Amino acids do not suppress proteolysis in premature neonates

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Amino acids do not suppress proteolysis in premature neonates. Am J Physiol Endocrinol Metab 281: E472–E478, 2001.—To determine whether increased amino acid availability can reduce proteolysis in premature neonates and to assess the capacity of infants born prematurely to acutely increase the irreversible catabolism of the essential amino acids leucine (via oxidation) and phenylalanine (via hydroxylation to form tyrosine), leucine and phenylalanine kinetics were measured under basal conditions and in response to a graded infusion of intravenous amino acids (1.2 and 2.4 g·kg⁻¹·day⁻¹) in clinically stable premature (~32 wk gestation) infants in the 1st wk of life. In contrast to the dose-dependent suppression of proteolysis seen in healthy full-term neonates, the endogenous rates of appearance of leucine and phenylalanine (reflecting proteolysis) were unchanged in response to amino acids (297 ± 21, 283 ± 19, and 284 ± 31 μmol·kg⁻¹·h⁻¹ for leucine and 92 ± 6, 92 ± 4, and 84 ± 7 μmol·kg⁻¹·h⁻¹ for phenylalanine). Similar to full-term neonates, leucine oxidation (40 ± 5, 65 ± 6, and 99 ± 7 μmol·kg⁻¹·h⁻¹) and phenylalanine hydroxylation (12 ± 1, 16 ± 1, and 20 ± 2 μmol·kg⁻¹·h⁻¹) increased in a stepwise fashion in response to graded amino acids. This capacity to increase phenylalanine hydroxylation may be crucial to meet tyrosine needs when exogenous supply is limited. Finally, to determine whether amino acids stimulate glucose production in premature neonates, glucose rate of appearance was measured during each study period. In response to amino acid infusion, rates of endogenous glucose production were unchanged (and near zero).

premature newborns; leucine; phenylalanine; protein turnover; stable isotope tracers

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noted to have a decreased incidence of hyperglycemia (21, 31). Consequently, the final aim of this study was to evaluate the potential effect of intravenous amino acids on glucose metabolism in premature newborns. We hypothesized that an exogenous amino acid supply would not stimulate glucose production in premature neonates. To test this hypothesis, we measured glucose Ra in response to a graded amino acid infusion.

METHODS

Subjects

The Institutional Review Board of Indiana University approved this study, and written informed consent was obtained from the parents of all infants who served as study subjects. Premature neonates between 28 and 34 wk gestation <14 days of age were eligible for study. Characteristics of the seven study subjects are summarized in Table 1. All infants were appropriate for gestational age, had no congenital anomalies, and had no clinical evidence of sepsis. At the time of study, none of the infants required oxygen or ventilatory assistance. Enteral feeds with Enfamil Premature Formula (Mead Johnson, Evansville, IN) had been initiated by 10.2±0.3 days of life, and all had normal saline. Infants were quiet or sleeping. During the final 2.5 h of the study, the rate of the amino acid infusion on protein and glucose metabolism.

Protocol

The study lasted a total of 8 h and consisted of three distinct periods: a basal period and two separate amino acid periods. A schematic of the overall study design is shown in Fig. 1. This protocol is identical to that used in our previously published study that evaluated the effect of graded amino acids on proteolysis in full-term neonates (23). One peripheral intravenous catheter was placed for the infusion of tracers and glucose/amino acids, and a second catheter was placed (in an opposite extremity) for the purpose of drawing blood samples. The sampling catheter was kept patent by a constant infusion of isotonic saline. At 3–4 h after an enteral feeding, a baseline blood sample (the volume of this and subsequent samples was ~0.5 ml) was obtained, and a priming dose (representing 90 min of infusion) of the tracers (in normal saline) was administered over 5 min. In addition, 0.5 μmol/kg of D2-tyrosine was given (prime only) to calculate rates of phenylalanine hydroxylation. For the remainder of the study, a constant infusion of L-[13C]leucine (7 μmol·kg⁻¹·h⁻¹), D2-phenylalanine (2.5 μmol·kg⁻¹·h⁻¹), D2-tyrosine (1.4 μmol·kg⁻¹·h⁻¹), and 6,6, D2-glucose (60 μg·kg⁻¹·min⁻¹) in normal saline was delivered via a multichannel infusion pump (IVAC MedSystem III, San Diego, CA). All isotopes were pyrogen tested before use in the studies. Infants received no enteral intake during the study.

