Placental delivery of arachidonic and docosahexaenoic acids: implications for the lipid nutrition of preterm infants

MA Crawford

ABSTRACT Arachidonic (AA) and docosahexaenoic (DHA) acids are major components of cell membranes and are of special importance to the brain and blood vessels. In utero, the placenta selectively and substantially extracts AA and DHA from the mother and enriches the fetal circulation. Studies indicate that there is little placental conversion of the parent essential fatty acids to AA and DHA. Similarly, analyses of desaturation and reductase activity have shown the placenta to be less functional than the maternal or fetal livers. There appears to be a correlation with placental size and plasma AA and DHA proportions in cord blood; therefore, placental development may be an important variable in determining nutrient transfer to the fetus and, hence, fetal growth itself. In preterm infants, both parenteral and enteral feeding methods are modeled on term breast milk. Consequently, there is a rapid decline of the plasma proportions of AA and DHA to one quarter or one third of the intrauterine amounts that would have been delivered by the placenta. Simultaneously, the proportion of linoleic acid, the precursor for AA, rises in the plasma phosphoglycerides 3-fold. An inadequate supply of AA and DHA during the period of high demand from rapid vascular and brain growth could lead to fragility, leakage, and membrane breakdown. Such breakdown would predictably be followed by peroxidation of free AA, vasoconstriction, inflammation, and ischemia with its biological sequelae. In the brain, cell death would be an extreme consequence. Am J Clin Nutr 2000;71(suppl):275S–84S.

KEY WORDS Arachidonic acid, premature infants, docosahexaenoic acid, enteral nutrition, parenteral nutrition, breast milk, linoleic acid, ω-linolenic acid, neurodevelopmental disorders, vascular-developmental disorders, preterm infant formulas especially important in endothelial growth. These facts should be recognized in terms of lipid nutrition. Deficits of the kind experienced by preterm infants would be expected to contribute to the pathogenesis of the disorders associated with the complications of prematurity.

NEURODEVELOPMENTAL DISORDERS The risk of developing central nervous system defects rises sharply as birth weight falls below 1.5 kg (1). A 4.5-y follow-up study in infants born weighing <1.75 kg in Scotland showed that of 896 infants born live, 29% did not survive, 16% were disabled, 47 had cerebral palsy, 7 were blind, and 11 were deaf (2). In another study in 184 very-low-birth-weight infants, 92 had retinopathy of prematurity; of those, 15 required cryotherapy or became blind (3). In a study in 26 extremely-low-birth-weight infants (<1000 g), grating visual acuity was assessed with use of Teller Acuity Cards (4). Although most scores were within the normal range, they were significantly lower than those of full-term infants at equivalent postconceptional ages, and especially after 9 mo of age. Moreover, the number of complications in the neonatal period (especially bronchopulmonary dysplasia) was associated with below-average visual acuity in infancy and early childhood.

A recent compilation of evidence compared all measures of visual function in very-low-birth-weight children in early adolescence with those of normal-birth-weight children of the same age. Reduced visual function and poor contrast sensitivity and strabismus, which are predictive of poor motor skills, were found in high proportions in the very-low-birth-weight children. Low birth weight, intraventricular hemorrhage, intraterine growth retardation, and low 1-min Apgar scores were predictive of reduced visual function. By using stereopsis and contrast sensitivity measures, impaired vision that was not detected by normal

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Fetal nutrition and low birth weight

There is good evidence that nutrition per se is a factor in neurodevelopmental disorders. Birth weight is associated with maternal nutrient intakes independent of smoking and alcohol in infants born weighing <3270 g (18). Neural tube and delayed feeding. These unequivocally showed that delayed feeding resulted in higher mortality and morbidity. After early feeding became practice, it was then associated with reduced mortality and morbidity.

