Essential and Non-essential Amino Acids in Neonatal Nutrition

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There has been an evolution in the appreciation of the functional roles that amino acids play in neonatal nutrition over the last 30 years. Up to the early 1960s primary interest was in the identification of those amino acids that had to be supplied in the diet in order to maintain growth and positive nitrogen balance (Table 1). Most of the experiments that were performed to identify these amino acids were conducted in animals or human adults; thus they often failed to take into account the special needs of the biochemically immature neonate, particularly the preterm neonate.

Appreciation of the special biochemical needs of the developing neonate resulted in the designation of a second group of amino acids as semiessential, conditionally essential, or developmentally essential (Table 2). Studies that have defined the role that the latter compounds play in early development have reflected on properties such as infant growth (histidine, cysteine) (1,2), the developmental pattern of enzymes that catalyze synthesis (cysteine, tyrosine) (3,4), stable isotope metabolism (glycine) (5), presence in human milk coupled with animal and human studies (taurine) (6–8), and prevention of adverse metabolic effects (arginine) (9). The data to support the "essentiality" of these amino acids have often been conflicting, as for cysteine (3,10) and glycine (5,11), making a final determination difficult at best.

The next stage in the understanding of the role that amino acids play in early nutrition evolved from the many functions that they were identified with, other than as precursors for protein synthesis. Some of this impetus came from a growing appreciation of the nutritional importance of the amino acid taurine, despite the fact that it could not be incorporated into protein as it is a sulfonic amino acid. Other functions of amino acids include supporting the synthesis of hormones, neurotransmitters, and bile acids. In addition, many amino acids may themselves function as neurotransmitters (Table 3).

Thus, monitoring the amino acid responses of neonates to different nutritional regimens may be of more functional importance than just determining the sufficiency of the protein synthesis precursor pool. Intakes of individual enteral formulas and total parenteral nutrition solutions are reflected by specific amino acid patterns in
TABLE 1. *Essential amino acids*

<table>
<thead>
<tr>
<th>Threonine</th>
<th>Phenylalanine</th>
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<tbody>
<tr>
<td>Valine</td>
<td>Lysine</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>Methionine</td>
</tr>
<tr>
<td>Leucine</td>
<td>Tryptophan</td>
</tr>
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</table>

* These amino acids have been accepted as the classic indispensable amino acids based on data regarding growth and nitrogen balance.

TABLE 2. *Proposed developmentally essential amino acids*

<table>
<thead>
<tr>
<th>Cysteine</th>
<th>Histidine</th>
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<tbody>
<tr>
<td>Taurine</td>
<td>Arginine</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>Glycine</td>
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* These amino acids may be conditionally essential during early development due to biochemical immaturity of the infant.

TABLE 3. *Central nervous system functions of amino acids*

Neurotransmitter precursors (neurotransmitters or putative neurotransmitters)
- Phenylalanine (catecholamines)
- Tyrosine (catecholamines)
- Histidine (histamine, carnosine)
- Tryptophan (serotonin)
- Serine (glycine)
- Glutamate (GABA)
- Methionine (cystathionine, cysteinesulfenic acid, taurine)
- Cysteine (cystathionine, cysteinesulfenic acid, taurine)

Neurotransmitter or putative neurotransmitter amino acids
- Glutamate
- GABA
- Aspartate
- Proline
- Taurine
- β-Alanine
- Cysteic acid
- Cysteinesulfenic acid
- Glycine
- Cystathionine

* Amino acids that serve as either metabolic precursors of neurotransmitters or which have been suggested to serve as neurotransmitters themselves.
the neonate. These patterns influence protein synthetic rates, but may also regulate future development of various organs, particularly of the central nervous system, via mechanisms other than the synthesis of new proteins.

In this brief review it is intended to present some of the features of plasma amino patterns that reflect specific nutritional regimens in neonates, a discussion of the proposed mechanisms by which these patterns may influence the development of the central nervous system, and some evidence to support the validity of these mechanisms.

