Estimation of gluconeogenesis in newborn infants

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†Schwartz Center for Metabolism and Nutrition, MetroHealth Medical Center, Case Western Reserve University School of Medicine, Cleveland, Ohio 44109; and ‡Erasmus University and Sophia Children’s Hospital, 3000 CB Rotterdam, The Netherlands

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Kalhan, Satish C., Prabhu Parimi, Ron Van Beek, Carol Gilfillan, Firas Saker, Lourdes Gruca, and Pieter J. J. Sauer. Estimation of gluconeogenesis in newborn infants. Am J Physiol Endocrinol Metab 281: E991–E997, 2001.—The rate of glucose turnover (Ra) and gluconeogenesis (GNG) via pyruvate were quantified in seven full-term healthy babies between 24 and 48 h after birth and in twelve low-birth-weight infants on days 3 and 4 by use of [13C6]glucose and 2H2O. The preterm babies were receiving parenteral alimentation of either glucose or glucose plus amino acid with or without lipids. The contribution of GNG to glucose production was measured by the appearance of 1H on C-6 of glucose. Glucose Ra in full-term babies was 30 ± 1.7 (SD) μmol·kg⁻¹·min⁻¹. GNG via pyruvate contributed ~31% to glucose Ra. In preterm babies, the contribution of GNG to endogenous glucose Ra was variable (range 6–60%). The highest contribution was in infants receiving low rates of exogenous glucose infusion. In an additional group of infants of normal and diabetic mothers, lactate turnover and its incorporation into glucose were measured within 4–24 h of birth by use of [13C3]lactate tracer. The rate of lactate turnover was 38 μmol·kg⁻¹·min⁻¹, and lactate C, not corrected for loss of tracer in the tricarboxylic acid cycle, contributed ~18% to glucose C. Lactate and glucose kinetics were similar in infants that were small for their gestational age and in normal infants or infants of diabetic mothers. These data show that gluconeogenesis is evident soon after birth in the newborn infant and that, even after a brief fast (5 h), GNG via pyruvate makes a significant contribution to glucose production in healthy full-term infants. These data may have important implications for the nutritional support of the healthy and sick newborn infant.

The fetus in utero, under normal unperturbed physiological circumstances, is entirely dependent on the mother for a continuous supply of glucose, and no significant production of glucose by the fetus has been demonstrated, either in human or in other mammalian species (see review in Ref. 15). In addition, although significant activity of key enzymes involved in gluconeogenesis has been documented early in gestation in human fetal liver, gluconeogenesis in vivo has not been documented (11, 19, 29, 32, 33). Whether cytosolic phosphoenolpyruvate carboxykinase, the key regulatory enzyme involved in gluconeogenesis, is expressed in human fetal liver is not known. In rodents, cytosolic phosphoenolpyruvate carboxykinase is first expressed immediately after birth and is associated with the appearance of gluconeogenesis (12, 15). Thus the newborn at birth relies entirely on the mobilization of accumulated hepatic glycogen stores and the initiation of gluconeogenesis for a continuous supply of glucose. Both of these processes, i.e., glycogenolysis and gluconeogenesis, are stimulated by the birth-associated surges of catecholamines and pancreatic glucagon (20). That the human newborn can incorporate alanine carbon into glucose as early as 6 h of age has been demonstrated by Frazer et al. with a 13C-labeled tracer (10). However, the contribution of gluconeogenesis to glucose production in healthy full-term newborns has not been quantified. In the present study, with stable isotopic tracers, we have quantified the turnover rate of lactate and its incorporation into glucose in the period immediately after birth. In addition, using the recently developed deuterium-labeled water method (4, 22, 27), we have quantified the contribution of gluconeogenesis via pyruvate to total glucose production in healthy, normal full-term babies. During adaptation to the extrauterine environment, perturbations in glucose homeostasis are often observed in preterm infants, in those born small for gestational age, and in those born to mothers with diabetes (20). Because both hyperglycemia and hypoglycemia are often seen in these babies, we also quantified the rates of glucose turnover and gluconeogenesis in clinically stable infants in these groups. Our data show that gluconeogenesis from lactate and pyruvate is established by 4–6 h after birth. Gluconeogenesis from pyruvate contributes as much as 30% to total glucose production in healthy term babies between 5 and 6 h after a feed.

