Metabolic Adaptation to Feeding and Fasting during Lactation in Humans

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The aim of these studies was to determine the metabolic adaptation to fasting and feeding during lactation. Normal lactating (L) and nonlactating (NL) women (n = 6 each) were studied using infusions of [U-13C]glucose and [2-13C]glycerol during: 1) a 24-h fast, and 2) ingestion of Sustacal (protocol 1). In addition, 8 L and 6 NL women were studied during infusion of [6,6-2H2]glucose and ingestion of a glucose meal containing [1-13C]glucose (protocol 2). Protocol 1: Glucose production rate (GPR) during fasting was 33% higher in the L women (12.5 ± 1.0 vs. 9.4 ± 0.5 μmol·kg⁻¹·min⁻¹; P < 0.05). Fractional gluconeogenesis (GNG), GNG rate, glucose, lactate, β-hydroxybutyrate, FFA, insulin, and C-peptide were similar in both groups during feeding and fasting, but glycogenolysis was 50% higher in fasting L women. Protocol 2: Although GPR was slightly increased in the L group (L, 1.8 ± 0.2 μmol·kg⁻¹·min⁻¹; NL, 1.2 ± 0.2 μmol·kg⁻¹·min⁻¹; P < 0.04), no other differences were observed in splanchnic and systemic metabolism of ingested glucose between L and NL women. Insulin concentrations were lower in L women compared with controls (L, 15 ± 3 μU/ml; NL, 28 ± 6 μU/ml; P = 0.05). In conclusion, the increased glucose demands of lactation are met by increased GPR as a result of increased glycogenolysis but not GNG or by increased use of FFA. During feeding, lactating women handle oral carbohydrates normally but have increased insulin sensitivity. (J Clin Endocrinol Metab 87: 302–307, 2002)

A new infant who is exclusively breast-fed receives approximately 800 ml of breast milk per day from his/her mother, providing approximately 560 kcal, 40% of which is lactose (1). Simple stoichiometry requires that the mother must consume excess calories when compared with her prepregnancy intake to maintain normal energy balance and body stores of fat and protein during lactation. Data derived from ruminants (2) and our recent human studies (3) demonstrate that the primary, but not exclusive, source of milk lactose, is plasma glucose. In addition, our data demonstrate that lactating (L) women may provide approximately 60 g of their glucose pool to meet their infants’ milk (lactose) demands. Little or no information is available concerning the metabolic adaptation of lactating mothers to either feeding or short-term fasting. In the fed circumstance, this could be met by 1) increasing the carbohydrate intake; 2) decreasing the normal suppression of endogenous glucose production; 3) reducing splanchnic extraction of dietary glucose; or 4) reducing glucose oxidation and/or storage. However, it is not known how a lactating mother would metabolically adapt were she unable to meet this increased nutritional requirement due to illness, voluntary or forced fasting, and/or starvation. With the increased demand for glucose required for lactose production, relatively few metabolic possibilities exist in the fasting condition: 1) the lactating mothers must produce more glucose than the nonlactating women; 2) the mothers must reduce their own body’s use of glucose via increased availability and use of FFA and ketone bodies; 3) the mothers will develop hypoglycemia; and/or 4) mothers will decrease lactose synthesis and, thus, milk production. On the basis of the propensity of adult women to relative fasting hypoglycemia and hyperketonemia when compared with men (4–6), we hypothesized that the primary mechanism for maternal adaptation to short-term fasting is decreased maternal glucose use by the early development of ketosis and fatty acidemia, thus maintaining a glucose supply for milk production and a constant milk supply for the infant. Furthermore, we would hypothesize that in the fed state, glucose production in lactating women would be incompletely suppressed.

Materials and Methods

Tracers

[U-13C]glucose (99+ atom % 13C), [1,1,2,3,3-2H5]glycerol (98+ atom % 2H), [2-13C]glycerol (99 atom % 13C), [6,6-2H2]glucose (99 atom % 2H) and [1-13C]glucose (99 atom % 13C) were obtained from Cambridge Isotope Laboratories (Andover, MA). The isotopes were dissolved in 0.45% saline, and the solution was filtered through a 0.2-μm Millipore Corp. (Bedford, MA) filter into sterile syringes. Sterile isotope solutions were prepared less than 48 h before study and maintained at 4°C until used. Isotope solutions were tested and found to be sterile and pyrogen free.