The basal study period lasted 3 h and consisted of an infusion of unlabeled glucose at 6 mg·kg⁻¹·min⁻¹ in addition to the tracer infusion. The tracer isotope and unlabeled glucose infusions were maintained for the duration of the study. Blood samples were obtained at 150, 165, and 180 min; the plasma was immediately separated and analyzed for glucose concentration. The remainder of the plasma was then frozen at −70°C for later analysis.

After the basal period, a 2.5-h infusion of amino acids (1.2 g·kg⁻¹·day⁻¹; Aminosyn PF, Abbott, N. Chicago, IL) was begun. The amino acid solution provided 46 μmol·kg⁻¹·h⁻¹ of leucine, 13 μmol·kg⁻¹·h⁻¹ of phenylalanine, and 1.2 μmol·kg⁻¹·h⁻¹ of tyrosine. Blood samples were obtained at 300, 315, and 330 min, analyzed for plasma glucose, and frozen for later analysis. Intravenous lipid was not administered so that we could precisely define the effect of a graded amino acid infusion on protein and glucose metabolism.

During the final 2.5 h of the study, the rate of the amino acid infusion was doubled to 2.4 g·kg⁻¹·day⁻¹. Blood samples were obtained at 450, 465, and 480 min, analyzed for plasma glucose, and frozen for later analysis.

The syringes containing the isotopes were weighed before and after infusion to quantitate the volume of tracer solution actually delivered. The concentrations of tracer leucine, phenylalanine, tyrosine, and glucose were measured in each infusate. Each bag of unlabeled glucose was also analyzed for glucose concentration to determine the actual unlabeled glucose infusion rate.

Open-circuit indirect respiratory calorimetry was performed to measure resting oxygen consumption and carbon dioxide production, as previously described (5). Measurements were taken in each of the three study periods while the subjects were quiet or sleeping.

Figure 1. Schematic of overall study design. AA, amino acid.

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Subj No.</th>
<th>Gestational Age, wk</th>
<th>Gender</th>
<th>Birth Wt, kg</th>
<th>Study Wt, kg</th>
<th>Age at Study, days</th>
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<tbody>
<tr>
<td>1</td>
<td>32</td>
<td>F</td>
<td>1.73</td>
<td>1.61</td>
<td>7</td>
</tr>
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<td>32</td>
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<tr>
<td>3</td>
<td>33</td>
<td>M</td>
<td>1.66</td>
<td>1.58</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>M</td>
<td>1.23</td>
<td>1.12</td>
<td>5</td>
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<tr>
<td>5</td>
<td>32</td>
<td>M</td>
<td>1.61</td>
<td>1.54</td>
<td>6</td>
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<td>7</td>
<td>29</td>
<td>F</td>
<td>0.99</td>
<td>0.99</td>
<td>12</td>
</tr>
</tbody>
</table>

Mean ± SE 32 ± 0.5 1.50 ± 0.11 1.42 ± 0.10 6 ± 1

*Open-circuit indirect respiratory calorimetry was performed to measure resting oxygen consumption and carbon dioxide production, as previously described (5). Measurements were taken in each of the three study periods while the subjects were quiet or sleeping.*
Analytic Methods

Plasma enrichments. The plasma enrichments of α-ketoisocaproic acid (KIC), phenylalanine, tyrosine, and glucose were determined by electron impact ionization and selected ion monitoring on a gas chromatograph-mass spectrometer (model 5970, Hewlett-Packard, Palo Alto, CA), as previously described (16, 23). Final values for all determinations were corrected using an enrichment calibration curve. The mean enrichment values of the three samples taken during enrichment plateau in each subject were used for further analysis. The 13C enrichment of carbon dioxide in blood bicarbonate was measured using isotope ratio mass spectrometry (model MAT 252, Finnigan, San Jose, CA) after separation of the carbon dioxide by cryogenic distillation in vacuum, as previously described (5).

