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Phenylalanine Kinetics in Sick Preterm Neonates with Respiratory Distress Syndrome

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ABSTRACT

The cause of hyperphenylalaninemia in sick preterm infants has yet to be determined; one reason may be reduced tolerance to phenylalanine as a consequence of immaturity of phenylalanine hydroxylase. Phenylalanine metabolism was studied *in vivo* in 23 ventilated preterm infants of gestational age 23 to 36 wk within the first 6 d of life using a continuous i.v. infusion of the stable isotope–labeled amino acids [$^2H_5$]phenylalanine, [$^2H_4$]tyrosine, and [$^2H_2$]tyrosine. Phenylalanine hydroxylation was calculated from two different methods. In the first method, used in all 23 infants receiving glucose and in seven of these infants who subsequently received parenteral nutrition, phenylalanine hydroxylation was calculated from the plasma enrichments of [$^2H_5$]phenylalanine and [$^2H_4$]tyrosine and from the molar ratio of tyrosine to phenylalanine in mammalian tissue protein. In this instance, the mean hydroxylation was 16.0 (SD 10.9) and 48.4 (SD 14.9) μmol/kg/h, which was 17.3% (SD 8.4%) and 33.2% (SD 9.8%) of the total phenylalanine flux for infants receiving glucose and parenteral nutrition, respectively. Additionally, in six infants receiving glucose, hydroxylation was calculated from the measured phenylalanine ($^2H_5$), independent tyrosine ($^2H_2$) fluxes, and the plasma enrichments of ($^2H_5$) phenylalanine and its hydroxylation product [$^2H_4$]tyrosine. In this case, hydroxylation was 20.5 (SD 13.0) μmol/kg/h, which represented 22.3% (SD 9.8%) of the phenylalanine flux. In the same six infants, phenylalanine hydroxylation derived using the first method was 22.2 (SD 13.1) μmol/kg/h, 23.6% (SD 9.9%) of the total phenylalanine flux. The close agreement between phenylalanine hydroxylation calculated from the enrichment of plasma with [$^2H_2$]tyrosine and estimated from the proportion of phenylalanine to tyrosine in body protein confirms that the independent measurement of tyrosine flux by a constant infusion of [$^2H_2$]tyrosine is not routinely required in the measurement of phenylalanine hydroxylation in preterm infants. These results do not support the hypothesis that phenylalanine hydroxylase activity is low in preterm infants. (***Pediatr Res* 36: 713–718, 1994**)

Abbreviations
PAH, phenylalanine hydroxylase
MPE, molecule percent excess

In normal newborn infants, plasma concentrations of the essential amino acid phenylalanine are less than 200 μmol/L. Concentrations in excess of 400 μmol/L are known to be toxic to the developing brain (1). Such raised levels are characteristic of infants with untreated phenylketonuria and nonphenylketonuria-hyperphenylalaninemia in which there are inherited defects of phenylalanine hydroxylation. More recently, hyperphenylalaninemia has been described in sick preterm infants as a complication of parenteral feeding with amino acid solutions. Although this is a transient phenomenon, levels have been reported in some infants in excess of 1000 μmol/L (2–5). The implications of these high phenylalanine concentrations over a relatively short period of time are unknown, but, in view of the high risk of fetal damage in maternal hyperphenylalaninemia (6), they may pose a significant risk to the preterm infant.

The cause of hyperphenylalaninemia in such infants has yet to be determined, but it is usually ascribed to a reduced tolerance to phenylalanine as a consequence of immaturity of PAH or enzymes of tyrosine metabolism, in particular 4-(OH)phenylpyruvate dioxygenase (7). Although postmortem studies with fetal hepatic tissue have demonstrated the presence of PAH activity comparable to adult levels from 20 wk of fetal life (8) and low activities of enzymes for tyrosine metabolism (9), there have been no reports of *in vivo* enzyme activity measurement in preterm infants. To determine the *in vivo* activity of PAH in sick preterm infants, we have studied, using stable isotope techniques, the rate of hydroxylation of phenylalanine to tyrosine in 23 such infants receiving intensive care.

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METHODS

Subjects. Twenty-three infants were studied. Their gestational ages were 23.4 to 36 wk (median 29.7 wk) as assessed by maternal dates and confirmed by ultrasound scan between 14 and 18 wk of pregnancy. All infants required respiratory support, either intermittent positive-pressure ventilation or constant positive airways pressure, for a primary diagnosis of respiratory distress syndrome and received variable amounts of supplemental oxygen. All infants were clinically stable during the course of the studies; no infant had an arterial blood pH of less than 7.25 or significant intraventricular hemorrhage. No infant had a major congenital abnormality. All infants were being nursed in incubators in a thermoneutral environment.