MATERIALS AND METHODS

Gluconeogenesis (GNG) was measured in normal, preterm, small-for-gestational-age (SGA) infants, and in infants of diabetic mothers either by use of the deuterium labeling of

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body water or by quantifying the incorporation of $^{13}$C from labeled lactate into glucose.

**Deuterium-Labeled Water Studies**

GNG was quantified in seven full-term infants and thirteen preterm infants with the method of deuterium labeling of body water (4, 27). The study protocol was approved by the institutional review board. Written informed consent was obtained from the mother and, when available, the father, after the procedure had been fully explained. The full-term infants were appropriate for gestational age, had normal Apgar scores, had no clinical problems, and were receiving either formula feeds or maternal breast milk (Table 1). Two infants (nos. 6 and 7) were born to mothers with gestational and insulin-dependent diabetes mellitus (IDDM). They had normal plasma glucose concentrations and did not develop any neonatal problems.

A majority of the term infants were studied on the 2nd day after birth in the General Clinical Research Center at MetroHealth Medical Center (Cleveland, OH). Two indwelling canulas were placed in the superficial vein of each hand to draw blood samples and infuse the isotopic tracer $^{13}$C-glucose (99% $^{13}$C; Isotec, Miamisburg, OH). The study protocol is displayed in Fig. 1. Approximately 3 h after the last feed, an oral dose (4 g/kg body wt) of $^2$H$_2$O (99% $^2$H; Isotec) mixed with sterile distilled water was administered. Two hours later, three blood samples for the measurement of $[^2$H$]enrichment of C-6 of plasma glucose were obtained at 20-min intervals. This was followed by intravenous administration of a prime constant-rate infusion of $[^{13}$C$]_{glucose}$ for the next 120 min to quantify the rate of appearance ($R_0$) of glucose. The bolus prime was 0.6 mg/kg body weight, and the constant rate infusion was 30 $\mu$g·kg$^{-1}$·min$^{-1}$. Blood samples were obtained for the measurement of glucose $m_6$ enrichment at 90, 105, and 120 min of $[^{13}$C$]_{glucose}$ infusion. The infants were comfortable throughout the study period and did not show any evidence of stress. Cardiopulmonary monitoring was performed and plasma glucose concentration measured with each blood sampling. Their plasma glucose concentration remained unchanged throughout the study. The blood samples were centrifuged at 4°C, and plasma was stored at $-70°C$ for later analysis. The study was completed at $\approx$8 h after the last feed. In one infant (no. 8, not reported here), the study was discontinued because of inability to obtain venous blood samples.

The preterm infants were studied between 48 and 72 h after birth with a similar protocol as described above, with minor modifications. As anticipated, all preterm infants were initially on ventilatory support. At the time of study, three infants were on ventilatory support and one required continuous positive airway pressure. No babies were on vasopressors at the time of study. All were receiving antibiotics, and three were on caffeine due to apnea or prematurity. All had indwelling vascular canulas for clinical indications. Within 24 h after birth, they were assigned to either glucose, glucose plus amino acids (1.2 g·kg$^{-1}$·day$^{-1}$), or glucose, amino acids (1.2 g·kg$^{-1}$·day$^{-1}$), and lipids (1.25 g·kg$^{-1}$·day$^{-1}$) as anticipated, all preterm infants were initially on ventilatory support. At the time of study, three infants were on ventilatory support and one required continuous positive airway pressure. No babies were on vasopressors at the time of study. All were receiving antibiotics, and three were on caffeine due to apnea or prematurity. All had indwelling vascular canulas for clinical indications. Within 24 h after birth, they were assigned to either glucose, glucose plus amino acids (1.2 g·kg$^{-1}$·day$^{-1}$), or glucose, amino acids (1.2 g·kg$^{-1}$·day$^{-1}$), and lipids (1.25 g·kg$^{-1}$·day$^{-1}$), and lipids (1.25 g·kg$^{-1}$·day$^{-1}$). The rate of glucose infusion was based on the clinical protocol and adjusted by the patient's physician on the basis of clinical and laboratory information. However, the rate of glucose infusion was constant for several hours before and throughout the tracer infusion study. Plasma samples for deuterium enrichment on C-6 of glucose were obtained 3, 4, and 5 h after the nasogastric dose of $^2$H$_2$O. $[^{13}$C$]_{glucose}$ infusion was started at 5 h, and blood samples for the $^{13}$C enrichment of glucose were obtained at 6.5, 6.75, and 7 h of the study. The doses of $^2$H$_2$O and $[^{13}$C$]_{glucose}$ were the same per kilogram of body weight as for term infants. These studies were performed at the Sophia Children's Hospital (Rotterdam, The Netherlands). The study protocol was approved by the institutional review board, and written informed consent was obtained from the parents after the protocol had been fully explained. The investigators were not responsible for the clinical care of the infants.