Substrate and hormone concentrations. Plasma glucose concentrations were determined by the glucose oxidase method (Yellow Springs Instruments, Yellow Springs, OH) on all samples obtained. The average glucose concentration during each of the three periods is reported. Because a limited amount of blood was obtained from these infants, plasma insulin concentrations were measured on only one sample during each of the three periods by double-antibody radioimmunoassay. Similarly, plasma concentrations of amino acids were measured on one sample during each of the three periods on an amino acid analyzer (model 6300, Beckman Instruments, Fullerton, CA).

Calculations

Plasma enrichments of KIC, phenylalanine, tyrosine, and glucose were used to calculate the total Ra of leucine, phenylalanine, tyrosine, and glucose, respectively. The enrichment of KIC was utilized because its plasma enrichment has been shown to closely approximate intracellular leucine enrichment, thereby providing a more accurate assessment of whole-body protein oxidation (20).

The total Ra values of leucine, phenylalanine, tyrosine, and glucose were each calculated by measuring the tracer dilution at steady state as modified for stable isotopic tracers, as previously described for amino acids (model 6300, Beckman Instruments, Fullerton, CA).

Inasmuch as leucine and phenylalanine are essential amino acids, their Ra in a subject receiving no exogenous protein reflects whole-body protein oxidation (6). During the study periods when the subjects were receiving exogenous amino acids, the endogenous Ra of leucine and phenylalanine was calculated by subtracting the rate of exogenous administration of unlabeled leucine and phenylalanine from the measured total Ra values.

Rates of leucine oxidation (1, 7) and phenylalanine hydroxylation to tyrosine (10, 30) were calculated as described previously.

The nonoxidative disposal of leucine (reflecting protein synthesis) was calculated by subtracting leucine oxidation from the total Ra of leucine (7, 9). Utilization of phenylalanine for protein synthesis was calculated by subtracting phenylalanine hydroxylation from the total Ra of phenylalanine (10, 30).

Endogenous glucose production was calculated as the difference between the total Ra of glucose and the rate of intravenous glucose delivery.

Statistics

Values are means ± SE. Data were analyzed using repeated-measures analysis of variance (RM-ANOVA). When the overall RM-ANOVA was significant with P < 0.05, a Bonferroni correction was used to define differences within the study periods.

RESULTS

Amino Acid Concentrations and Leucine, Phenylalanine, and Tyrosine Kinetics

Plasma amino acid concentrations measured during the studies are shown in Table 2. As expected, graded infusion of amino acids resulted in a stepwise increase in the plasma concentration of most essential amino acids, including leucine and phenylalanine. Plasma concentrations of tyrosine did not change to any significant degree during any of the three study periods (reflecting the negligible amount of tyrosine provided by the amino acid solution that was given). Concentrations of cysteine decreased in a stepwise fashion throughout the study; the amino acid solution provided no cysteine.

Isotopic steady state was achieved for [13C]KIC, D5-phenylalanine, D2-tyrosine, D4-tyrosine, and 6,6-D2-glucose during each of the three study periods (Fig. 2).

The total Ra values for leucine and phenylalanine are shown in Fig. 3. In response to graded amino acid infusion, the total Ra of leucine and phenylalanine increased significantly. Total tyrosine Ra decreased slightly (overall RM-ANOVA P < 0.05) during the amino acid infusion periods (75 ± 6, 70 ± 6, and 68 ± 6 μmol·kg⁻¹·h⁻¹; P < 0.05, basal vs. 2nd amino acid period).

The endogenous release of leucine and phenylalanine (reflecting proteolysis) is also shown in Fig. 3. In response to graded infusion of amino acids, there was no change in proteolysis on the basis of either leucine or phenylalanine kinetics. A power analysis demonstrated that we had 80% power to detect a 5% differ-

Table 2. Amino acid concentrations in the basal state and during graded amino acid infusion

