Reciprocal inhibition of umbilical uptake within groups of amino acids

Maciej Jóźwik, Cecilia Teng, Randall B. Wilkening, Giacomo Meschia, and Frederick C. Battaglia

Department of Gynecology, Medical University of Białystok, 15-276 Białystok, Poland; and Division of Perinatal Medicine, Department of Pediatrics, University of Colorado Health Sciences Center, Aurora, Colorado 80010

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THE INFUSION OF AN AMINO ACID MIXTURE into the maternal circulation is a potentially useful means for improving fetal nutrition in conditions such as maternal hypoa minoacidemia and fetal growth restriction (1). To be effective, the infusion should increase the fetal supply of all the essential amino acids and at least some of the nonessentials that are normally delivered to the fetus from the placenta.

The present study presents results of infusing in normal-pregnancy ewes two mixtures of different composition. One mixture contained only the essential amino acids, and the other contained all the essentials plus some nonessentials. The study compares maternal concentrations of amino acids with their uptakes and is focused on the interaction among related groups of amino acids on their umbilical uptakes. Both mixtures failed to increase the fetal uptake of all the infused amino acids despite an increase in their maternal concentrations. Quantitative analysis of the pooled data from these and other similar infusion experiments demonstrates that the transport of several amino acids from placenta to fetus is subject to inhibition by coinfused amino acids of similar physicochemical characteristics. As a consequence, the umbilical uptake of an amino acid that is infused as part of an amino acid mixture can either increase, remain unchanged, or decrease depending upon the composition of the mixture. This knowledge provides a rationale for designing amino acid infusates that would satisfy fetal nutritional requirements.

MATERIALS AND METHODS

Surgery and animal care. Eight pregnant cross-bred Columbia-Rambouillet ewes with singleton gestations were studied. After a 48-h fast, the ewes were given general anesthesia using intravenous pentobarbital sodium (initial dose, 20 mg/kg) and spinal anesthesia (intrathecal tetracaine hydrochloride, 20 mg). Polyvinyl catheters (1.4 mm outer diameter) were placed in the following locations, as previously described (6, 8): maternal femoral artery and vein, maternal uterine vein draining the pregnant uterine horn, fetal abdominal aorta via a pedal artery, common umbilical vein, and fetal pedal vein. An additional catheter was placed in the amniotic cavity for the administration of antibiotics (500 mg of ampicillin daily). All catheters were tunneled subcutaneously through a maternal skin incision and kept in a plastic pouch secured to the ewe’s flank. These catheters were flushed daily with a solution of heparin in isotonic saline (35 IU heparin/ml). Analgesics were given to the ewes during the first two postoperative days. The animals were given ≥4 days to recover from surgery before study.

After surgery, each ewe was housed in a temperature-controlled room (18 ± 2°C) in a 1.5 × 1.0 m cart. At least two sheep were kept in adjacent carts at all times to create a less stressful environment for the animals. The animals had ad libitum access to a standard diet of alfalfa pellets, water, and mineral block. All studies were conducted during daytime when the mean intake of nitrogen from alfalfa pellets is ~6.4 g nitrogen/12 h (6). At the end of the study, the ewes were injected intravenously with a barbiturate euthanasia solution (Fort Dodge Laboratories, Fort Dodge, IA).

All animal experimentation was performed in adherence to the American Physiological Society’s Guiding Principles in the Care and Use of Animals. The study protocol was approved by the Institutional Animal Care and Use Committee of the University of Colorado Health Sciences Center.

Study design. Two experiments were performed in each of the eight ewes (Table 1). In each experiment, uterine and umbilical amino acid uptakes were measured under control conditions. After the control period, the measurements were repeated in the last 90 min of a 3.5-h infusion of an amino acid solution into the maternal femoral vein. Two solutions were tested. One solution (solution E) contained only essential amino acids; the other (solution EN) contained both essential and nonessential amino acids. To achieve different maternal amino acid concentrations, this infusate was given at two different rates. The

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Address for reprint requests and other correspondence: G. Meschia, Univ. of Colorado Health Sciences Center, 13243 E. 23rd Ave., Bldg. 260, Aurora, CO 80010-0508.

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composition of the two infusates and the infusion rates are presented in Table 2.