Study design

Subjects. The study was approved by the Institutional Review Board for Human Subject Research at Baylor College of Medicine and the General Clinical Research Center (GCRC) Advisory Committee at Texas Children’s Hospital (Houston, TX). Written consent was obtained from each of the subjects. Fourteen (six and eight in protocols 1 and 2, respectively) normal lactating women and their infants were recruited for these studies (see below). The women were between 18–35 yr of age, and between 6 wk and 3 months postpartum (Table 1). The term infants of these women were healthy and exclusively breast-fed at the time of the study.
TABLE 1. Demographics of the subjects studied

<table>
<thead>
<tr>
<th>Protocol 1</th>
<th>Lactating controls (n = 6)</th>
<th>Nonlactating controls (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>27 ± 3</td>
<td>26 ± 2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69 ± 5</td>
<td>62 ± 4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Twelve (six in each of protocols 1 and 2) healthy nonpregnant, age-matched, nonlactating women were recruited as controls (Table 1). All volunteers had a normal physical examination, normal hemoglobin and screening studies for liver and renal function, and a negative pregnancy test before they were accepted into the study.

The women were studied using two different protocols. In protocol 1, each woman was studied on two occasions: once in the fed state and once during a 24-h fast. In protocol 2, each woman was studied on a single occasion, during ingestion of glucose.

In protocol 1, we attempted to maintain energy neutrality and used a commercially available preparation containing unlabeled complex carbohydrate. As a result, we were unable to estimate glucose splanchnic extraction and endogenous glucose production. Therefore, protocol 2 was designed to address these issues.

Protocol 1: Sustained feeding and short-term fasting. Each woman and her infant were admitted to the Metabolic Research Unit at the Children’s Nutrition Research Center (CNRC) or the GCRC on the evening before infusion and the other in the contralateral arm for blood sampling. The women had a normal physical examination, normal hemoglobin and screening studies for liver and renal function, and a negative pregnancy test before they were accepted into the study.

Each woman and her infant were admitted to the Metabolic Research Unit at the Children’s Nutrition Research Center (CNRC) or the GCRC on the evening before each infant was admitted to the Metabolic Research Unit at the Children’s Nutrition Research Center (CNRC) or the GCRC on the evening before

Enteral glucose Ra

Equations. Plasma glucose was measured using an enzyme-specific method (YSI, Inc. Glucose Analyzer, Yellow Springs, OH). Plasma insulin and C-peptide were measured using commercially available RIA kits (Linco Research, Inc., St. Charles, MO). Plasma FFA and β-hydroxybutyrate were determined by microfluorometric enzyme analyses using a Cobas Fara II Analyzer (Roche Diagnostic Systems, Inc., Montclair, NJ). Plasma glycerol concentrations were determined by reverse isotope dilution and gas chromatography-mass spectrometry (GCMS) using [13C3]glycerol as an internal standard (11, 12).

The pentacetate derivative of glucose and the triacetate derivative of glycerol were prepared as described previously (13-14). The isotopic enrichments of [6,6-2H2]glucose were measured by GCMS using a quadrupole instrument (HP 5890/HP5970; Hewlett-Packard Co., Palo Alto, CA) and an HP-1701 column (30 m × 0.25 mm × 0.25 μm) (Agilent Technologies, Wilmington, DE). Electron impact ionization mode was used with selected ion monitoring of m/z 242-244. The 13C isotopic enrichments in plasma glucose and in the glucose drinks provided were measured by gas chromatography-combustion-isotope ratio mass spectrometry (GC-C-IRMS): GC, HP 5890 (with a HP1701 column, 30 m × 0.25 mm × 1 μm); C, Europa, Orchid; IRMS, Europa 2020 (Europa Scientific, Crewe, UK). Enrichments of 13CO2 in breath samples were measured by IRMS using Europa, Roboprep G and TracePrep (Europa Scientific). Enrichments of [2-13C]glycerol, [2H5]glycerol, [U-13C]glucose, and the glucose isopomers were measured by GCMS using a quadrupole instrument (HP 6890/HP5973, Hewlett-Packard Co.) and an HP-1701 column (30 m × 0.25 mm × 0.25 μm) (Agilent Technologies). Positive chemical ionization mode was used with methanol as the reagent gas and selected ion monitoring of m/z 331-337 for glucose, and m/z 159, 160, and 164 for glycerol. All measurements were made in the Stable Isotope Core Laboratory of the CNRC.

