 and 7 days on the carbohydrate restricted diet (Fig. 4D). Additionally, postabsorptive plasma lactate concentration tended to be lower after 2 days ($0.75 \pm 0.09$ mmol/l, $P = 0.14$) and 7 days ($0.70 \pm 0.06$ mmol/l, $P = 0.08$) of carbohydrate restriction compared with baseline levels ($0.89 \pm 0.06$ mmol/l).

**Carbohydrate Oxidation and Nonoxidative Glucose Disposal**

Carbohydrate restriction reduced postabsorptive carbohydrate oxidation $43 \% \pm 8\%$ ($P < 0.001$) after 1 day and further suppressed carbohydrate oxidation by $74 \% \pm 8\%$ ($P < 0.001$) below basal levels after 7 days (Table 2). Although the observed reduction in glucose uptake (glucose $R_d$) might have contributed to this decline in carbohydrate oxidation, the proportion of glucose uptake that was oxidized ($\%$glucose $R_d$ oxidized) was also reduced (Table 2). Because the reduction in carbohydrate oxidation was greater than the decline in glucose uptake, the carbohydrate-restricted diet actually increased the rate of nonoxidative glucose disposal (i.e., carbohydrate storage) in the postabsorptive state more than threefold (Table 2).

**Muscle Glycogen**

Despite the reduction in carbohydrate oxidation and restricted physical activity during the dietary intervention in the hospital, carbohydrate restriction reduced muscle glycogen concentration by more than 20% ($P = 0.04$; Fig. 5).

**DISCUSSION**

The reliance of the central nervous system on blood glucose for fuel requires glucose availability to be tightly regulated. Due to limited endogenous carbohydrate stores, dietary restriction of carbohydrate requires marked metabolic adaptations to prevent hypoglycemia. In the face of dietary carbohydrate restriction, adaptations in the uptake and oxidation of carbo-

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**Table 2. Carbohydrate oxidation, $\%$glucose $R_d$ oxidized, and nonoxidative glucose disposal before and during carbohydrate-restricted diet**

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After 2 Days</th>
<th>After 7 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate oxidation, $\mu$mol/kg$^{-1}$min$^{-1}$</td>
<td>8.2±0.7</td>
<td>5.2±0.5*</td>
<td>3.2±0.5*</td>
</tr>
<tr>
<td>$%$Glucose $R_d$ oxidized</td>
<td>86±7</td>
<td>66±7†</td>
<td>38±6*†</td>
</tr>
<tr>
<td>Nonoxidative glucose disposal, $\mu$mol/kg$^{-1}$min$^{-1}$</td>
<td>1.6±0.8</td>
<td>2.7±0.5</td>
<td>5.2±0.5†+</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SE. $R_d$, rate of disappearance. *Significantly different from before carbohydrate-restricted diet, $P < 0.001$. †Significantly different from after 2 days of carbohydrate-restricted diet, $P = 0.04$. ‡Significantly different from before carbohydrate-restricted diet, $P = 0.05$. 

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**Fig. 5. Muscle glycogen concentration before and after 7-day carbohydrate-restricted diet. Values are means ± SE. *Significantly different from before diet.**
hydrates help prevent hepatic glycogen depletion and maintain plasma glucose concentration. The main finding of this study was that, although endogenous glucose production and systemic glucose uptake were reduced with dietary carbohydrate restriction, the reduction in whole body carbohydrate oxidation exceeded the reduction in systemic glucose uptake. Therefore, the nonoxidative rate of glucose disposal actually increased in the postabsorptive state with carbohydrate restriction. This adaptation can help prevent liver glycogen depletion and thereby may play an important role in preventing hypoglycemia when dietary carbohydrate availability is very low.