On the day of the experiment, a solution of tritiated water (325 μCi/20 ml) was infused at the rate of 3.0 ml/h into the fetal pedal vein, starting 1 h before sampling. This infusion had the purpose of measuring uterine and umbilical blood flows by the steady-state distillation method (19). In the control period, four sets of blood samples were drawn at 30-min intervals for analysis of amino acids, O2 content, hematocrit, and tritiated water from the maternal artery (A), the uterine vein (V), the umbilical vein (γ), and the fetal abdominal aorta (α). In the experimental period, the blood sampling routine was repeated, beginning 2 h after the start of the infusion. Before and after each sampling period, 10 ml of blood were transfused into the fetus as a replacement for fetal sampling. The transfusion aimed at maintaining fetal blood volume within ±4% of normal.

Chemical methods. The amino acids to be infused were purchased in the lectoratory crystalline form. Concentrated glacial acetic acid was used to solubilize the amino acid mixture, and the final pH of the infusate was adjusted to 5.0–6.0. The infusate was passed through a Millipore (Bedford, MA) filter and then administered by means of a peristaltic pump. Maternal and fetal blood O2 content was measured in duplicate in a hemoximeter (OSM-3, Radiometer, Copenhagen, Denmark). Blood samples for amino acid measurements were centrifuged at 4°C, and the plasma was frozen immediately at −70°C until analysis. Plasma amino acid concentrations were determined using a Dionex HPLC Amino Acid Analyzer (Dionex, Sunnyvale, CA). The samples were analyzed by cation exchange chromatography with three buffers changed by gradient isothermally. All of the instrument operation and data processing were controlled by Dionex AS-450 software. Samples from each study were analyzed on a single column in the same run, with a variance of ±2%. Radioactivity was determined in a Packard Tri-Carb 460C scintillation counter (Packard, Meriden, CT).

Calculations. Uterine and umbilical blood flows were calculated using the tritiated water data as previously described (19).

Uterine and umbilical O2 uptakes were calculated as the product of blood flow and arteriovenous differences of O2 content across the uterine and umbilical circulation, respectively.

The umbilical uptake of each amino acid was calculated by means of the equation

\[
\text{umbilical uptake} = f(\gamma - a)(1 - \text{Hct})
\]

where \( f \) is the umbilical blood flow in ml/min, \((\gamma - a)\) is the umbilical vein − umbilical artery plasma concentration difference of the amino acid (μmol/ml), and Hct is the fetal fractional hematocrit (i.e., hematocrut = 100). Similarly, the uterine uptake of each amino acid was calculated using uterine blood flow, the maternal artery minus umbilical vein plasma concentration difference, and the maternal fractional hematocrit. The rationale for these uptake calculations is that, in sheep, amino acid exchange between the placenta and the maternal and fetal circulation is limited to the plasma compartments of the two circulations (3).

Statistical analysis. For each of the concentration and uptake measurements, the control and experimental data were subjected to paired t-test analysis. Before analysis, the four repeated measurements within each sampling period were averaged, and the uptake measurements were expressed per kilogram of fetus. The fetal weight measured at autopsy was used for calculation because control uptakes measured 2 to 3 days before autopsy were not significantly different from the uptakes measured on the last day of the study. P values were considered significant at \( P < 0.05 \).

The mean amino acid uptake data from this and other similar studies in our laboratory (3, 9, 13, 14, 20) were pooled and used to derive equations that relate umbilical uptake to maternal plasma concentrations. To this end, we used the method that was applied previously for the analysis of threonine uptake (14). This method assumes that the uptake vs. concentration relationship can be modeled by a Michaelis-Menten equation that includes the effect of competitive inhibition. Multiple regression analysis was applied to the following linear transformation of the equation

\[
\frac{A}{Q} = \frac{K_m}{V_{max}} - \frac{1}{V_{max}} (A + i_1) + \frac{Ci_2}{V_{max}}
\]