![Fig. 1. Study design for the quantification of gluconeogenesis using $^2$H$_2$O. Three hours after the last feed, the infants were given $^2$H$_2$O (4.0 g/kg body weight) mixed in sterile water. Plasma samples for the measurement of $^2$H enrichment in body water and on C-6 of glucose were obtained starting at 120 min after $^2$H$_2$O administration. A prime constant-rate infusion of $[^{13}$C$]_{glucose}$ was started at 180 min and continued for 2 h to quantify the rate of appearance of glucose. The plasma glucose concentration (●) mg/dl, glucose $m_6$ enrichment, and $^2$H enrichment on C-6 glucose from 1 study are displayed.](image-url)
Table 2. Clinical characteristics of the infants; lactate kinetics

<table>
<thead>
<tr>
<th>Birth Weight, g</th>
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<tr>
<td>Normal infants (n = 10)</td>
<td>3,230 ± 349</td>
<td>39 ± 1</td>
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<td>2,435 ± 105</td>
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<tr>
<td>Infants of IDDM mothers (n = 6)</td>
<td>3,365 ± 694</td>
<td>39 ± 1</td>
<td>12.2 ± 8.6</td>
</tr>
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</table>

Values are means ± SD. SGA, small for gestational age; IDDM, insulin-dependent diabetes mellitus.

Lactate Kinetics

Glucose and lactate kinetics were quantified in ten normal infants of a size appropriate for their gestational age (AGA), six infants of IDDM mothers, and four SGA infants (Table 2). The mothers with IDDM were managed with multiple insulin doses per day or by continuous subcutaneous insulin infusion to maintain normoglycemia throughout the day. Their hemoglobin A1 concentrations at delivery were within the normal range. All infants were born at term gestation and had no intrapartum or neonatal problems. They had normal physical examinations and no apparent clinical problems. The tracer isotope infusions were started within 4–5 h after birth in eight normal AGA infants and three IDDM infants. Other infants were studied between 8 and 24 h after birth in eight normal AGA infants and three IDDM infants. The tracer isotope infusions were started within 4–5 h after birth in eight normal AGA infants and three IDDM infants. Other infants were studied between 8 and 24 h after birth in eight normal AGA infants and three IDDM infants. The tracer isotope infusions were started within 4–5 h after birth in eight normal AGA infants and three IDDM infants. Other infants were studied between 8 and 24 h after birth in eight normal AGA infants and three IDDM infants.

Analytical Methods

Plasma glucose was measured by the glucose oxidase method. Blood lactate levels were measured using lactate dehydrogenase. Deuterium enrichment of hydrogens on C-6 of glucose was measured as described previously (4, 22). Briefly, C-6 of glucose with its hydrogens, after preparatory isolation and purification, was cleaved by periodate oxidation to formaldehyde, which, when condensed with ammonium hydroxide, forms hexamethylenetetramine. The latter was analyzed on a gas chromatography-mass spectrometry (GC-MS) system (HP 5970 equipped with an HP 5890 gas chromatograph; Hewlett-Packard, Palo Alto, CA). The GC-MS conditions were as follows: a nonpolar cross-linked methyl siloxane capillary column (HP-1, Hewlett-Packard) was used. Its dimensions were 30 m in length, 0.25 mm ID, 0.25 μm film thickness, 220°C injection temperature, 105°C oven initial temperature for 5.6 min, final temperature 230°C, and 45°C/min ramp rate. The retention time for hexamethylene tetramine was ~4.2 min. Electron impact ionization (70 eV) was used, and ions of mass-to-charge ratios 140 and 141 were monitored using selective ion monitoring technique.