Of the 23 infants, seven were studied a second time when receiving parental nutrition (Vamin 9 Glucose, Kabi Pharmacia Ltd., Milton Keynes, UK). Individual characteristics of these two groups of infants are summarized in Tables 1 and 2. At the time of the studies, as part of their routine care, each infant had an indwelling superficial venous catheter in the hand or foot and a peripheral or umbilical arterial catheter for blood sampling. Informed written consent was obtained from all the parents, and the study was approved by the Bristol and Weston District Research Ethical Committee.

Study protocol. Isotopes, L-[ring-$^2H_5$]phenylalanine, L-[ring-$^2H_4$]tyrosine, and L-[ring-$^2H_2$]tyrosine (all 98% ^2H), were obtained from Cambridge Isotopes Laboratories (Woburn, MA). They were dissolved in saline with the exception of [$^2H_2$]tyrosine, which was in a 10% dextrose solution. All preparations were shown to be sterile and pyrogen free.

Table 1. *Description of infants studied receiving glucose**

Study no.	Gestation (wk)	Age (h)	Birth weight (kg)	Study weight (kg)	Inspired oxygen concentration (%)
1	31.0	65.0	1.600	1.320	48.0
2	28.6	61.0	1.475	1.480	26.0
3	28.3	55.0	1.430	1.250	32.0
4	29.4	107.0	1.295	1.295	26.0
5	33.9	72.0	2.290	2.290	60.0
6	30.1	59.0	1.765	1.765	25.0
7	27.4	61.0	1.070	0.940	Air
8	31.7	60.0	1.875	1.875	55.0
9	31.7	60.0	1.700	1.700	68.0
10	29.7	83.0	1.550	1.570	Air
11	30.0	84.0	1.340	1.740	Air
12	34.0	66.0	2.170	2.180	35.0
13	36.0	47.0	2.500	2.500	57.0
14	31.3	72.0	1.600	1.600	55.0
15	26.9	72.0	0.895	0.740	35.0
16	29.0	42.0	1.300	1.300	40.0
17	25.0	82.0	0.720	0.695	Air
18	29.7	68.0	1.040	1.080	45.0
19	29.6	49.0	1.320	1.210	52.0
20	24.1	105.0	0.670	0.645	30.0
21	28.4	48.0	1.100	0.975	40.0
22	31.9	51.0	1.525	1.525	Air
23	23.4	132.0	0.780	0.760	31.0
Mean	29.6	69.6	1.435	1.410	
SD	3.0	21.6	0.483	0.512	

* The individual gestation at birth (wk), age at the time of study (h), birth weight (kg), and study weight (kg) are shown. In addition, the inspired oxygen concentration (%) is shown; "Air" indicates that the infants were in room air.

Baseline blood samples were collected, and i.v. priming boluses of [$^2H_4$]tyrosine (0.3 mg/kg) and [$^2H_5$]phenylalanine (1.8 mg/kg) were given before a [$^2H_5$]phenylalanine continuous infusion (1.8 mg/kg/h) in all study subjects for 6 to 8 h whether subjects were receiving dextrose or parental nutrition. In six subjects receiving dextrose, an i.v. bolus of [$^2H_2$]tyrosine (0.25 mg/kg) followed by a continuous infusion of [$^2H_2$]tyrosine (0.25 mg/kg/h) was also given concurrently. All infusions were through the indwelling venous catheter and were delivered by an accurately calibrated syringe pump (model 711, Ivac, San Diego, CA) at rates between 0.4 and 1.2 mL/h. One hundred to 250 μL of whole blood were sampled through the indwelling arterial catheter, kept patent by an infusion of heparinized saline, at hourly intervals from 2 h after the commencement of the infusion. To reduce the amount of blood sampled in those infants of less than 1500 g, the number of samples taken was reduced to one baseline and three hourly samples taken during the last 3 h of the infusion. Blood was immediately centrifuged and the plasma stored at −20°C until required for analysis.

Analytical methods. Plasma phenylalanine and tyrosine were derivatized to their t-butyldimethylsilyl derivatives, and their concentrations and deuterium enrichments were determined by electron ionization gas chromatography–mass spectrometry using selected ion monitoring and β-methylphenylalanine or α-methyltyrosine as internal standards, respectively, with a method similar to that described previously (10). Final values for all determinations were corrected using calibration curves for enrichments and concentrations. Isotopic enrichment was expressed as MPE.