where \( A \) is the maternal arterial plasma concentration of the amino acid (μM), \( Q \) is its umbilical uptake (μmol/min−1·kg−1), \( i_1 \) (μM) is the concentration of inhibiting amino acids that are assumed to have virtually the same affinity for the transport system as \( A \), \( i_2 \) (μM) is the concentration of inhibitory amino acids that are assumed to have a different affinity for the transport system, and \( C \) is a coefficient that defines the strength of the inhibitory effect of \( i_2 \). This regression analysis had two aims. The first was to establish whether \( CV_{max} \) is statistically significant, i.e., whether there is a demonstrable inhibitory effect of \( i_2 \). The second purpose was to obtain numerical values for the \( K_m \), \( V_{max} \), and \( C \) coefficients. These coefficients were used to calculate \( Q \) from the measured values of \( A \), \( i_1 \), and \( i_2 \). The correlation of measured \( Q \) to calculated \( Q \) was then used to estimate the ability of the model to describe the experimental data. The correlation coefficient that results from the multiple regression analysis was not used for this purpose because the \( A \) variable appears on both sides of the equation (spurious correlation).

**RESULTS**

Mean gestational age, maternal, fetal, and placental weights, uterine and umbilical flows, and O2 uptakes are presented in...
Infusion of the essential amino acid mixture (solution E) yielded the results summarized in Table 4. Maternal arterial concentration increased significantly for each of the infused amino acids. Eight of the amino acids that were not infused showed a significant decrease in concentration. The fetal concentration increased significantly for seven of the nine amino acids infused but decreased significantly for valine and remained unchanged for threonine. The uterine uptake of each infused amino acid increased significantly. The seven essential amino acids with significantly increased fetal concentrations also showed an increase in umbilical uptake that attained statistical significance for all but isoleucine. Among the non-infused amino acids, tyrosine and arginine showed a significant decrease in umbilical uptake.

Infusion of the mixture of essential and nonessential amino acids (solution EN) at two different rates (240 and 120 ml/h, respectively) yielded the results summarized in Tables 5 and 6.

**DISCUSSION**

Attempts to increase the umbilical uptake of amino acids by infusing an amino acid mixture into the maternal circulation (6,
Maternal and fetal arterial plasma concentrations and uterine and umbilical uptakes of amino acids in the control period and during infusion of solution EN at 240 ml/h

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Control</th>
<th>EN240</th>
<th>Control</th>
<th>EN240</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ile</td>
<td>197 ± 23</td>
<td>632 ± 40†</td>
<td>131 ± 13</td>
<td>289 ± 15†</td>
</tr>
<tr>
<td>Leu</td>
<td>300 ± 44</td>
<td>653 ± 33†</td>
<td>211 ± 23</td>
<td>304 ± 15†</td>
</tr>
<tr>
<td>Val</td>
<td>450 ± 71</td>
<td>1,420 ± 65†</td>
<td>638 ± 71</td>
<td>1,017 ± 40†</td>
</tr>
<tr>
<td>Met</td>
<td>41 ± 35</td>
<td>370 ± 36†</td>
<td>83 ± 4</td>
<td>250 ± 15†</td>
</tr>
<tr>
<td>Phe</td>
<td>85 ± 10</td>
<td>256 ± 31*</td>
<td>105 ± 9</td>
<td>166 ± 20*</td>
</tr>
<tr>
<td>Thr</td>
<td>301 ± 44</td>
<td>551 ± 23†</td>
<td>384 ± 49</td>
<td>293 ± 30*</td>
</tr>
<tr>
<td>Trp</td>
<td>43 ± 4</td>
<td>88 ± 9*</td>
<td>32 ± 3</td>
<td>37 ± 4</td>
</tr>
<tr>
<td>Lys</td>
<td>169 ± 12</td>
<td>1,415 ± 180†</td>
<td>48 ± 7</td>
<td>110 ± 12†</td>
</tr>
<tr>
<td>His</td>
<td>39 ± 2</td>
<td>386 ± 69†</td>
<td>54 ± 9</td>
<td>73 ± 10†</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 5. EN240, solution EN at 240 ml/h. *P < 0.05; †P < 0.01; ‡P < 0.001.