Restricting daily carbohydrate intake to very low levels reduces hepatic glycogen content (19), thereby suppressing hepatic glucose production. Similar to the present findings, Bisschop et al. (2) reported a 15% reduction in postabsorptive glucose $R_T$ after 11 days of a weight-maintaining diet containing ≤5% of total calories as carbohydrate (i.e., ≤25 g carbohydrate/day). The present study expands on these findings by demonstrating that endogenous glucose production does not decline progressively over several days of dietary carbohydrate restriction but rather declines after 1 day of the diet and remains at this suppressed level for at least 1 wk. The magnitude of reduction in glucose $R_T$ during carbohydrate restriction while maintaining energy balance was about one-half of the reported reduction in postabsorptive glucose $R_T$ after 4 days of total fasting (13). Because the very small amount of carbohydrate ingested in this study represented <10% of 24-h systemic glucose availability, this difference in glucose $R_T$ between our carbohydrate-restricted diet and total fasting cannot simply be due to the small amount of exogenous carbohydrate we provided. Therefore, maintaining energy balance while restricting carbohydrate intake attenuates the reduction in endogenous glucose production compared with fasting. In contrast to our findings, Koutsari and Sidossis (16) reported that 2 wk of a weight-maintaining, low-carbohydrate diet did not affect endogenous glucose production. However, their diet provided 30% of the daily caloric content as carbohydrate (i.e., ~150 g of carbohydrate), which was likely enough to prevent a suppression of endogenous glucose production.

The reduction in endogenous glucose production with carbohydrate restriction is primarily due to a suppression of hepatic glycogenolysis (2). In a classic study, Nilsson, and Hultman (19) found glycogen concentration in liver biopsy samples to be essentially depleted after a short-term, low-carbohydrate diet. However, several more recent studies report that, although carbohydrate restriction reduced hepatic glycogenolysis, liver glycogen continued to contribute substantially to total hepatic glucose production (2, 11). In fact, Hellerstein et al. (11) found that hepatic glycogenolysis still contributed about one-third of the total glucose production after nearly 3 days of fasting. If liver glycogen continues to be a major contributor to hepatic glucose production, in contrast to the findings of Nilsson and colleagues (18, 19), it is unlikely that short-term carbohydrate restriction depletes liver glycogen concentration. This issue is confounded by the fact that during carbohydrate deprivation the rate of hepatic glycogenolysis is high enough to deplete liver glycogen in about 1 day (2). This suggests that liver glycogen must be resynthesized from glucose derived from gluconeogenesis and from glucose being taken up from the systemic circulation. In the present study, we suspect that liver glycogen concentration continued to contribute to hepatic glucose production, which helped to maintain blood glucose concentration.

Coinciding with the decline in glycogenolysis, gluconeogenesis is modestly increased in response to restriction of dietary carbohydrate (2). However, the increase in gluconeogenesis cannot fully compensate for the reduction in glycogenolysis, and therefore glucose $R_T$ is reduced. Gluconeogenesis is partially regulated by both plasma insulin (10) and circulating fatty acids (7). In the present study, although postabsorptive plasma insulin concentration was not significantly reduced with carbohydrate restriction, 24-h insulin concentration was greatly affected because of the marked difference in postprandial insulin concentrations before compared with during the diet. This reduction in 24-h insulin exposure may act directly on hepatic glucose production by stimulating the gluconeogenic pathway (4, 10) or indirectly by increasing lipolytic rate and subsequently increasing the availability of gluconeogenic precursors (e.g., glycerol) (6). Although lipolytic rate is known to increase with carbohydrate restriction (16, 32) (as noted in the present study by a marked increase in plasma fatty acid concentration), we did not find an increase in plasma glycerol concentration, which is commonly used as a marker for lipolysis. This disparity between the changes in plasma fatty acid and glycerol concentrations suggests that glycerol uptake may be increased in an effort to enhance the rate of gluconeogenesis. Additionally, an increase in fatty acid availability can also stimulate gluconeogenesis (25) and acutely increase endogenous glucose production when plasma insulin is low (3). Although the contribution of reduced insulin concentration and/or increased fatty acid availability on gluconeogenesis and hepatic glucose production cannot be quantified in the present study, it is likely that both mechanisms play a role in the maintenance of glucose homeostasis in response to short-term dietary carbohydrate deprivation.