From the mid-1950s to the late 1960s there was a significant decline in the prevalence of cerebral palsy among low-birthweight infants (8, 9). In the late 1960s, while mortality continued to fall, morbidity began to rise. The prevalence of cerebral palsy in low-birth-weight infants rose 3-fold and is now back to its early 1950s level (8–10). This reversal occurred despite improvements in obstetric and pediatric care, better control of oxygen use, asphyxia management, and supplementation with vitamin E. In 2618 preterm infants of <34 wk gestation, the survival rate in 1989 was 56% greater than in 1980 (11). The increase in prevalence of cerebral palsy among low-birth-weight infants may be a consequence of lower mortality and more multiple births (12). Currently, cystic periventricular leukomalacia seems the more likely antecedent to cerebral palsy (13, 14), suggesting that the predominant form of cerebral palsy is different now from that in the 1950s, with a greater association with ischemia than with hemorrhage (15). Stanley and Watson (16) concluded that the rise in prevalence since the mid-1960s is due to prenatal conditions and early postnatal events.

Previously, we discussed the importance of the essential fatty acids, AA and DHA, in neurovascular development and the possibility that long-term consequences may follow from pre- and postnatal deficits of AA and DHA (17). In this article, we provide additional data to the evidence on the special role of the placenta that show the difference between intrauterine nourishment and the current substitutes available for preterm infants.

**TABLE 1**

<table>
<thead>
<tr>
<th>Correlation</th>
<th>r</th>
<th>r²</th>
<th>n</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight with AA</td>
<td>0.56</td>
<td>0.32</td>
<td>22</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Head circumference with DHA</td>
<td>0.66</td>
<td>0.39</td>
<td>32</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Gestational age with DHA</td>
<td>0.66</td>
<td>0.45</td>
<td>33</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

1 Data from references 23 and 24. r², coefficient of determination.
alpha-Linolenic acid, brain cholesterol, and docosahexaenoic acid synthesis

Administration of [13C]ALA to rat pups during brain development showed that, of the small amount recovered from the brain, several times more ALA was used for synthesis of brain cholesterol rather than for that of brain DHA. The isotopic data suggest that of the ALA carbon chain that reaches the brain, as much as 5 or more times is broken down for cholesterol rather than de novo DHA synthesis from ALA (35; and S Cunnane, personal communication, 1998). Brain cholesterol synthesis is vital. The

![Graph showing percentage of fatty acids (%) by wt for LA Maternal, AA, AA Cord, and DHA]

**FIGURE 1.** Placental weight and choline phosphoglyceride linoleic (LA), arachidonic (AA), and docosahexaenoic (DHA) acids in maternal and cord plasma, in relation to placental weight in the highest ( □ > 620 g; n = 23) and lowest (■ < 425 g; n = 21) 20th percentiles. Two-tailed t test results were significant (P < 0.01) between upper and lower groups for DHA and LA but not for AA.

| TABLE 2 | Regression data of umbilical artery choline phosphoglyceride and ethanolamine phosphoglyceride fatty acids versus birth weight and head circumference