Model description. Phenylalanine is an essential amino acid and therefore available only through dietary sources (11). It is metabolized to tyrosine by hydroxylation of the phenyl ring at position 4 primarily in the liver, although some hydroxylase activity exists in kidney and pancreas in adults (12). No conversion of tyrosine to phenylalanine is possible *in vivo*.

The model assumes that the free phenylalanine and tyrosine pools are homogeneous and in rapid equilibrium, that in the fasting state phenylalanine enters the pool only from protein catabolism, and that the only pathways of phenylalanine removal from the pool are to protein synthesis and by hydroxylation to tyrosine.

In the infant not receiving supplemental amino acids via parenteral nutrition, the total flux of the infused amino acid (Q; μmol/kg/h) can be calculated from isotope dilution principles using the following equation:

$$Q = i \cdot (Ei/Ep) \quad (1)$$

where i is the rate of infusion of the tracer (μmol/kg/h) and Ei and Ep are the enrichments of the infusate and of

Table 2. *Description of infants studied while receiving parenteral nutrition**

Study no.	Gestation (wk)	Age (h)	Birth weight (kg)	Study weight (kg)	Inspired oxygen concentration (%)	Protein intake (g/d)	Phenylalanine intake (μmol/kg/h)
8	31.7	219.0	1.875	1.650	46.0	1.9	44.8
9	31.7	146.0	1.700	1.480	30.0	2.6	60.6
16	29.0	128.0	1.300	1.150	40.0	2.3	55.4
17	25.0	82.0	0.720	0.695	20.9	2.0	47.6
19	29.6	148.0	1.320	1.150	40.0	2.4	56.5
20	24.1	225.0	0.670	0.625	40.0	1.3	35.8
23	23.4	204.0	0.780	0.725	31.0	2.2	51.5
Mean	27.8	164.6	1.195	1.068		2.1	50.3
SD	3.5	53.1	0.486	0.403		0.4	8.4

* The individual gestation at birth (wk), age at the time of study (h), birth weight (kg), and study weight (kg) are shown. Inspired oxygen concentration (%), amount of protein received (g/d), and phenylalanine intake (μmol/kg/h) from the parenteral nutrition are also shown.

the amino acid, respectively, in plasma at isotopic plateau. The rate of phenylalanine conversion to tyrosine (Qpt; μmol/kg/h) can be derived similarly:

$$Qpt = Qt \cdot (Et/Ep) \quad (2)$$

where Qt is tyrosine flux (μmol/kg/h) estimated independently by the primed constant infusion of [$^2H_2$]tyrosine and Et and Ep are the enrichments of [$^2H_5$]phenylalanine and [$^2H_4$]tyrosine, respectively, in plasma. Given that tyrosine has limited solubility, it is beneficial if the phenylalanine conversion to tyrosine can be calculated without the need for a separate estimation of tyrosine flux. It can be assumed that the movement of any two amino acids into and out of protein will be of a constant ratio that will be related to the amino acid composition of the protein (13); therefore,

$$Qt = [Qp \cdot (Pt/Pp)] + Qpt \quad (3)$$

where Pt/Pp is the molar ratio of the fluxes of tyrosine and phenylalanine arising from protein catabolism. This ratio has been derived from the measured protein amino acid composition of mammalian tissue and found to be 0.73 (14). Qp is the phenylalanine flux (μmol/kg/h). By combining equations 2 and 3, Qpt can be calculated without measuring the tyrosine flux separately:

$$Qpt = (Pt/Pp) \cdot Qp \cdot \frac{1}{[(Ep/Et) - 1]} \quad (4)$$

These formulas for infants not receiving parenteral nutrition are similar to those published previously (15), but no correction is made for the infusion of phenylalanine and tyrosine isotopes because we wished to measure total phenylalanine flux, tyrosine flux, and phenylalanine hydroxylation, which will necessarily include the infused phenylalanine and tyrosine labeled tracers. At steady state, in infants fed dextrose solutions only, the sole other source of phenylalanine will be protein catabolism. This can be measured with the following formula:

$$Qp(protein) = Qp - ip \quad (5)$$

where Qp(protein) is the phenylalanine entering the amino acid pool from protein catabolism and ip is the infusion of the phenylalanine tracer.