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Basal</th>
<th>AA1</th>
<th>AA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phe*</td>
<td>44 ± 3</td>
<td>51 ± 2</td>
<td>65 ± 2</td>
</tr>
<tr>
<td>Leu*</td>
<td>55 ± 4</td>
<td>87 ± 4</td>
<td>127 ± 6</td>
</tr>
<tr>
<td>Ile*</td>
<td>16 ± 3</td>
<td>36 ± 2</td>
<td>62 ± 3</td>
</tr>
<tr>
<td>Val*</td>
<td>87 ± 3</td>
<td>109 ± 2</td>
<td>149 ± 4</td>
</tr>
<tr>
<td>Thr*</td>
<td>229 ± 52</td>
<td>250 ± 50</td>
<td>281 ± 50</td>
</tr>
<tr>
<td>Lys*</td>
<td>82 ± 8</td>
<td>94 ± 7</td>
<td>134 ± 8</td>
</tr>
<tr>
<td>Trp*</td>
<td>38 ± 6</td>
<td>44 ± 5</td>
<td>49 ± 3</td>
</tr>
<tr>
<td>Met*</td>
<td>32 ± 4</td>
<td>35 ± 2</td>
<td>39 ± 1</td>
</tr>
<tr>
<td>His*</td>
<td>54 ± 3</td>
<td>61 ± 4</td>
<td>80 ± 5</td>
</tr>
<tr>
<td>Tyr*</td>
<td>68 ± 9</td>
<td>65 ± 9</td>
<td>61 ± 7</td>
</tr>
<tr>
<td>Cys*</td>
<td>39 ± 3</td>
<td>35 ± 3</td>
<td>31 ± 2</td>
</tr>
<tr>
<td>Pro*</td>
<td>108 ± 18</td>
<td>113 ± 12</td>
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<td>Ser*</td>
<td>105 ± 11</td>
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<td>Arg*</td>
<td>46 ± 8</td>
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<td>Asn</td>
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<td>Glu*</td>
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<td>23 ± 2</td>
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<td>Gln*</td>
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</tr>
<tr>
<td>Cit*</td>
<td>32 ± 6</td>
<td>34 ± 6</td>
<td>41 ± 7</td>
</tr>
</tbody>
</table>

Values are means ± SE in μmol/l. AA1 and AA2, 1st and 2nd amino acid periods, respectively. *P < 0.01 (repeated-measures ANOVA).
ence in endogenous leucine and phenylalanine Ra (α ≤ 0.05).

Utilization of phenylalanine for protein synthesis increased by ~13% in response to graded amino acid infusion (79 ± 6, 89 ± 3, and 90 ± 6 μmol·kg⁻¹·h⁻¹; RM-ANOVA P < 0.05). Utilization of leucine for protein synthesis increased, but not significantly (256 ± 16, 264 ± 16, and 277 ± 26 μmol·kg⁻¹·h⁻¹, RM-ANOVA P = 0.27).

Leucine oxidation and phenylalanine hydroxylation (the irreversible losses of leucine and phenylalanine) are shown in Fig. 3. Leucine oxidation increased in a stepwise fashion (by 63% between the basal and the 1st amino acid period and again by 52% between the 1st and 2nd amino acid period). Similar to the irreversible loss of leucine, there was also a stepwise increase in phenylalanine hydroxylation to form tyrosine in response to graded amino acid infusion (by 33% between the basal and the 1st amino acid period and again by 25% between the 1st and 2nd amino acid period).

Balance of the essential amino acids leucine and phenylalanine (calculated by subtracting irreversible loss from intake) improved in response to graded amino acid infusion (~40 ± 5, ~19 ± 6, and ~7 ± 7 μmol·kg⁻¹·h⁻¹ for leucine and phenylalanine; ~12 ± 1, ~3 ± 1, and 6 ± 2 μmol·kg⁻¹·h⁻¹ for phenylalanine, RM-ANOVA P < 0.0001). Although leucine balance improved significantly, the infants remained in negative leucine balance throughout the study.

**Glucose and Insulin Concentrations and Glucose Kinetics**

Plasma glucose and insulin concentrations are shown in Table 3. Plasma glucose concentrations decreased slightly but not significantly (P = 0.07) over the course of the three study periods. Insulin concentrations were unchanged. The actual glucose infusion rate during the study was 6.77 ± 0.23. Glucose kinetics during the basal period and during the two amino acid infusion periods are also shown in Table 4. Endogenous glucose production was unchanged in response to graded amino acid infusion. In
each of the study subjects, endogenous glucose production was suppressed (but not zero) during all three study periods.

Respiratory Calorimetry

The respiratory calorimetry data are reported in Table 4. Oxygen consumption decreased in response to the graded amino acid infusion (overall RM-ANOVA $P < 0.05$). The respiratory quotient significantly increased in response to provision of amino acids (overall RM-ANOVA $P < 0.01$).