**PLASMA AMINO ACID RESPONSES TO NUTRITION**

The majority of enteral infant formulas fed to neonates are based upon cow's milk proteins, supplied usually as either casein-protein-predominant or whey-protein-predominant preparations. Other available formulas include various hydrolysates (usually of cow's milk casein or whey proteins) and soy preparations. The standard against which these preparations are compared is human milk. This comparison is influenced by the fact that formulas generally contain more protein per volume than does human milk, and that cow's milk proteins contain different amino acids than those of human milk proteins (even though they belong to the same classes of proteins, casein or acid-insoluble and whey or acid-soluble). The result is that formulas generally provide not only more amino acids than human milk but also a different pattern of amino acids, and different formulas provide different ratios or patterns of amino acids, reflecting the primary source of protein (Fig. 1).

![Graph showing amino acid intakes](image)

**FIG. 1.** Intakes of individual amino acids in breast-fed, casein-protein-predominant formula-fed, and whey-protein-predominant formula-fed term infants expressed as μmol intake per kg body weight per day. Developed from data collected in the author's laboratory.
The effect of these varying amino acid intakes is to cause distinct plasma amino acid patterns in the recipient infants, reflecting the source and amount of protein intake. These plasma amino acid patterns have been thoroughly documented in a number of different studies in both term and preterm infants (12–19). Typically, the overall pattern of plasma amino acid concentrations is increased in formula-fed infants compared to breast-fed infants and specific amino acids (such as threonine in infants fed whey-protein-predominant formulas and tyrosine in infants fed casein-protein-predominant formulas) are particularly increased and may actually be utilized as markers in the plasma to determine the protein composition fed to a particular infant.

Total parenteral nutrition (TPN) provides yet another pattern of amino acids to the infant, reflecting a variety of factors, such as chemical stability, solubility, and cost of the individual compounds. First-generation solutions were prepared from casein hydrolysates, but subsequent preparations have been prepared directly from crystalline amino acids. These preparations include second-generation solutions or "adult" preparations and third-generation solutions or "pediatric" preparations. The so-called "pediatric" preparations have been modified to attempt to provide a more balanced solution (the adult solutions contain large percentages of the cheaper amino acids glycine and alanine relative to other amino acids) and to include amino acids such as tyrosine, cysteine, and taurine that are felt to be essential for the neonate.

The plasma amino acid patterns of infants fed total parenteral nutrition also reflect the amounts of the individual compounds included in the solutions. Typically, such infants have low concentrations of tyrosine and cystine, reflecting the low or absent concentrations of these amino acids in the TPN solutions due to the difficulty in solubilizing adequate amounts of tyrosine and in stabilizing cysteine from being oxidized into cystine (which is also insoluble).

The reduced concentrations of tyrosine and cystine observed in the plasma of infants fed TPN occur despite usually very large amounts of their respective precursors, phenylalanine and methionine, in the amino acid solutions. This illustrates the biochemical immaturity of these infants with respect to the aromatic amino acid and sulfur-containing amino acid metabolic pathways.

Route of administration may play an important role in the ability of the infants to synthesize tyrosine. Data on the maturity of the enzymes required to catalyze tyrosine synthesis and catabolism indicate that phenylalanine hydroxylase is far more active than the tyrosine oxidizing system (4,20,21). This finding is compatible with the response of infants to excessive aromatic amino acid enteral intake with large increases in plasma tyrosine (14). However, it does not explain why parenterally fed infants have low plasma tyrosine in the presence of more than adequate phenylalanine intake. Even adult rats, which are reported to have no problems synthesizing tyrosine (22), have low plasma tyrosine concentrations when nourished parenterally (23). Similarly, reduced plasma cystine has been much more evident in parenterally fed (24) than in enterally fed (13) infants.

Taurine, a metabolite of cysteine, is also found in low concentrations in both enterally and parenterally fed infants when it is not included in the feeding regimens. Until
about 8 years ago taurine was not added to either enteral formulas (which contained only trace amounts of this compound) or parenteral solutions (which contained none). Human milk contains relatively large amounts of taurine, so breast-fed infants manage to remain taurine-sufficient (6,15). Human infants appear to be dependent on a dietary supply of taurine; in fact, human beings do not ever appear to develop much hepatic activity of the enzyme cysteine sulfenic acid decarboxylase, responsible for catalyzing taurine synthesis, so are probably dependent on a dietary source throughout the life cycle (13).