In those infants receiving parenteral nutrition, phenylalanine flux can be calculated from equation 1. Phenylalanine production from protein catabolism is determined wtih the following formula:

$$Qp(protein) = Qp - ip - Phe(tpn) \quad (6)$$

where Phe(tpn) is the amount of phenylalanine entering the infant by i.v. nutrition (μmol/kg/h). In the infants receiving parenteral nutrition, equation 3 becomes

$$Qt = [Qp \cdot (Pt/Pp)] + Qpt + Tyr(tpn) \quad (7)$$

where Tyr(tpn) is the amount of tyrosine entering the infant by i.v. nutrition. Thus, combining equations 7 and 2, phenylalanine hydroxylation for the infant receiving i.v. nutrition is

$$Qpt = [Qp \cdot (Pt/Pp) + Tyr(tpn)]/[(Ep/Et) - 1] \quad (8)$$

Statistics. All values are expressed as mean ± 1 SD. Significance tests were performed using a Wilcoxon signed rank test.

RESULTS

Amino acid concentrations. Phenylalanine concentrations were 72 (40.7) μmol/L and 103 (35.4) μmol/L for those infants receiving glucose and those receiving parenteral nutrition, respectively.

Phenylalanine turnover. The majority of studies were completed within 6 h, the longest lasting 8 h. All studies reached plateaus as judged by visual inspection for phenylalanine concentrations and enrichments.

For infants studied while receiving only glucose, coefficients of variation at plateaus were less than 11.4% [mean 5.3% (3.1%)] for phenylalanine enrichments. Mean enrichments for [$^2H_5$]phenylalanine were 12.4 (2.8) MPE, and a plateau was reached by 6 h with priming of the [$^2H_5$]phenylalanine pool before commencing the [$^2H_5$]phenylalanine infusions. Calculated rates of total phenylalanine flux were 87.6 (17.3) μmol/kg/h. Phenylalanine entering the plasma pool from protein catabolism was 76.9 (17.3) μmol/kg/h.

For infants studied while receiving parental nutrition, mean coefficient of variation at plateaus was 5.1% (3.4%) for phenylalanine enrichments. Mean enrichment for

$[^2H_5]$phenylalanine was 7.6 (0.9) MPE, and a plateau was reached by 6 h with priming of the $[^2H_5]$phenylalanine pool before commencing the $[^2H_5]$phenylalanine infusions. The calculated rate of total phenylalanine flux was 145.6 (9.4) μmol/kg/h. The rate of phenylalanine entering the plasma pool from protein catabolism was 84 (16.2) μmol/kg/h.

Tyrosine turnover. In the infants receiving glucose alone, enrichment for $[^2H_4]$tyrosine was 2.2 (0.5) MPE and for $[^2H_2]$tyrosine 1.6 (0.5) MPE. In infants receiving parenteral nutrition, enrichment for $[^2H_5]$tyrosine was 2.3 (0.5) MPE.

Phenylalanine hydroxylation. In 23 infants receiving glucose alone, phenylalanine hydroxylation was derived as 16.0 (10.9) μmol/kg/h, which was 17.3% (8.4%) of the total phenylalanine flux. In those infants in whom tyrosine flux was measured separately using $[^2H_2]$tyrosine, phenylalanine hydroxylation was 20.5 (13.0) μmol/kg/h, which was 22.3% (9.8%) of the total phenylalanine flux. In the same six infants, the derived value using the constant ratio between tyrosine and phenylalanine was 22.2 (13.1) μmol/kg/h; this was 23.6% (9.9%) of the total phenylalanine flux. There was no significant difference between these two values ($p > 0.1$). For a full summary of the results, see Table 3.

In the seven infants who were also studied while receiving parenteral nutrition, phenylalanine hydroxylation was derived as 48.4 (14.9) μmol/kg/h, which was 33.2% (9.8%) of the total phenylalanine flux. For a full summary of the results, see Table 4.

DISCUSSION

Previously reported levels of amino acids in preterm infants receiving parenteral nutrition included a number with increased plasma phenylalanine concentrations (3–5, 16). In contrast, Clark *et al.* (17) found a low incidence of increased phenylalanine concentrations, with only one infant out of 109 very low birth weight babies receiving parenteral nutrition having a concentration greater than 600 μmol/L, although a number of infants were found to have increased tyrosine levels.

The implications of increased phenylalanine concentrations for newborn infants over a short period are unknown, but the consequences to the fetus of maternal hyperphenylalaninemia are known to be severe (6, 18). Published case reports also raise the possibility of neurologic damage related to high tyrosine levels in the newborn (19, 20).