Calculations

The rates of appearance (R_a) of glucose and lactate were calculated from the dilution of tracer glucose in plasma, as described (39)

\[ R_a (\mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) = \frac{[E_i/E_p] - 1}{I} \times 1 \]

where \( E_i \) and \( E_p \) are the enrichments of isotopic tracer infused and of the substrate in plasma, respectively, and \( I \) is the rate of tracer infusion (in \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \)).

The contribution of GNG from pyruvate was calculated as

\[ \text{GNG from pyruvate} = 100 \times 0.5 \times \frac{2H \text{ enrichment of glucose C-6}}{2H \text{ enrichment in H}_2\text{O}} \]

As discussed previously (16, 27), it is assumed that methyl hydrogens of pyruvate C-3, which forms C-6 of glucose, exchange with hydrogens in body water, so that 2H enrichment of hydrogens bound to C-3 of pyruvate or to that of phosphoenolpyruvate becomes similar to that of water. This exchange reaction in fasting adults has been shown to be over 80% complete. It has not been examined in the neonate.

The enrichment in C-6 is multiplied by 0.5 because of two hydrogens on C-6. Total GNG is calculated by multiplying the fractional contribution of GNG with total glucose 100.

The R_c of lactate was calculated using the tracer dilution equation, as in the first equation and in Ref. 39. The incorporation of lactate carbon into glucose was estimated by precursor-product relationship. The fraction of glucose from lactate equals the \( ^{13C}/^{12C} \) ratio of glucose C-1 divided by the \( ^{13C}/^{12C} \) ratio of lactate. It was assumed that the \( ^{13C}/^{12C} \) ratio of glucose C-1 represents the enrichment of all carbons of glucose. No correction was made for the loss of tracer carbon via exchange in the tricarboxylic acid cycle and, therefore, the estimates of lactate C incorporation into glucose represent minimal estimates.

All data are reported as means ± SD. Group comparisons were made using parametric and nonparametric statistical methods with Statistix software (Analytical Software, La Jolla, CA).

RESULTS

Gluconeogenesis via Pyruvate \( ^{2H}_2\text{O} \) Studies

Term infants. As displayed in Table 1, the term infants were appropriate for gestational age and were

\[ \text{Birth Weight, g} \]

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Gluconeogenesis via Pyruvate \( ^{2H}_2\text{O} \) Studies

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The rate of appearance of glucose (Rₐ) was quantified using [13C₆]glucose tracer dilution. GNG, gluconeogenesis.

The 2H enrichment of plasma water and that of glucose plus amino acids with or without intravenous lipids. There was no correlation (r = 0.12) between glucose Rₐ and the contribution of GNG.

Preterm babies. The preterm infants were studied between days 3 and 4 after birth. As anticipated in this group, because of clinical considerations, they were receiving a wide range of total calories (64–143 kcal·kg⁻¹·day⁻¹). The rate of exogenous glucose infusion (I) ranged between 3 and 10.6 mg·kg⁻¹·min⁻¹ (16–59 μmol·kg⁻¹·min⁻¹; Table 4). Their plasma glucose concentration ranged between 4 and 7 mmol/l.