Unlike endogenous glucose production and systemic glucose uptake, which decreased rapidly after 1 day of the carbohydrate-restricted diet and remained at low levels at the end of the week, the reduction in carbohydrate oxidation with carbohydrate restriction occurred more gradually during the dietary intervention. The relatively slow rate of this adaptation in the relative contribution of carbohydrate and fat to total energy expenditure is linked with changes in glycogen concentration (26). During the first few days of carbohydrate restriction, the reduction in carbohydrate intake was greater than the decline in carbohydrate oxidation. This requires increased reliance on endogenous carbohydrate stores for fuel, which can slowly reduce muscle and/or liver glycogen concentrations. Although we did not measure liver glycogen content, this adaptive response is supported by our finding that muscle glycogen declined ~20% after 1 wk of carbohydrate restriction despite very limited physical activity while the subjects were confined to the hospital. The increase in plasma fatty acid concentrations also likely contributed to the adaptive suppression of carbohydrate oxidation by inducing pyruvate dehydrogenase kinase (PDK) expression and activity in the liver (8) and skeletal muscle (30), with a resultant inhibition of pyruvate dehydrogenase (PDH) activity. Indeed, the suppression of carbohydrate oxidation induced by a short-term carbohydrate-restricted diet has been associated with increased PDK (21, 23, 24) and decreased PDH activity (21, 29) in human skeletal muscle. Therefore, the progressive decline in carbohydrate oxidation in
response to the carbohydrate restricted-diet may be influenced by both a reduction in endogenous glycogen stores and increased systemic availability of fatty acids.

The greater suppression in carbohydrate oxidation in relation to the decline in glucose uptake after 1 wk of carbohydrate restriction indicates that a smaller proportion of systemic glucose uptake was being oxidized. Because postabsorptive plasma lactate concentrations were lower during our low-carbohydrate diet and muscle lactate concentration has previously been shown to decline after carbohydrate restriction (29), it is probable that the increased rate of nonoxidative glucose disposal was preferentially partitioned toward glycogen synthesis and not the glycolytic pathway. Our observation that muscle glycogen concentration decreased despite minimal physical activity suggests that much of the nonoxidized glucose disposal occurred primarily in the liver and not in skeletal muscle. It is likely that the nonoxidative glucose disposal during carbohydrate restriction is part of a cycle whereby a portion of the glucose derived through gluconeogenesis and uptake from the circulation is converted to glycogen to maintain an adequate rate of glycogenolysis (11). Such a cycle may be advantageous for maintaining liver glycogen concentration at a level sufficient to maintain euglycemia even during extended periods of carbohydrate deprivation.

The ~20% reduction in plasma glucose concentration we found after 2 days of the low-carbohydrate diet was comparable to the reduction in plasma glucose concentration reported after 2 days of fasting (17). With more prolonged fasting, plasma glucose concentrations continue to decline, at least through ~4 days (13). In contrast, we found that plasma glucose concentration returned to basal levels after 3 days of carbohydrate restriction. Plasma glucose concentration is determined by the balance between glucose delivery into the systemic circulation and glucose uptake. Because our measurements of glucose kinetics were performed in metabolic steady state (i.e., glucose delivery = glucose uptake), the alterations in plasma glucose concentration must occur in the postprandial state. Ingesting ~20 g of carbohydrate per day in the present study (~5% daily energy intake) represents ~10% of systemic glucose availability. Therefore, it is unlikely that the maintenance of plasma glucose concentration, compared with fasting, is due to the provision of this small amount of exogenous carbohydrate. Alternatively, providing enough exogenous energy to maintain energy balance [primarily from fat (60%) and protein (35%)] prevented this further decline in plasma glucose concentration, presumably by increasing the pool of gluconeogenic precursors without eliciting the hormonal stress response (2) (e.g., enhanced catecholamine release) observed with prolonged fasting (5).

In conclusion, the results from this study indicate that systemic carbohydrate availability is maintained after 1 wk of dietary carbohydrate restriction through alterations in endogenous glucose production, glucose uptake, and carbohydrate oxidation. Because the decline in carbohydrate oxidation was greater than the reduction in glucose uptake, a larger proportion of glucose taken up was converted to glycogen rather than being oxidized. It is also apparent from these data that ingesting adequate calories, even when carbohydrate intake is minimal, helps prevent hypoglycemia.

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