<table>
<thead>
<tr>
<th></th>
<th>Pearson’s coefficient</th>
<th>t</th>
<th>n</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ethanalamine phosphoglycerides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight versus 20:4n−6</td>
<td>0.53</td>
<td>2.98</td>
<td>14</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>Head circumference versus 20:4n−6</td>
<td>0.44</td>
<td>2.34</td>
<td>12</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Birth weight versus 22:6n−3</td>
<td>0.54</td>
<td>2.19</td>
<td>14</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Head circumference versus 22:6n−3</td>
<td>0.49</td>
<td>1.78</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>Birth weight versus 16:0</td>
<td>−0.52</td>
<td>1.93</td>
<td>13</td>
<td>NS</td>
</tr>
<tr>
<td>Head circumference versus 16:0</td>
<td>−0.45</td>
<td>1.49</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>Birth weight versus 18:0</td>
<td>−0.52</td>
<td>2.11</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>Head circumference versus 18:0</td>
<td>−0.48</td>
<td>1.68</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Choline phosphoglycerides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight versus 20:4n−6</td>
<td>0.35</td>
<td>1.28</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>Head circumference versus 20:4n−6</td>
<td>0.37</td>
<td>2.08</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Ethanalamine phosphoglycerides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triene-tetraene ratio (EFA deficit)</td>
<td>−0.87</td>
<td>6.46</td>
<td>14</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Head circumference versus 20:3n−9/20:4n−6</td>
<td>−0.83</td>
<td>5.14</td>
<td>12</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pentane-tetraene ratio (DHA deficit)</td>
<td>−0.79</td>
<td>5.07</td>
<td>14</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Head circumference versus 22:5n−6/22:4n−6</td>
<td>−0.83</td>
<td>5.09</td>
<td>12</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Choline phosphoglycerides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triene-tetraene ratio (EFA deficit)</td>
<td>−0.68</td>
<td>3.86</td>
<td>14</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Head circumference versus 20:3n−9/20:4n−6</td>
<td>−0.63</td>
<td>3.20</td>
<td>12</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Pentane-tetraene ratio (DHA deficit)</td>
<td>−0.66</td>
<td>3.74</td>
<td>14</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Head circumference versus 22:5n−6/22:4n−6</td>
<td>−0.46</td>
<td>2.42</td>
<td>12</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

1NS, nonsignificant. EFA, essential fatty acid; DHA, docosahexaenoic acid (22:6n−3). t, Student’s t test statistic. Data from reference 29.
brain does not import cholesterol from the liver but synthesizes its own. Few substrates can penetrate the blood-brain barrier, but small amounts of ALA can. ALA’s high rate of oxidation produces breakdown products that provide substrates for cholesterol and palmitic acid (16:0) synthesis. The proportion of brain cholesterol coming from ALA is as yet unknown. Nonetheless, cholesterol synthesis is critical for brain development and it seems that ALA is more important to the brain as a substrate for cholesterol than for brain DHA. However, the striking species differences need to be borne in mind when interpreting animal experiments in the context of human metabolism.

It has been known since the 1950s that ALA can be converted to DHA. That, however, is not the question. Studies in young men showed that, even as a general substrate for DHA, deuterated ALA falls short of providing for the synthesis of the long-chain n-3 fatty acids to meet daily requirements in some, but not all, adults (36). The DHA requirements of infants, born preterm or full-term, are substantially greater because of the rapid growth of lipid-rich membranes; isotopic studies to date suggest that reliance on ALA alone to provide for membrane DHA is inadequate (37, 38). The fact that formula-fed term infants who died from unexplained causes had less brain DHA than did those previously fed their mothers milk (which contains DHA) is inconsistent with the idea that ALA meets the optimal DHA requirement of term infants (39, 40).

Rate limitations in conversion of precursor essential fatty acid to arachidonic and docosahexaenoic acids

A proposed route for the synthesis of DHA is via chain elongation of 22:5n-3 to 24:5n-3 followed by Δ6-desaturation to 24:6n-3. This fatty acid then has to migrate to the peroxysomes where 2 carbons are cleaved to result in DHA (32). This circuitous route involves more metabolic time, an additional rate-limiting Δ6-desaturation, translocation of 24:6n-3 to the peroxysomes for the final oxidation step, and then export to the reticuloendothelial system.

DHA synthesis requires 2 rate-limiting Δ6-desaturations, whereas AA synthesis requires only 1. This dual rate limitation could explain why, in fast-growing ungulate species, the process pools at the n-3 docosapentaenoic acid (22:5n-3) rather than at DHA outside the brain. This failure to take the metabolic sequence to completion with DHA occurs despite an abundance of precursors. It is associated with a logarithmic decline in relative brain size (41). There is now compelling evidence that the transition from small-brained hominids to Homo sapiens, marked by rapid cerebral expansion, occurred in the presence and extensive use of DHA-rich foods. This chemistry would have conferred a selective advantage that would have been reflected in placental transfer and human milk composition during the period of cerebral expansion (42, 43).