Calculations. The Ra of glucose and glycerol into the systemic circulation and the GPR during fasting were calculated under near steady-state condition using standard isotope dilution equations:

\[ \text{Ra}_{\text{total systemic}} = \left( \frac{E_t}{E_p} - 1 \right) \cdot I \]

where Ra_{total systemic} is the rate of appearance, E_t and E_p are the enrichments of the isotope in the infusate and plasma, respectively, and I is the rate of infusion of the isotope of interest.

The fraction of glucose production derived from gluconeogenesis and the rate of gluconeogenesis were estimated using mass isotope distribution analysis as described by Hellerstein et al. (12, 15, 16). In the fasting state, rates of glycolysis were estimated by subtracting the rate of gluconeogenesis from the total glucose Ra.

We assume that the enterally delivered glucose ingested in protocol 2 was completely absorbed. The rate of entry of the dietary glucose into the systemic circulation was calculated tracing the Ra of the enterally ingested tracer ([1-13C]glucose) using the infused tracer (6,6-2H4 glucose) and correcting for the enrichment of the ingested tracer in the oral glucose using the following equation (17):

\[ \text{Enteral glucose Ra}_{\text{systemic}} = \frac{\text{Ra}_{\text{total systemic}} \cdot [1-13C]\text{glucose plasma}}{[1-13C]\text{glucose meal}} \]
where Enteral glucose Ra
_{\text{systemic}} is the Ra of enterally ingested glucose into the systemic circulation, \([1-\text{\textsuperscript{13}}\text{C}]\text{glucose}_{\text{plasma}} is the enrichment of the \([1-\text{\textsuperscript{13}}\text{C}]\text{glucose} in the plasma, and \([1-\text{\textsuperscript{13}}\text{C}]\text{glucose}_{\text{mucosal}} is the enrichment of the \([1-\text{\textsuperscript{13}}\text{C}]\text{glucose} in the glucose drinks.

The fraction of dietary glucose entering the systemic circulation was calculated as the ratio between the enteral glucose Ra
_{\text{systemic}} and the rate of glucose ingestion.

The rate of glucose production (GPR) during ingestion of the glucose drink was calculated using the following equation:

$$GPR = Ra_{\text{total systemic}} - \text{Enteral glucose Ra}_{\text{systemic}}.$$ 

During fasting, Enteral glucose Ra
_{\text{systemic}} is 0, and thus Ra
_{\text{total systemic}} is the GPR. The rate of splanchnic extraction of glucose was calculated using the following equation:

$$\text{Rate}_{\text{splanchnic extraction}} = \text{Rate}_{\text{glucose ingestion}} - \text{Enteral glucose Ra}_{\text{systemic}}$$

and the fractional splanchnic extraction of dietary glucose was calculated using the following equation:

$$\text{Fraction}_{\text{splanchnic extraction}} = \frac{\text{Rate}_{\text{splanchnic extraction}}}{\text{Rate}_{\text{glucose ingestion}}}.$$ 

The rate of glucose oxidation was calculated using the following formula:

$$\text{Glucose}_{\text{oxidation}} = \frac{(\text{\textsuperscript{13}}\text{CO}_2)^V}{\text{\textsuperscript{13}}\text{CO}_2}\text{plasma}/([1-\text{\textsuperscript{13}}\text{C}]\text{glucose}_{\text{plasma}}0.8),$$

where Glucose
_{\text{oxidation}} is the rate of glucose oxidation, \(\text{\textsuperscript{13}}\text{CO}_2\) is the \(\text{\textsuperscript{13}}\text{C} in \text{enriched } CO_2, VCO_2 is the rate of \text{CO}_2 \text{expired} (\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}), [1-\text{\textsuperscript{13}}\text{C}]\text{glucose}_{\text{plasma}} is the enrichment of [1-\text{\textsuperscript{13}}\text{C}]\text{glucose} in the systemic circulation, and 0.8 corrects for recovery of labeled CO_2.