Essential Ile 168 ± 16 363 ± 11† | 124 ± 8 228 ± 9† | 5.1 ± 0.4 9.2 ± 10† | 3.2 ± 0.3 5.1 ± 0.3† |
| Leu 247 ± 30 420 ± 20† | 196 ± 21 262 ± 11† | 7.2 ± 0.6 10.7 ± 10* | 5.4 ± 0.4 6.6 ± 0.5* |
| Val 367 ± 47 835 ± 42† | 603 ± 64 864 ± 29† | 9.0 ± 1.1 17.2 ± 1.5† | 7.4 ± 1.2 9.0 ± 1.0 |
| Met 34 ± 2 173 ± 9† | 73 ± 8 168 ± 25† | 1.0 ± 0.2 3.2 ± 0.5† | 1.4 ± 0.3 2.7 ± 0.2† |
| Phe 70 ± 6 140 ± 7† | 95 ± 9 131 ± 13* | 1.6 ± 0.1 2.3 ± 0.1* | 2.0 ± 0.2 2.5 ± 0.2 |
| Thr 223 ± 22 362 ± 11† | 343 ± 32 294 ± 36 | 3.7 ± 0.6 3.9 ± 0.8 | 3.8 ± 0.5 2.8 ± 0.4* |
| Ala 128 ± 5 359 ± 45† | 279 ± 29 289 ± 22 | 1.7 ± 0.3 7.4 ± 1.2* | 3.0 ± 0.4 3.2 ± 0.4 |
| Tyr 94 ± 12 75 ± 9* | 127 ± 10 84 ± 4 | 1.7 ± 0.4 11.0 ± 0.6 | 2.1 ± 0.2 14.0 ± 1.0* |
| Orn 146 ± 13 173 ± 12† | 60 ± 6 49 ± 6 | 3.5 ± 0.9 2.7 ± 0.4 | 0.4 ± 0.3 0.6 ± 0.2 |
| Arg 170 ± 10 355 ± 43† | 84 ± 3 53 ± 6 | 3.2 ± 0.7 7.3 ± 1.0* | 3.5 ± 0.1 2.7 ± 0.3* |

Values are means ± SE; n = 6. EN120, solution EN at 120 ml/h. *P < 0.05; †P < 0.01; ‡P < 0.001.
amino acids may be accompanied by a decrease in their fetal concentration and uptake. During infusion of solution \( E \), fetal valine concentration decreased significantly despite an increase of maternal valine. During infusion of solution \( EN \) at 240 ml/h, the increase in maternal threonine was accompanied by a significant decrease in fetal threonine concentration, and the increase in maternal valine was accompanied by a significant decrease in both the fetal concentration and uptake of arginine. The failure to induce a significant increase of fetal threonine concentration and uptake (14). Following this line of reasoning, we made an attempt to fit the threonine data to an equation that is based on two assumptions. The first is that the umbilical uptake depends on a saturable, rate-limiting transport process. The second is that the umbilical uptake of an amino acid is a function of both its own concentration and the maternal concentration of inhibitory amino acids. This attempt succeeded in showing that a group of neutral amino acids, i.e., the branched-chain amino acids plus phenylalanine and methionine, has a statistically significant inhibitory effect on threonine umbilical uptake (14). In the present study, we have extended this type of analysis to the other essential amino acids and arginine. The results of the analysis are summarized in Table 7 and Figs. 1–3. No interaction could be demonstrated between the neutral and cationic amino acids. Within each group, however, there were significant interactions. The branched-chain amino acids have similar transplacental pulse clearances (13). The clearance data have suggested the hypothesis that the transplacental flux of these amino acids is mediated by a rate-limiting transport system for which they compete with nearly equal affinity (13). In agreement with this hypothesis, the umbilical uptakes of leucine, isoleucine, and valine could be described fairly accurately by three equations that have similar coefficients and are based on the assumption of equal affinity for a common transport system. We could not demonstrate a significant inhibitory effect of phenylalanine and methionine on the valine and leucine uptakes. Their inhibition of isoleucine uptake was of borderline significance. However, the phenylalanine and methionine uptakes could be described by a single equation that shows a significant decrease in both the fetal concentration and uptake of arginine.

The failure to induce a significant increase of fetal threonine concentration and uptake (14). Following this line of reasoning, we made an attempt to fit the threonine data to an equation that is based on two assumptions. The first is that the umbilical uptake depends on a saturable, rate-limiting transport process. The second is that the umbilical uptake of an amino acid is a function of both its own concentration and the maternal concentration of inhibitory amino acids. This attempt succeeded in showing that a group of neutral amino acids, i.e., the branched-chain amino acids plus phenylalanine and methionine, has a statistically significant inhibitory effect on threonine umbilical uptake (14).