DISCUSSION

In the present study, we have evaluated the effect of a graded amino acid infusion on whole body proteolysis and the capacity to catabolize the essential amino acids leucine and phenylalanine in premature neonates in the 1st wk of life. Our results demonstrate that premature neonates are resistant to suppression of proteolysis in response to intravenous amino acids. The catabolism of leucine (via oxidation) and phenylalanine (via hydroxylation to tyrosine) increased in a dose-dependent manner in response to intravenous amino acids. In addition, amino acids had no effect on endogenous glucose production in these premature infants.

In human adults, numerous studies have demonstrated that insulin mediates suppression of proteolysis (3, 8, 12, 29). Other investigators have evaluated the separate effect of amino acids on protein metabolism and have shown that intravenous amino acids (with maintained basal insulin levels) also inhibit proteolysis (3, 13). Giordano et al. (13) measured endogenous leucine flux (reflecting proteolysis) in response to graded hyperaminoacidemia in healthy adults. With small increases in plasma amino acid concentration (25, 50, and 100% increase above basal), there was a stepwise reduction of proteolysis (7, 13, and 24% reductions from basal during infusion of 0.7, 1.4, and 2.8 g amino acids·kg$^{-1}$·day$^{-1}$, respectively). No change in insulin concentration was observed at these low amino acid infusion rates (13).

Similar to the adult data, we have shown that healthy full-term newborns also reduce proteolysis in response to increased amino acid availability alone. We studied full-term neonates at 3 days and 3 wk of age under a protocol identical to that used in the present study. In response to 1.2 g amino acids·kg$^{-1}$·day$^{-1}$, proteolysis was reduced by 10%. When the amino acid infusion was doubled, proteolysis was suppressed by 20%. Insulin concentrations remained unchanged from basal values during amino acid administration. This dose-dependent reduction in proteolysis was consistent throughout the neonatal period, suggesting that amino acid availability is one of the primary regulators of proteolysis in healthy full-term neonates (23).

In striking contrast to adults and full-term neonates, rates of proteolysis were unchanged in response to graded amino acid infusion in premature neonates in the present study. It is important to point out that the magnitude of change in plasma amino acid concentration in the present study is similar to that used by Giordano et al. (13) in their study of adults and to that of our study in full-term infants (23). The amino acid infusion rates in the present study (1.2 and 2.4 g·kg$^{-1}$·day$^{-1}$) were identical to that of our study in full-term neonates.

Despite no change in proteolysis, overall amino acid balance improved on the basis of leucine and phenylalanine kinetics. The fact that leucine balance improved but remained negative in response to graded amino acids is consistent with the findings of other investigators who have measured leucine balance on the basis of leucine oxidation at low caloric intakes (24, 33).

Although the lack of suppression of proteolysis in premature infants is in contrast to that in adults and full-term neonates, a similar resistance to suppression of proteolysis has been demonstrated in the ovine fetus (18, 19), suggesting a developmental aspect of the ability to suppress proteolysis. Rates of proteolysis are inversely related to gestational age (6, 10, 14, 15, 26). In a comparison of the premature infants in the present study with the full-term infants we previously studied under an identical protocol, rates of proteolysis (based on phenylalanine kinetics) during the basal period are ~30% higher in the premature infants (23). Higher rates of proteolysis are presumably required to support the higher rates of growth in the most immature neonates.

The obvious question raised by this study is as follows: why are premature infants different from full-term infants and adults with regard to their ability to suppress proteolysis in response to intravenous amino acids? One possibility is that less-than-optimal energy intake during the study limited the suppression of proteolysis in these infants. The concept that energy intake influences proteolysis is further supported by a previous study in a similar population of premature infants who responded to provision of complete parenteral nutrition with increased protein synthesis as well as a reduction in proteolysis (4). On the other hand, the healthy full-term neonates in our previous study were subjected to the same low level of caloric intake, and this did not limit suppression of proteolysis in response to amino acids alone (23).