The rate of glucose storage was calculated using the following equation:

$$\text{Glucose}_{\text{storage}} = \text{Glucose Ra}_{\text{total systemic}} + \text{Rate}_{\text{splanchnic extraction}} - \text{Glucose}_{\text{oxidation}} - \text{Glucose}_{\text{lactose}} - \text{Glucose}_{\text{glucagon}},$$

where Glucose
_{\text{Ra total systemic}} is the rate of entry of glucose into the systemic circulation, Rate
_{\text{splanchnic extraction}} is the rate of splanchnic extraction of ingested glucose, and Glucose
_{\text{lactose}} = \text{Glucose} is the plasma glucose contribution to the rate of lactose synthesis (estimated at the rate of 80% of the lactose production in the lactating women) (3).

Statistical analysis. Data within a group were compared using a paired t test. Data between groups were compared using a nonpaired t test. In Protocol 1, in both the fed and the fasting condition, the baseline substrate and hormone values from the overnight 12-h fasts (0600 h) were averaged for each individual and compared with those obtained between 1615–1800 h, i.e., after 22.25–24 h of fasting or 10.25–12 h of feeding. The glucose kinetic data, (glucose Ra, GPRs, and gluconeogenesis) represent the average of the values measured between 1615–1800 h, i.e., after 22.25–24 h of fasting or 10.25–12 h of feeding. In Protocol 2, substrate and hormone data from the overnight 12-h fast (baseline, 0600 h) were compared with the values measured from 1245–1500 h, i.e., after 6.75–9 h of glucose ingestion. The glucose kinetic data (glucose Ra, glucose production, splanchnic extraction of dietary glucose, oxidation and storage rates) represent the average of the values measured between 1245–1500 h, i.e., after 6.75–9 h of glucose ingestion. It should be noted that neither the hormone and substrate data nor the glucose kinetic data obtained during the 1 h of frequent sampling (every 15 min) differed from the results obtained during the above mentioned time periods used for statistical analyses (data not shown). All data are expressed as mean ± se.

Results

Plasma substrate and hormone concentrations. After a 12-h overnight fast, the plasma concentrations of glucose, lactate, \(\beta\)-hydroxybutyrate, FFA, insulin, and glucagon were similar in both groups. After 12 additional hours of fasting (24-h total fast), plasma glucose and insulin decreased similarly \((P < 0.01)\) in both groups. Plasma \(\beta\)-hydroxybutyrate and FFA increased as anticipated, but the increases were similar \((P < 0.01)\) in both groups of women. Plasma lactate and glucagon were similar in both groups and did not change over time in either group with fasting (Table 2). One of the subjects in the control group was excluded from the glucagon analysis, because the values at all time points were more than 10 sd values higher than the group mean.

Glucose kinetics. After 22.25–24 h of fasting, glucose Ra (also GPR) was 33.5% higher in the lactating women when compared with the fasting nonlactating women \((12.5 \pm 1.0\text{ vs. } 9.4 \pm 0.5\ \mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}, P < 0.03)\) (Fig. 1). The fractions of glucose derived from gluconeogenesis were similar in the lactating and nonlactating women \((0.30 \pm 0.03\text{ vs. } 0.38 \pm 0.03, \text{ respectively; } P > 0.1)\). The rates of gluconeogenesis in the lactating and nonlactating women were indistinguishable \((3.65 \pm 0.34\text{ vs. } 3.53 \pm 0.34\ \mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}, P = \text{NS})\). In contrast, the rates of glycolysis were 50% higher \((P < 0.05)\) in the lactating women when compared with the controls \((8.66 \pm 1.06\text{ vs. } 5.85 \pm 0.50\ \mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1})\) (Fig. 1).