In summary, plasma amino acid patterns reflect the amount, type, and route of protein intake. The question that has to be asked is how important are these variations in concentrations. As mentioned above (Table 3), the aromatic and sulfur amino acids are precursors for a variety of biologically active compounds that could have consequences for normal development of the central nervous system if they were present in either excess or deficiency.

CONSEQUENCES OF CHANGES IN AMINO ACID PATTERNS

As noted earlier, amino acids subserve a variety of functions that could potentially be affected by changes in concentrations due to diet. Of particular interest is the influence that such changes might have on the developing central nervous system. Such interest is particularly acute in the light of reports that the intellectual outcome of infants, both term and preterm, may reflect their early feeding history (25,26). The nutrients supplied in human milk appear to have a real benefit in respect to such neurologic outcome when breast-fed infants are compared to bottle-fed infants.

One proposed mechanism for such an effect is relevant to the class of large neutral amino acids (which includes valine, isoleucine, leucine, tyrosine, phenylalanine, tryptophan, methionine, threonine, and histidine). This group of amino acids includes several important neurotransmitter precursors (phenylalanine and tyrosine for the catecholamines, tryptophan for serotonin) as well as compounds important to the synthesis and catabolism of amino acids (methionine is a precursor of the methylation donor S-adenosylmethionine utilized in the catabolism of catecholamines, serotonin, and histamine).

The large neutral amino acids are transported across the blood-brain barrier by a common carrier, which has varying affinity constants and velocity maximums for each member of the group. The implication of this system is that any variation in the plasma concentration of one member of the group will affect the precursor pool for all members of the carrier group. The simplest expression of this relationship is as a ratio of the plasma concentration of the amino acid in question (as the numerator) to the sum of all the other members of the transport group (as the denominator) (27,28). The true velocities of each compound may actually be expressed in terms of their influx rates modified for individual affinity and velocity constants (Table 4) (29,30).

The general implication of this system is that if the concentration of one amino
### TABLE 4. Expression of competition of the large neutral amino acids at the blood-brain barrier

1. **Ratio:**

   \[
   \frac{[AA]}{\sum [AA]}
   \]

   - \([AA]\) = individual plasma amino acid concentrations
   - \(\sum [AA]\) = sum of large neutral plasma amino acid concentrations

2. **Kinetic equation:**

   \[
   K_{m_{\text{app}}} = K_m \left(1 + \sum \frac{[AA]}{K_{m_{\text{app}}}}\right)
   \]

   \[
   v = \frac{V_{\text{max}} [AA]}{K_{m_{\text{app}}} + [AA]}
   \]

   - \(aa\) = individual amino acid
   - \(K_m\) = affinity constant, \(\mu M\)
   - \(K_{m_{\text{app}}}\) = modified affinity constant reflecting amino acid pattern, \(\mu M\)
   - \([AA]\) = plasma amino acid concentration, \(\mu M\)
   - \(V_{\text{max}}\) = velocity constant, \(\mu mol/min/g\)
   - \(v\) = brain amino acid influx, \(\mu mol/min/g\)

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* The ratio gives all amino acids the same weight, while the kinetic method allows for the difference in affinities of each amino acid for the carrier. For example, tyrosine has a much higher affinity \((K_m = 160 \mu M)\) than that of valine \((K_m = 630 \mu M)\).

When the plasma concentration of a specific amino acid is increased (phenylalanine, for example), transport into the brain of the others in the group will be decreased. The ratio approach gives equal weight to all the amino acids in the group; however, some have lower affinity constants than others (such as tyrosine compared to threonine), so may have a greater actual impact on the transport system.