### Table 7

<table>
<thead>
<tr>
<th>Eq. No.</th>
<th>Amino Acids</th>
<th>Equations</th>
<th>( P ) Value</th>
<th>( CV_{\text{max}} ) Coefficient</th>
<th>Correlation Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ile (I)</td>
<td>( Q_t = 47.3690 + V + I + L + 0.7(F + M) )</td>
<td>0.052</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Leu (L)</td>
<td>( Q_t = 41.01130 + V + I + L + 0.1(F + M) )</td>
<td>NS</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Val (V)</td>
<td>( Q_t = 35.61413 + V + I + L + 0.7(F + M) )</td>
<td>NS</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Phe (F) + Met (M)</td>
<td>( Q_{V+M} = 14.5_{325 + F + M + 0.124(V + I + L)} )</td>
<td>0.008</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Thr (T)</td>
<td>( Q_t = 10.8_{126 + T + 0.473(V + I + L + F + M)} )</td>
<td>&lt;0.001</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Lys (K)</td>
<td>( Q_k = 5.5_{91 + K + 0.74R} )</td>
<td>0.001</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Arg (R)</td>
<td>( Q_k = 6.0_{97 + R + 0.23K} )</td>
<td>&lt;0.001</td>
<td>0.89</td>
<td></td>
</tr>
</tbody>
</table>

Maternal concentrations are designated by standard 1-letter symbols (e.g., I represents isoleucine concentration). NS, not significant.

### Fig. 1

Plot of measured mean branched-chain amino acid umbilical uptakes vs. umbilical uptakes of these amino acids calculated on the grounds of Eqs. 1–3 in Table 7. The uptakes are in \( \mu \text{mol} \cdot \text{min}^{-1} \cdot \text{kg fetus}^{-1} \). No. of observations, 16. Identity line is shown for comparison.
significantly inhibitory effect of the branched-chain amino acids. Within the group of cationic amino acids, the lysine and arginine uptakes fit two equations that show significant reciprocal inhibition of lysine uptake by arginine and arginine uptake by lysine. Our analysis failed to provide an equation that fits the histidine measurements accurately. No attempt was made to analyze quantitatively the tryptophan data, because the present set of experiments provides the only information about the response of tryptophan uptake to changes in maternal concentration.

The effect of amino acid infusions on the uterine uptake of amino acids is distinctly different from the effect on umbilical uptake. In response to an increase in maternal concentration that demonstrates saturable transport to the fetus, uterine uptake increases, with no clear evidence of approaching a maximum and no evidence of reciprocal inhibitory effects. The responses of the uterine and umbilical uptakes of branched-chain amino acids to changes in maternal concentration are compared in Fig. 4. The two uptakes are virtually equal at the lowest concentrations. As the maternal concentration increases, uterine uptake becomes progressively greater than umbilical uptake. The divergence of the two uptakes implies an increase in the placental catabolism of branched-chain amino acids. This implication is supported by the evidence that an increase in maternal branched-chain amino acids concentration is accompanied by an increase in the placental output of ammonia (7). The other essential amino acids also show that, at high maternal concentrations, their uterine uptakes become greater than umbilical uptakes. This discrepancy between uterine and umbilical uptakes suggests that placental catabolism of all essential amino acids increases in response to an increase of maternal concentration. However, there is no independent evidence, as yet (comparable to the increased placental ammonia production in response to branched-chain amino acid infusion), that would confirm the validity of this generalization.

Transport of an amino acid from mother to fetus depends on the activity of two sets of transport systems that are located on the maternal and the fetal surfaces of the trophoblast, respectively (12, 17). In each set, more than one transport system may be involved in the transport of an individual amino acid, and each system reacts with more than a single amino acid (17). Net transport across each surface (i.e., uptake) is the balance of fluxes in opposite directions. Opposing fluxes may be due to reversibility of individual transporters as well as to different types of transporters promoting transport in the opposite direction. Given this complexity, the coefficients of the uptake equations do not represent the coefficients of any single transport system and several aspects of the connection between in vivo data and the molecular biology of placental amino acid transporters remain unclear. A fundamental property of amino acid transporters is that, with few exceptions, each transporter reacts with more than a single amino acid (2). Therefore, allosteric effects and competitive inhibition of transport via shared transport sites are likely to be the underlying mechanisms of umbilical uptake inhibition.
The reciprocal inhibition of lysine and arginine uptakes agrees with the knowledge that, in the placenta, both amino acids utilize transporters for cationic amino acids (4, 12). On the fetal surface of the trophoblast, the transport of cationic amino acids into the umbilical circulation is mediated by the "y+L" system, which couples the efflux of cationic amino acids from placenta to fetus to the influx of neutral amino acids from fetus to placenta (10). The lack of evidence for a neutral vs. cationic amino acid interaction in the maternal infusion experiments is an example of the difficulty of predicting the outcome of in vivo experiments from current knowledge of placental transporters.