Glycerol kinetics. During fasting, the Ra of glycerol, an indicator of lipolysis, was similar in the lactating and nonlactating women \((5.92 \pm 0.88\text{ and } 5.63 \pm 0.65\ \mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}, \text{ respectively (NS)})\).

Milk volumes. During the fast, the milk volume production was 99 ± 9 ml/feeding.

Response to feedings

Substrate and hormone concentrations. After 10.25–12 h of frequent feeding of Sustacal, plasma substrate and hormone concentrations were essentially the same between the lactating and nonlactating women despite a 30% higher rate of

<table>
<thead>
<tr>
<th>TABLE 2. Plasma substrate and hormone concentrations after a 12-h overnight fast, after 22.25–24 h of fasting, and after 10.25–12 h of continuous feedings with Sustacal in lactating women (n = 6) and nonlactating controls (n = 6).</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-h fast</td>
</tr>
<tr>
<td>Lactating</td>
</tr>
<tr>
<td><strong>Glucose (mM)</strong></td>
</tr>
<tr>
<td><strong>Lactate (mM)</strong></td>
</tr>
<tr>
<td><strong>FFA (mM)</strong></td>
</tr>
<tr>
<td><strong>(\beta)-hydroxybutyrate (mM)</strong></td>
</tr>
<tr>
<td><strong>Insulin (µU/ml)</strong></td>
</tr>
<tr>
<td><strong>C-peptide (ng/ml)</strong></td>
</tr>
<tr>
<td><strong>Glucagon (pg/ml)</strong></td>
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</table>
Sustacal intake in the lactating women (Table 2). Similarly, no differences were observed in the plasma concentrations of substrates and hormones between the two groups of women during ingestion of identical rates of glucose labeled with [1-13C]glucose (Table 3). However, during glucose ingestion, insulin concentrations were lower in the lactating women compared with controls (L, 14.9 ± 3 μU/ml; NL, 28.23 ± 6.0 μU/ml; P = 0.05) (Table 3). Although a similar trend was observed for the C-peptide values, the difference did not reach statistical significance (L, 3.51 ± 0.5 ng/ml; NL, 5.16 ± 0.6 ng/ml; P = 0.08).

Glucose kinetics during Sustacal ingestion. Total glucose Ra was higher in the lactating women when compared with the controls during Sustacal ingestion (33.3 ± 2.2 vs. 25.3 ± 1.9 μmol·kg⁻¹·min⁻¹; P < 0.02) (Fig. 2). The fraction of glucose Ra derived from gluconeogenesis was similar in the lactating and nonlactating women (0.16 ± 0.01 vs. 0.16 ± 0.03). Assuming that endogenous glucose production was exclusively from gluconeogenesis, a minimal estimate of GPR during meal ingestion, was similar in both groups (4.79 ± 0.48 vs. 4.61 ± 1.08 μmol·kg⁻¹·min⁻¹ in lactating women and controls, respectively) (P = NS) (Fig. 1). The rates of carbohydrate ingested were intentionally different between the lactating and nonlactating women, and no tracers were included in the complex starches of the feeding (see protocol design). Therefore, we were unable to measure the rate of splanchnic extraction, endogenous glucose production, and the fraction of the dietary glucose entering the systemic circulation. These issues were addressed in protocol 2, below.

**Table 3.** Plasma substrate and hormone concentrations after a 12-h overnight fast and after 9 h of continuous feedings with glucose in lactating subjects (n = 8) and nonlactating controls (n = 6)