Such a system may put the synthesis of catecholamines at particular risk in the TPN-fed infant who has a combination of an increased plasma phenylalanine and a decreased plasma tyrosine, particularly limiting tyrosine access to the brain. Such a situation is significant because the brain has little capacity to synthesize tyrosine from phenylalanine and so is dependent on an exogenous source of this amino acid (31). Indeed, tyrosine should be considered an essential amino acid for the brain, which raises the concept of essentiality at the level of individual tissues as well as at that of the whole body.

Limitations on access of tyrosine to the brain (as well as of other neurotransmitter precursors) are important because the enzymes responsible for regulating the catalysis of neurotransmitter synthesis (e.g., tyrosine hydroxylase and tryptophan hydroxylase) have affinity constants that are higher than the endogenous concentrations of their precursors (32, 33). The effective result of this situation is that changing brain tyrosine (or tryptophan) concentrations will change the concentrations of the catecholamine (or serotonin) products. Thus a biochemical sequence of events exists to permit modification of central nervous system neuroactive compounds when peripheral concentrations of plasma amino acids are modified.
Animal studies support this general mechanism; the data indicate that varying the protein in the diet causes modifications of plasma amino acid concentrations, which are reflected by changes in brain concentrations (34). These changes appear to reflect particularly the calculated brain influxes of amino acids (29,30) rather than just plasma concentrations (35). It is interesting to note that even peripheral catecholamine concentrations (synthesized in the adrenal gland) may reflect a dietary supply of tyrosine (36).

These animal studies lay a foundation for understanding the results of a number of studies in humans that have associated amino acid modifications due to diet with cognitive outcome. High protein intake in preterm infants [similar to that reported to result in abnormal amino acid patterns (12,14)] has been associated with an increased incidence of low IQ scores (37). Both term and preterm infants exposed to dietary (high protein, casein-predominant formula)-induced tyrosinemia during early infant feeding have been reported to have reduced intellectual outcome (38,39). Preterm infants have also been reported to have reduced behavior indices when exposed to low protein diets (40,41). Such changed behavior appears to be related to the amount of the protein intake as well as to changes in specific plasma amino acid concentrations, particularly of the large neutral amino acids (41).

There is additional experimental evidence that specific short-term infant behaviors may be modified by just such a mechanism as that described above. When healthy infants were fed tryptophan, sleep (modulated by serotonin) was induced more rapidly than when the infants were fed unmodified formula (42). In contrast, when the infants were fed the tryptophan transport competitor valine, sleep was induced much later than when formula was fed alone (42). Secondary dietary effects, such as modification of carbohydrate, which would cause increased branched-chain amino acid uptake into muscle as a result of stimulating insulin secretion, also might affect sleep by reducing competing amino acid concentrations (43). While carbohydrate feeding resulted in changing sleep patterns compared to either water or balanced formula, it did not increase sleep more than formula (43). Thus the situation may be more complex than simple modification of tryptophan concentrations. Human milk and formulas are complex nutrient mixtures and it is probably unreasonable to expect the properties of single nutrients to be unaffected by the presence of all the other nutrients in these preparations.

The sulfur-containing amino acids have not been analyzed in like manner in human infants, but animal data (and some human data) indicate that modifications in concentrations of these compounds also affect brain development. Cysteine has been shown to be neurotoxic in the developing rodent hypothalamus, suggesting that giving excessive amounts to compensate for the lack in situations such as TPN may backfire (44). Taurine, on the other hand, has been shown to be important for retinal and cerebellar development in both cats and monkeys (7,8,45,46), so situations that limit its presence may be of concern. One study of children on long-term total parenteral nutrition lacking taurine found similar retinal changes to those observed in taurine-deficient cats associated with very low plasma taurine concentrations (47). This finding suggests that human infants may be liable to retinal damage when exposed to
long-term taurine-free nutrition. Although only minimal experimental evidence sup-
port this hypothesis in human infants, the pediatric TPN solutions and all infant
formulas are now supplemented with taurine.

CONCLUSION

Appropriate protein nutrition of the infant is important for structural growth and
development. However, less appreciated is the importance of such nutrition for the
support of other functions, particularly within the central nervous system. The emerg-
ing data that demonstrate improved intellectual development in infants fed human
milk suggests that characterizing the role of nutrients, such as amino acids, in the
central nervous system is of great importance in establishing the most appropriate
composition of early nutrition for the support of optimal outcome.