Factors responsible for the increased concentrations of phenylalanine and tyrosine may include rapid infusions of parenteral amino acids, liver disease, sepsis, and inadequate calorie intake (21). Additionally, in the preterm neonate, immaturity of enzymes concerned with the metabolism of phenylalanine and tyrosine, particularly PAH, tyrosine aminotransferase, and 4-hydroxyphenylpyruvate dioxygenase, may theoretically be responsible. PAH controls the hydroxylation of phenylalanine to tyrosine, the major pathway for metabolism of phenylalanine not incorporated into body protein. To assess *in vivo* in sick preterm infants the maturity of this enzyme,

Table 3. *Summary of results for infants receiving glucose*

Study no.	Phenylalanine flux (μmol/kg/h)	Phenylalanine production from protein catabolism (μmol/kg/h)	Phenylalanine hydroxylation calculated from $[^2H_4]$tyrosine enrichments (μmol/kg/h)	Phenylalanine hydroxylation as a percentage of total phenylalanine flux (%)	Phenylalanine hydroxylation calculated from $[^2H_2]$tyrosine enrichments (μmol/kg/h)
1	92.2	78.8	9.9	10.8	
2	109.7	98.9	19.1	17.4	
3	90.7	78.5	10.7	11.8	
4	57.3	46.3	7.6	13.2	
5	111.3	101.3	15.9	14.3	
6	95.6	84.7	23.4	24.5	
7	81.1	70.1	9.3	11.4	
8	92.9	82.8	15.4	16.6	
9	94.3	83.7	21.0	22.3	
10	77.2	67.4	8.7	11.3	
11	75.5	67.1	7.6	10.0	
12	65.5	54.9	7.3	11.2	
13	102.9	91.8	17.4	16.9	
14	59.9	48.9	6.0	10.0	
15	120.5	111.4	57.2	47.4	45.7
16	79.8	69.1	11.1	13.9	10.8
17	101.3	90.6	26.7	26.3	
18	64.9	55.3	14.1	21.7	15.9
19	97.4	87.9	26.6	27.4	27.8
20	108.0	97.1	21.2	19.6	
21	85.8	73.9	13.0	15.2	11.4
22	72.7	62.2	11.4	15.7	11.7
23	78.8	67.6	8.4	10.7	
Mean	87.6	76.9	16.0	17.3	20.5
SD	17.3	17.4	10.9	8.4	13.8

Table 4. *Summary of results for infants receiving parenteral nutrition*

Study no.	Phenylalanine flux (μmol/kg/h)	Phenylalanine production from protein catabolism (μmol/kg/h)	Phenylalanine hydroxylation calculated from $[^2H_4]$tyrosine enrichments (μmol/kg/h)	Phenylalanine hydroxylation as a percentage of total phenylalanine flux (%)
8	163.1	107.3	50.9	31.2
9	138.1	65.9	41.4	30.0
16	139.2	71.5	54.0	38.8
17	141.0	82.7	24.1	17.1
19	147.5	81.4	73.1	49.6
20	152.3	105.3	52.6	34.6
23	137.9	74.3	42.6	30.9
Mean	145.6	84.0	48.4	33.2
SD	9.4	16.2	14.9	9.8

we have measured the conversion of phenylalanine to tyrosine using primed constant infusions of the stable isotopes $[^2H_5]$phenylalanine, $[^2H_4]$tyrosine, and $[^2H_2]$tyrosine.

By restricting the frequency of blood sampling and using micromethods for analysis, we have found it possible to adapt stable isotope techniques to measure phenylalanine flux, tyrosine flux, and phenylalanine hydroxylation in sick preterm infants. The amount of $[^2H_5]$phenylalanine infused per kilogram body weight was higher than that previously reported for adult studies. In preliminary work, we had found that lower infusion rates of $[^2H_5]$phenylalanine resulted in plasma tyrosine ($^2H_4$) enrichments that were too low to measure with sufficient precision.

For the calculation of phenylalanine hydroxylation, we assumed a constant relationship between the breakdown of protein to phenylalanine and to tyrosine based on the proportion of these two amino acids in body protein (14). We were able to validate this assumption by measuring tyrosine flux independently in six infants using a $[^2H_2]$tyrosine infusion. The close relation between phenylalanine hydroxylation calculated from the enrichment of plasma with $[^2H_2]$tyrosine and estimated from the proportion of phenylalanine to tyrosine in body protein (20.5 and 21.3 μmol/kg/h, respectively, $p > 0.1$) confirms that the independent measurement of tyrosine flux by a constant infusion of $[^2H_2]$tyrosine is not routinely required in the measurement of phenylalanine hydroxylation in preterm infants as in adults (15).