<table>
<thead>
<tr>
<th></th>
<th>Lactating</th>
<th>Controls</th>
<th>Glucose feeding</th>
<th>Lactating</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12-h fast</td>
<td></td>
<td></td>
<td>9-h feeding</td>
<td></td>
</tr>
<tr>
<td>Glucose (mM)</td>
<td>5.35 ± 0.11</td>
<td>5.51 ± 0.36</td>
<td>6.51 ± 0.19</td>
<td>6.34 ± 0.32</td>
<td></td>
</tr>
<tr>
<td>Lactate (mM)</td>
<td>0.80 ± 0.11</td>
<td>0.93 ± 0.08</td>
<td>1.02 ± 0.06</td>
<td>1.13 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>FFA (mM)</td>
<td>0.55 ± 0.06</td>
<td>0.29 ± 0.06</td>
<td>&lt;0.2</td>
<td>&lt;0.2 (n = 4)</td>
<td></td>
</tr>
<tr>
<td>β-hydroxybutyrate (mM)</td>
<td>0.19 ± 0.06</td>
<td>0.12 ± 0.05</td>
<td>0.04 ± 0.01</td>
<td>0.04 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>Insulin (μU/ml)</td>
<td>4.3 ± 1.0</td>
<td>6.5 ± 1.0</td>
<td>14.9 ± 3.0*</td>
<td>28.2 ± 6.0</td>
<td></td>
</tr>
<tr>
<td>C-peptide (ng/ml)</td>
<td>1.1 ± 0.2</td>
<td>1.5 ± 0.2</td>
<td>3.5 ± 0.4</td>
<td>5.2 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>Glucagon (pg/ml)</td>
<td>62 ± 5</td>
<td>73 ± 3</td>
<td>56 ± 3</td>
<td>59 ± 6 (n = 5)</td>
<td></td>
</tr>
</tbody>
</table>

* Lactating women vs. controls, P = 0.05.
TABLE 4. Glucose kinetics during continuous ingestion of glucose labeled with [1-13C]glucose in normal lactating women (n = 8) and nonlactating controls (n = 6)

<table>
<thead>
<tr>
<th>Glucose Kinetic Parameter</th>
<th>Lactating</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of ingested glucose</td>
<td>31.7 ± 0.2</td>
<td>31.7 ± 0.2</td>
</tr>
<tr>
<td>Glucose Ra_Total systemic</td>
<td>28.4 ± 1.1</td>
<td>27.2 ± 1.1</td>
</tr>
<tr>
<td>Enteral Glucose Ra_systemic</td>
<td>26.6 ± 1.0</td>
<td>26.0 ± 1.2</td>
</tr>
<tr>
<td>Glucose exogenous extraction</td>
<td>5.1 ± 1.0</td>
<td>5.7 ± 1.2</td>
</tr>
<tr>
<td>Dietary glucose enteriing</td>
<td>85 ± 3</td>
<td>82 ± 4</td>
</tr>
<tr>
<td>systemic circulation (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose OXIDATION</td>
<td>12.5 ± 0.6</td>
<td>12.9 ± 1.4</td>
</tr>
<tr>
<td>Glucose LACTOSE -Glucose</td>
<td>2.9 ± 0.6</td>
<td>No data</td>
</tr>
<tr>
<td>GPR</td>
<td>1.8 ± 0.2</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td>Glucose Storage</td>
<td>18.0 ± 0.8</td>
<td>20.0 ± 1.5</td>
</tr>
</tbody>
</table>

Data are expressed as μmol.kg⁻¹.min⁻¹ unless stated otherwise.

* Lactating women vs. controls, P < 0.05.

Glycerol kinetics. During Sustacal ingestion, the Ra of glycerol was similar in the lactating and nonlactating women [2.93 ± 0.30 and 2.56 ± 0.23 μmol.kg⁻¹.min⁻¹, respectively (P = NS)].

Discussion

In the present studies, we explored for the first time the kinetic regulation of glucose metabolism in both the fed and briefly fasted states in normal lactating women. The primary findings during short-term fasting are: 1) glucose production was 33% higher in the fasting lactating than the nonlactating women, and 2) during a short-term fast (24 h), the lactating women did not adapt to these increased glucose demands created by lactose synthesis by increasing their rates of gluconeogenesis, altering hormone secretion or rates of lipolysis or ketogenesis.