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DISCUSSION FOLLOWING THE PRESENTATION OF DR. RASSIN

Dr. Raiha: Do you think that the reason why we don't see lesions in humans on a taurine-deficient diet is that if it takes 10 weeks in the cat, it may take much longer in the human? Most human infants are starting to be fed with supplementary food after 3-4 months, so it is possible that the reason that we don't see the lesions is because the infants are getting supplementary foods that contain taurine.

Dr. Rassin: I think that is an extremely important consideration. The only cases in which human infants have been shown to develop abnormal electroretinograms have been in a small cohort of children studied by Ament (1). They were given total parenteral nutrition for more than 6 months because they had no gut, and when they were examined, four out of six had abnormal electroretinograms; they also had low plasma taurine because they were getting no taurine in their TPN solution. When taurine was supplemented I think three of the four abnormal ones responded. It is interesting to note that they found no abnormal electroretinograms among a group of adults on TPN.

Dr. Raiha: The second question relates to the Brazelton score in those infants who were fed various levels of protein intake derived from formula. Do you have any data on the same taurine intakes supplied with human milk? I think this would be a good control.

Dr. Rassin: Unfortunately, unlike in Sweden, we were unable to find human-milk-fed infants in our population. It is a real problem. John Tyson in Dallas has done a study comparing breast-fed and formula-fed preterms, looking at the Brazelton score and relating it to the lower protein in human milk (2). He found lower Brazelton scores in the breast-fed infants, which I think is a matter for concern, but I would remind you that we don't really know what the Brazelton score means in the long term. There are some indications that is related to long-term cognitive outcome, but on the other hand, it may only reflect the current status of the infant.

Dr. Raiha: In the rabbits that received the low tyrosine TPN, was it low plasma tyrosine or brain tyrosine?

Dr. Rassin: Both were low.
Dr. Räihä: Did they have enough phenylalanine hydroxylase to synthesize tyrosine from phenylalanine? The preterm infant has.

Dr. Rassin: Every study I have ever seen that has looked at total parenteral nutrition in infants has shown a low plasma tyrosine and some have shown high phenylalanine. Enterally fed infants on casein formulas have very high tyrosine levels. They seem to be able to convert phenylalanine to tyrosine efficiently. However, when we look at parenterally fed infants, this is not the case.

Dr. Kashyap: Was the amino acid mixture you used one of the older ones without added tyrosine, or was it one of the newer ones where tyrosine is added?

Dr. Rassin: The TPN solution we use is one of the older ones—I have to admit that we use it for selfish reasons, because it has no taurine in it and we were interested in taurine and cysteine metabolism when these compounds were given as supplements. In the babies we have looked at who have been treated with one of the newer formulations containing more tyrosine, plasma tyrosine is still low. I think this is in agreement with other studies.

Dr. Kashyap: Do plasma taurine levels increase with age because the infants are taking additional taurine in their diet or because of maturation of enzymes that convert cysteine to taurine?

Dr. Rassin: I don't think the taurine synthetic enzyme, cysteine sulfenic acid decarboxylase, has any maturational pattern in humans. Everybody in this room has the same activity of this enzyme as preterm babies. We probably have better stores of taurine and so can last longer than babies without becoming deficient, but in fact we cannot synthesize it any better than babies can.

Dr. Kashyap: Does this mean that we should regard taurine as an essential nutrient?

Dr. Rassin: If taurine is indeed important to us, then we have to maintain our supplies. We know that vegetarians become taurine-deficient and the milk of vegetarian mothers is also taurine-deficient because there is very little taurine in non-meat products. Taurine and zinc are similar in that they are both nutrients that we probably need to get from some kind of meat ingestion.

Dr. Fern: By and large, vegetarians live normal lives without complications. We should be careful about what we call "deficient" and what is simply a lowering of the plasma concentrations. Just because taurine levels go down in the plasma does not mean that there is a deficiency state. You said at the beginning of your talk that the cat could make more taurine than humans. We have been doing a lot of work with $^{15}$N and we think it is the other way round.