Table 4. GNG in the preterm babies

<table>
<thead>
<tr>
<th>Infants by Treatment</th>
<th>Birth Weight, g</th>
<th>Gestational Age, wk</th>
<th>Glucose Ra, μmol·kg⁻¹·min⁻¹</th>
<th>GNG %</th>
<th>μmol·kg⁻¹·min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Glucose</td>
<td>960</td>
<td>26.0</td>
<td>82.29</td>
<td>39.23</td>
<td></td>
</tr>
<tr>
<td>2 Glucose</td>
<td>1,220</td>
<td>26.0</td>
<td>83.35</td>
<td>46.62</td>
<td></td>
</tr>
<tr>
<td>3 Glucose</td>
<td>1,770</td>
<td>30.4</td>
<td>46.32</td>
<td>13.99</td>
<td></td>
</tr>
<tr>
<td>4 Glucose</td>
<td>1,545</td>
<td>32.0</td>
<td>48.79</td>
<td>31.57</td>
<td></td>
</tr>
<tr>
<td>5 Glucose</td>
<td>1,335</td>
<td>32.7</td>
<td>60.09</td>
<td>43.59</td>
<td></td>
</tr>
</tbody>
</table>

Glucose + aa          | 1,470           | 29.6                | 41.39                       | 11.56 |

Glucose + aa + lipids | 1,265           | 30.0                | 56.39                       | 18.67 |

Ra, rate of glucose appearance measured by [13C₆]glucose tracer dilution; I, rate of infusion of glucose; Re, endogenous rate of appearance of glucose; aa, amino acids.
measured rates of glucose Ra when [6,6-2H2]glucose was used were slightly lower than those estimated using [13C6]glucose tracer. The reason for this difference remains undetermined (17). The estimated rate of plasma lactate turnover was 38 μmol·kg−1·min−1 in normal babies. It was slightly lower in the SGA babies and higher in the infants of IDDM mothers (P = 0.07 by one-way ANOVA). The fractional contribution of GNG estimated from the incorporation of lactate carbon into glucose was also similar in the three groups and accounted for 18% of glucose Ra. This (uncorrected) estimation does not take into consideration the loss of tracer carbon via exchange in the tricarboxylic acid cycle intermediates. There was no significant correlation (r = 0.29; P = 0.23) between glucose Ra and lactate Ra, or between glucose Ra and the fractional contribution of lactate.

**DISCUSSION**

In the present study, we have documented for the first time that healthy full-term neonates establish GNG from lactate 4–6 h after birth, and that GNG from pyruvate contributes ~30% of total glucose release at ~5 h after the last feed. In preterm infants, even in the presence of exogenous glucose and other nutrient administration, GNG is a significant contributor to the total glucose turnover. These data are important for the nutritional management of sick newborns and contribute to our understanding of extrauterine adaptation of the human neonate.

Although GNG has been estimated indirectly in the human newborn by quantifying the glucose carbon recycling (8, 18), or in the SGA infants by estimating incorporation of alanine C into glucose (10), no data exist documenting the contribution of GNG or the appearance of GNG in the full-term healthy newborn infant. In the present study, using the method of deuterium labeling of body water, we have documented that, in the healthy newborn between 35 and 68 h after birth and 5 h after the last feed, GNG contributed ~30% to the total glucose Ra. These estimates are of a similar magnitude to those seen in normal healthy adults after an overnight fast (13, 37). The deuterium incorporation in the hydrogens of C-6 of glucose quantifies the contribution of pyruvate to glucose and does not include the contribution of glycerol (4, 27). In addition, because of a lack of complete equilibrium between deuterium in body water and methyl hydrogens (C-3) of pyruvate, the measurement of 2H enrichment on C-6 of glucose results in underestimation (by ~10%) of the contribution of GNG via pyruvate to total glucose Ra. The incorporation of 2H on C-5 of glucose, although more precise for the estimation of total GNG, is difficult to use in neonates because of the very large sample size requirements (3, 4).

These measurements of GNG via pyruvate are similar to the estimates of glucose carbon recycling made by us in similar neonates with [13C6]glucose (8). In that study, the estimated glucose Ra from tracer dilution in eleven healthy full-term infants after an 8- to 9-h fast was 28 μmol·kg−1·min−1, and glucose C recycling amounted to 35% or 10.4 μmol·kg−1·min−1. Because glucose carbon recycling involves return of lactate and pyruvate from the periphery back to the liver and their incorporation into glucose, estimation of glucose C recycling gives an estimation of GNG via pyruvate. If the contribution of glycerol, ~4.5 μmol·kg−1·min−1 (31, 35), is also included, then the total GNG in a healthy newborn will amount to ~14 μmol·kg−1·min−1, or ~46% of the total glucose Ra of 30 μmol·kg−1·min−1. This is significant and implies an important role of GNG in glucose homeostasis even after a brief fast. The quantitative contribution of various precursors to GNG via pyruvate remains undetermined.