An alternative explanation for the lack of suppression of proteolysis is that currently available amino acid solutions may be incomplete for the premature neonate. Several amino acids are thought to be conditionally essential for premature infants, yet they are not supplied by currently available amino acid solutions. Tyrosine and cysteine are two such amino acids. To the extent that need for the particular amino acid is exceeded by the infant’s ability to accomplish synthesis, proteolysis may persist to maintain the supply of the amino acid. The role of each of these amino acids obviously requires further study, particularly in devising strategies to improve the composition of amino acid solutions used in the neonatal intensive care unit.

As mentioned previously, tyrosine is not supplied by most intravenous amino acid solutions available for
use in neonates. As a result, the ability of the infant to synthesize tyrosine from phenylalanine is quite critical. Previous studies have clearly demonstrated the ability of even the extremely premature neonate to hydroxylate phenylalanine and form tyrosine. In fact, on a per kilogram basis, rates of phenylalanine hydroxylation are higher in premature than in full-term infants (10). The capacity to acutely increase phenylalanine hydroxylation in response to increased phenylalanine supply had not been previously studied. If it is assumed that the infant can increase phenylalanine hydroxylation without limit, one means of ensuring adequate tyrosine supply would be via increased phenylalanine intake in parenteral solutions. On the other hand, if there exists a maximum capacity to increase rates of hydroxylation, the addition of another source of tyrosine might be preferable. Although the premature infants in the present study did increase rates of phenylalanine hydroxylation, the Ra of tyrosine declined during the study. We speculate that tyrosine supply may play a role in the lack of suppression of proteolysis in these infants. Future studies are needed to evaluate the effect of supplemental tyrosine on protein kinetics in these infants.

Similar to full-term neonates, in this study, leucine catabolism increased in a stepwise fashion in response to intravenous amino acids. The fact that leucine oxidation increases more than phenylalanine hydroxylation is probably related to the much higher ratio of leucine to phenylalanine in the amino acid mixture than in body protein. Another possible explanation is that the enzyme for leucine oxidation, branched-chain keto acid dehydrogenase, is highly regulated and responds quickly to changes in α-KIC concentration (22).

In this study, we also evaluated the effect of glucose and intravenous amino acids on glucose metabolism. Defining the regulation of glucose homeostasis in premature newborns is of clinical interest because of the occasional problem of hyperglycemia in these infants. We previously showed that even extremely premature (~26 wk gestation) infants can suppress endogenous glucose production in response to intravenous glucose delivered at 9–10 mg·kg⁻¹·min⁻¹ (15). The present study also demonstrated that slightly more mature premature neonates suppress glucose production to near zero during intravenous glucose delivered at ~7 mg·kg⁻¹·min⁻¹; this suppression occurred at moderate glucose concentrations (~90 mg/dl) and low insulin concentrations (~3.5 μU/ml) in the present study. Furthermore, providing intravenous amino acids as potential gluconeogenic substrates did not increase endogenous glucose production in these premature infants.

This result in premature infants is different from that in human adults. Using a similar study design, Tappy et al. (28) demonstrated that intravenous amino acids significantly increase endogenous glucose production in healthy human adults. It is important to note that the rate of amino acid infusion in this adult study was approximately twice the highest rate used in the present study, perhaps accounting for the findings in adults and premature neonates. It seems likely, however, that developmental differences play at least some role.

In the present study, the significant increase in the respiratory quotient suggests that amino acids stimulate glucose oxidation in premature infants; the increase in amino acid oxidation may also contribute to the increase in respiratory quotient. A slight increase in glucose oxidation during amino acid infusion (with an increase in plasma insulin concentration) has also been observed in adults (28). Although the mechanism remains obscure, amino acid stimulation of glucose oxidation may help explain the clinical observation of improved glucose tolerance in premature infants with the addition of intravenous amino acids (21, 31).

In summary, clinically stable, premature infants are resistant to suppression of proteolysis in response to an increase in amino acid availability alone. This response is in contrast to that of healthy newborns born at full term. These premature infants are able to acutely increase the catabolism of leucine and phenylalanine in response to increased amino acid supply. The capacity to increase phenylalanine hydroxylation to form tyrosine may be crucial to meet tyrosine needs when exogenous supply is limited. Finally, intravenous amino acids do not appear to acutely increase endogenous glucose production and most likely stimulate glucose oxidation in stable premature infants.

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