The quasi-linear relation of uterine uptake to maternal concentration for the branched-chain amino acids indicates that their transport from maternal plasma into the placental epithelium is mediated by a low-affinity transport system (K_m ≈ 5,000 μM). Because the presence of the sodium-independent "L" system on the microvillous surface of the human placenta is well documented (12), the assumption has been made that this system transports the branched-chain amino acids into the placenta in exchange for other neutral amino acids (5). It is not clear, however, whether the L system has the required low affinity for explaining the in vivo data. The presence on the maternal trophoblastic surface of additional, low-affinity transport systems for neutral amino acids may have been overlooked.

Physiological evidence about the saturability of amino acid umbilical uptakes at relatively low maternal concentrations does not establish that the umbilical uptakes are controlled by high-affinity transporters. The efflux of amino acids from placenta to fetus depends on transport systems that are located on the fetal surface of the trophoblast. These systems interact with intracellular concentrations that are severalfold higher than maternal concentrations. The effect of maternal concentration changes on placenta-to-fetus transport is indirect, through the induction of changes in intracellular concentrations. Furthermore, an increase in the efflux of any given amino acid into the umbilical circulation increases its fetal concentration. Such an increase is likely to elevate the fetus-to-placenta backflux of the amino acid and decrease its net transport to the fetus.

From a practical point of view, it is important to note that the inhibitory interactions among amino acids do not preclude a solution to the problem of designing a maternal amino acid infusate that increases simultaneously the umbilical uptake of all the essential amino acids. Let us assume, for example, that the concentration ratios of the essential amino acids and arginine in the infusate, and the infusion rate, are set with the goal of doubling the normal maternal concentration of each infused amino acid. The umbilical uptake equations predict that the uptakes of the branched-chain amino acids, phenylalanine and methionine would increase between 40 and 50%, lysine and arginine uptakes would increase ~15%, and threonine uptake would increase 9%. To produce a more even increase in uptakes, one could take advantage of the finding that threonine has virtually no inhibitory effect on the amino acids by which it is inhibited. According to the transport equations, an infusate that would cause the maternal concentrations of the branched-chain amino acids phenylalanine and methionine to increase 1.5 times and the threonine concentration to increase two times above normal would cause the uptake of all of these amino acids to increase ~25%. In more general terms, an amino acid infusion that aims at improving fetal nutrition should be designed to produce percent concentration increases in maternal concentrations that either are of similar value or are biased in favor of the amino acids with weak inhibitory power. Commercially available amino acid solutions do not follow these criteria. For example, the infusion of Freemine 8.5% III (Baxter Healthcare, Deerfield, IL) in normal human pregnancies caused the branched-chain amino acids, phenylalanine and methionine to increase 2.9-fold above baseline, arginine 3.8-fold, lysine 2.3-fold, and histidine and threonine 1.6-fold, respectively (15). Not surprisingly, no significant increase in uptake could be demonstrated for lysine, histidine, and threonine (15). Similarly, the infusion of Trophamine (Kendall-McGaw Laboratories, Irvine, CA) in pregnant sheep, with the aim of correcting the maternal and fetal hypoaminoacidemia caused by a chronic maternal glucose infusion, failed to in-

Fig. 4. Comparison of responses of uterine (ut.) and umbilical (umb.) branched-chain amino acid (BCAA) uptakes to changes in maternal BCAA concentration. No. of observations, 16. Note the convergence of the two uptakes at lower concentrations, and their divergence at higher concentrations.
crease the fetal concentration of lysine and caused a significant decrease in the fetal concentrations of histidine and threonine (18).

GRANTS

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