Dr. Rassin: I can only say that our enzymatic data show that this is not true. Perhaps in the adult, vegetarianism does not have any severe consequences, but I would refer you to the literature on babies breast-fed by vegetarian mothers and there seem to have been fairly serious consequences to a cohort of these infants (3,4). I don't think it is entirely benign to be vegetarian; I think it does have consequences and it is consequences for the baby that we are perhaps most interested in.

Dr. Heine: You mentioned that there is no phenylalanine hydroxylase in the brain. Has this any consequences for long-term nutrition?

Dr. Rassin: I don't think that is known. We are very actively looking at catecholamine metabolism. The only studies we have done so far have looked at whole brain catecholamine concentrations, which is probably not a very good way to look at what happens in response to the low brain tyrosine. You really need to look at specific areas, such as the hypothalamus, and that is the direction we are going toward now. If we find low concentrations of those
compounds in catecholamine-rich areas, it really raises important concerns about reducing
the access of tyrosine into the brain.

Dr. Heine: My other question is related to the essentiality of glycine in premature infants.
Alan Jackson claims that it is an essential amino acid and we know it is incorporated in many
metabolic processes. What is known about the concentration of glycine in preterm infant
formulas? Are these concentrations sufficient to meet the requirements of preterm infants?

Dr. Rassin: We never saw any differences in glycine concentrations among the three
feeding groups that I showed you. There is an enormous amount of glycine in parenteral
nutrition solutions. We have found that puppies on TPN tend to be somnolent. Glycine is
thought to be an inhibitory neurotransmitter and I have sometimes wondered, based on the
very large concentrations of glycine that we found in the brains of these puppies, whether
we were making them somnolent with millimolar concentrations of cerebral glycine. This
illustrates the fact that these compounds do have neurologic activity on their own as well as
through some of their metabolic interactions.

Dr. Bremer: I think we are half blind if we measure only amino acids because there are
so many steps of degradation. If you analyze urine from premature infants, you find spectra
of organic acids in the urine very comparable to inborn errors of metabolism. These are usually
combined with coenzyme A, and this certainly has very profound effects on metabolism. We
need to extend our techniques into this marginal area.

Dr. Cooper: I am interested in whether anyone has looked at taurine in relation to retinopa-
thy of prematurity and whether there is any association of taurine deficiency with that disease.

Dr. Rassin: In the few studies that I have seen there has been no close relationship between
taurine and the retinopathy of prematurity, and ROP develops much earlier than the taurine-
deficient lesions in cats. The lesions themselves are also different.

Dr. Marini: You have an indirect estimation in the human of amino acids going into the
brain, by looking at the levels in venous blood and at the $K_m$ value of the particular amino
acid. Was this system validated by measuring arteriovenous extraction and brain blood flow?

Dr. Rassin: No, but we discussed this with Dr. Partridge, who developed this approach.
His group has done comparative studies across a variety of species and found that although
the individual $K_m$ values may differ somewhat, the relative $K_m$ values don’t, and certainly
if you go from the rat to the guinea pig to the rabbit you get essentially the same relative
influxes by this kind of calculation. I could not tell you for certain whether those $K_m$ values
are the true $K_m$s, but I think that the relative $K_m$ values for each amino acid are probably
appropriate, so you get a fairly solid relative competition and influence for each amino acid.

Dr. Marini: Do you think that the amino acid content of red blood cells can be an indicator
of what is going on in other tissues?

Dr. Rassin: We have tried to use this because we have been very interested in glutathione
metabolism and red blood cells are the primary repository for glutathione in the circulation.
We found that the red cell values did not reflect liver or brain glutathione concentration
changes that we observed in our animals. I think this is of some concern. Tom Hanson’s
group has similar findings. They have also been trying to relate glutathione levels in the
plasma to what goes on in the tissues, which we haven’t tried to do yet. That is difficult
because there is very little glutathione in the plasma, but it may be a better reflection of what
goes on in the tissues than what is actually in the red cells.
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