Our model assumes that phenylalanine is lost primarily from the plasma pool to protein synthesis or is converted to tyrosine by hydroxylation. Walker and Mills (22) have reported significant concentrations of metabolites arising from minor catabolic pathways for phenylalanine in the urine of preterm infants receiving parenteral nutrition. Values were varied, which may be explained at least partly by the high rates of amino acid infusion. Infants in the study were given their full daily parenteral nutrition by infusion over 6 to 12 h. If such losses were significant for infants during our studies, although the amount of phenylalanine leaving the plasma pool for protein synthesis would be altered, the calculations for phenylalanine flux, hydroxylation, and production from protein catabolism would not be altered.

No infant had plasma phenylalanine concentrations that would be considered toxic to the CNS. A number of infants had low phenylalanine concentrations of less than 50 μmol/L, which were similar to values previously reported in infants receiving dextrose or amino acids at the level of 1.5 g/kg/d (17).

In fasted adults, mean phenylalanine production rates from protein catabolism have been found to be 31.4 (15) and 39.92 μmol/kg/h (25). For the preterm infants in this study, the mean production rate of phenylalanine from protein catabolism was much greater at 76.9 and 84 μmol/kg/h in infants receiving glucose and parenteral nutrition, respectively, suggesting a rapid rate of phenylalanine production from protein breakdown. Limited data from research in seven normal growing newborns aged 20 d have been reported with endogenous production rates of phenylalanine equal to a mean of 87 μmol/kg/h (23). In 12 low-birth-weight infants, the phenylalanine flux, calculated from infusions of L-[1-^{13}C]phenylalanine, during enteral and parenteral feeding was 106 and 56 μmol/kg/h, respectively (24).

Phenylalanine hydroxylation as calculated from $[^2H_2]$tyrosine enrichments was 16.0 μmol/kg/h, which was 17.3% of the total phenylalanine turnover rate in infants receiving glucose. In those infants receiving parenteral nutrition, this was further increased to 48.4 μmol/kg/h, which was 33.2% of the total phenylalanine turnover rate. Thus, infants are able to respond with an increase in phenylalanine load from i.v. nutrition by increasing the amount of phenylalanine conversion to tyrosine. The difference in rates of phenylalanine hydroxylation for the seven infants studied while receiving glucose and then i.v. nutrition was significant ($p < 0.05$).

For fasted adults, Clarke and Bier (25), using separate $[^2H_5]$phenylalanine and $[^{13}C]$tyrosine infusions, calculated a mean value of 5.8 μmol/kg/h, which accounted for 16.4% of the total mean phenylalanine turnover rate. Thompson *et al.* (15) also found that the hydroxylation values for adults were lower at 5.5 μmol/kg/h. In relation to values for term infants, previous work has demonstrated similar hydroxylation rates of 22 μmol/kg/h for conversion of phenylalanine to tyrosine. This constituted 25% of the total phenylalanine flux (24).

The estimation of the rate of phenylalanine conversion to tyrosine depends on the assumption that the free phenylalanine and tyrosine pools are homogeneous and in rapid equilibrium throughout the body. Because the major hydroxylation site in humans is the liver, it is particularly important that the phenylalanine and tyrosine enrichments in plasma are the same as the hepatic intracellular enrichments. Previous authors have raised the possibility that there is delayed equalization of the [$^2H_5$]phenylalanine with the intrahepatic PAH pool (25) and also that there may be dilution of the tracer as a result of local intracellular protein degradation. Both of these would result in an underestimate of the rate of phenylalanine conversion to tyrosine as calculated by our method and not produce an artificially high level. From our studies, with a plateau for [$^2H_4$]tyrosine being reached within 4 to 8 h, we would suggest that equalization with the hydroxylase substrate pool was achieved.

In summary, we measured phenylalanine turnover, tyrosine turnover, and phenylalanine hydroxylation rates in sick preterm infants in the fasting state and while receiving parenteral nutrition. Phenylalanine hydroxylation rates equaled or exceeded those found in adults and increased with the phenylalanine load of parenteral nutrition. These results do not support the hypothesis that PAH activity is low in preterm infants. Transiently high levels of phenylalanine and tyrosine in preterm infants are more likely due to immaturity of enzymes for tyrosine metabolism.

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