This increased glucose demand is not trivial and amounts to more than 50 g/d above that of the fasted controls. We clearly demonstrated that over the period of study the lactating women met their increased glucose demands by increasing their rates of glycogenolysis, and not by 1) increasing their rates of gluconeogenesis or glycerol turnover (indicator of lipolysis), or 2) decreasing glucose use or milk production. There was, however, a great intersubject variation in milk production. Considering the anecdotal histories of lactating women always being hungry and constantly eating, we were reluctant to extend their fast further until more data were available. As a result, we recognize that the fast that we used may have been an inadequate challenge to elucidate clearly the maternal adaptation to caloric restriction. However, it would appear that one potential adaptive mechanism that cannot be proved from this short-term fasting study is the potential of decreasing milk (and thus, lactose) production.

Of equal interest is the potential mechanism(s) by which lactating women meet their increased carbohydrate needs in the fed state. Increased peripheral glucose demands could be met in the fed condition by incomplete suppression of hepatic glucose production, altered hepatic glucose uptake, and/or decreased storage of glucose after a meal. No differences were observed in splanchnic and systemic metabolism of ingested glucose between lactating women and controls. Although a significant difference was observed in the GPRs between the two groups, quantitatively, this is probably not of any physiological importance. Within the limitation of the methods used, it would appear that lactating women handle a glucose load in a fashion that is essentially identical to that of the nonlactating women.

It is of interest to note that in both the lactating and nonlactating women, the rate of gluconeogenesis was at least the same and perhaps slightly increased with feeding. Because the only source of doubly labeled glucose could be from the [2-13C]glycerol via gluconeogenesis, our data demonstrate that even after 12 h of continuous stimulation of enteral feedings, glucose continues to be released into the systemic circulation via the gluconeogenic pathway. This would suggest that during meal ingestion, the rate of glucose appearing from gluconeogenesis is not acutely regulated by insulin but that the primary role of insulin, under these conditions, may be to modulate the rate of systemic glucose derived from glycogen alone.

During ingestion of identical amounts of glucose, plasma glucose concentrations were similar but insulin concentrations were lower in the lactating women compared with controls. In addition, during ingestion of Sustacal, insulin concentrations were similar in the two groups, although by study design the lactating women received approximately 30% more carbohydrate than the nonlactating controls. Thus, on the basis of insulin to glucose ratios, the results of these studies indicate a change in insulin sensitivity during lactation. Human as well as animal studies suggest an insulin-independent mechanism for glucose uptake by the mammary gland; Neville et al. (18) observed no effect on milk volume, milk glucose concentration, total fat content, or lactose secretion rate during a 4-h hyperinsulinemic euglycemic clamp. Hyperglycemia induced by acute withdrawal of insulin infusion did not change lactose levels in goats, (19) although chronic insulin deficiency was associated with a reduction in milk production (20). To explore these issues and determine the potential role of insulin during lactation will require further studies.

In conclusion, the increased glucose demands of lactation are met by increased GPR as a result of increased glycogenolysis but not by gluconeogenesis or increased use of FFA. During feeding, lactating women handle oral carbohydrates normally but have increased insulin sensitivity. Many women increase their body fat mass with each consecutive pregnancy, because they are unable to lose this fat in the postpartum period regardless of breast-feeding or not (21). This progressive increase in body fat is associated with increased risks of diabetes mellitus, hypertension, and macrovascular disease. By providing insight into some aspects of maternal metabolism during lactation, these data might have great importance in establishing sound dietary guidelines for the lactating woman.

Acknowledgments

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References


Summer Institute on Aging Research 2002

The National Institute on Aging (NIA) announces the annual Summer Institute on Aging Research, a weeklong workshop for investigators new to aging research, focused on current issues, research methodologies, and funding opportunities. The program will also include consultations on the development of research interests. The 2002 Summer Institute will be held July 27–August 2 in Airlie, Virginia. Support is available for travel and living expenses. Applications are due March 8th. To increase the diversity of participants, minority investigators are strongly encouraged to apply. For additional information and an application form, contact: Office of the Director, Office of Special Populations, National Institute on Aging, National Institutes of Health, Building 31, Room SC-35, 31 Center Drive MSC-2292, Bethesda, Maryland 20892-2292. Telephone: (301) 496-0756; Fax: (301) 496-2525; E-mail: Hardent@exmur.nia.nih.gov; or see the What’s New section of the NIA Web page at http://www.nih.gov/nia.