The data in preterm babies, although variable, are also significant in that they underscore the quantitatively large contribution of GNG to glucose production, even when the endogenous rate of glucose production was low, e.g., infants infused with glucose plus amino acids with or without lipids. It is of interest that, in these babies also, GNG via pyruvate contributed 20–40% to endogenous production of glucose. In babies who were receiving glucose alone parenterally, the contribution of GNG was variable. It was highest (~50%) in the two infants (nos. 4 and 5) who were receiving intravenous glucose at the lowest rate. These measurements are of similar magnitude to those reported by Sunehag et al. (36) and Keshen et al. (25) in studies of low-birth-weight babies in which different isotopic tracer methods were used.

These data suggest that GNG should be considered as one of the several substrate cycles, like the triglyceride fatty acid cycle and protein turnover, which are active at all times and which can be rapidly accelerated at the time of acute demand.

Only one other study has quantified lactate turnover in the human newborn. Cowett and Wolfe (7), using the [13C6]lactate tracer dilution technique, reported the rate of lactate turnover to be 77.2 ± 13.0 μmol·kg−1·min−1 in full-term infants between 9 and 42 h after...
birth, and 100 ± 19.2 μmol·kg⁻¹·min⁻¹ in preterm infants. Their estimates are much higher than those reported in the present study. The differences may be related to age of the infants, intercurrent illness, or relationship to the last feed. Whereas a majority of the infants in the present study were investigated during the first few hours after birth (8/10 normal and 4/6 IDDM) and were not receiving any intravenous fluids or antibiotics, such was not the case in the study of Cowett and Wolfe. Our data on lactate turnover are similar to those reported in infants and children aged 1–25 mo, which range between 25 and 44 μmol·kg⁻¹·min⁻¹ (2), and they are much higher than those reported in normal and diabetic adult subjects on the basis of similar tracer methods (9). The calculated contribution of lactate to glucose in our study, without account for loss of tracer in the tricarboxylic acid cycle, was ~18%. Correction for the loss of tracer (correction factor ~1.5) (14, 24) would yield lactate’s contribution to be ~27%, similar to that observed using the ²H₂O method.

Of interest, the Rₐ of lactate turnover was almost twofold the Rₐ of glucose turnover. This is in contrast to the data in adults, in which lactate turnover has been reported to be much lower than the rate of glucose turnover (in lactate equivalents) (5, 6, 9, 14, 24, 26, 28, 34). This would suggest either a rapid rate of equilibration of the tracer between various compartments of lactate (plus pyruvate plus alanine) in babies or an influx of carbon into the lactate pool from nonglucose sources, e.g., amino acids. Such an hypothesis remains to be examined. The high rate of lactate turnover is also significant, because lactate has been suggested to be an important metabolic fuel for the brain in the newborn period (30). Finally, the lack of any significant difference among normal infants, SGA infants, and infants of IDDM mothers was not surprising. It essentially reflects the clinical practice of rigorous intrapartum regulation of maternal metabolism. Furthermore, because a large fraction of lactate C is derived from glucose, a difference in lactate kinetics will not be anticipated in the presence of similar rates of glucose turnover (41).

In summary, the present data show that GNG from lactate is apparent soon after birth in the healthy newborn infant and that it contributes ~30% of the total glucose produced. Significant contribution of GNG to glucose Rₐ could be observed in healthy babies within 5 hours of last feed and was also seen in preterm infants while they received parenteral glucose and other nutrients.

We appreciate the assistance of the nursing staff of the General Clinical Research Center at MetroHealth Medical Center, the expert support of Alicia O’Brien and Ed Burkett, and the secretarial support of Joyce Nolan.

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