PLACENTAL TRANSFER

Experimental studies on the placenta

The placenta provides the fetus with AA and DHA during the brain growth spurt; therefore, it is important to describe its role. To establish the proportions fed to the fetus by the placenta, analyses of maternal and cord blood have been done at term and at midterm (17, 44). The reduction of the proportion of LA and almost doubling of the proportion of AA and DHA in the placenta is shown in Figure 3. Studies in midterm abortions could elucidate the events occurring close to the birth of a preterm baby. The transplacental gradient in proportions of AA and DHA appears to be greater at term than midterm. This difference is consistent with the finding that, whereas DHA is mobilized at the beginning of pregnancy, its plasma concentrations fall toward the end, raising the suggestion that the placenta is progressively depleting maternal DHA stores during fetal growth (30).

Tracer studies on synthesis and transfer of docosahexaenoic acid in animals

To determine whether the placental transfer of fatty acids involved desaturation and chain elongation by the placenta, we conducted several isotope and enzyme studies. Oral administration of [13C]ALA to pregnant guinea pigs was followed in time over 96 h (45). From the total isotope recovery data it was found that a high proportion of the tracer was oxidized in the first 24 h, similar to results in rat studies (34). The progression of the remaining tracer was from mother to placenta to fetus and along
the metabolic chain, first appearing in eicosapentaenoic acid, then in docosapentaenoic acid, and finally in DHA, while it diminished in the precursors (Table 3). The proportion of tracer reaching DHA in the maternal liver was only 1.8% of all isotope recovered; 15% and 9.2% remained in ALA and eicosapentaenoic acid, respectively, after 96 h (45). Only 2.6% of the tracer reached ALA in the placenta; the remainder was distributed among the longer-chain intermediates and DHA. By contrast, the isotope in fetal DHA rose from 12% in the first 24 h to 50% at 96 h, with that in the ALA diminishing from 12% at 12 h to 0.8% at 96 h. In total, however, ≈0.5–0.1% of the isotope administered at the start was recovered in the fetus at 96 h (Table 3).

Even at 96 h it seemed that the proportion of 14C in the precursors would have continued to decrease, leaving the isotope largely in the fetal DHA. This slow accretion of the small amount of synthesized DHA is in contrast to findings in the rat studies, in which DHA synthesis appeared to be faster. Nonetheless, preformed DHA was incorporated directly into the developing brain at an order of magnitude greater than synthesis from ALA (33). Both the guinea pig and rat data are consistent with the suggestion that, in humans, the placenta is taking DHA from the mother toward the latter half of pregnancy (30).

**Enzyme systems**

To assess the reductase capacity of the placenta, we measured the activity of NADH cytochrome C reductase, ferricyanide, and B5 reductase systems in guinea pig, maternal liver, placenta and fetal liver. The results showed that there was more activity in the maternal liver than in the placenta or fetal liver (D Fornel, D Kuhn, unpublished observations, 1985) (Fig. 4). To examine the metabolic efficiency of the placenta, we isolated microsomes from maternal liver, placenta, and fetal liver tissues of pregnant guinea pigs at their equivalent of midterm. They were separately incubated with uniformly 14C-labeled LA. By using preparative gas-liquid chromatography combined with liquid scintillation counting, we found relatively little radioactivity in the products of desaturation in the placenta. Both maternal and fetal livers produced significant quantities of [14C]γ-linolenic acid (18:3n–6), the immediate desaturation product. The desaturation activity, as measured by the appearance of isotope in γ-linolenic acid and higher derivatives, was barely detectable in the placenta compared with the fetal and maternal livers (D Fornel, Douglas Kuhn, unpublished observations, 1985) (Fig. 5). In these tests, the activities for the placenta would have had to be far higher than the maternal and fetal livers to explain the biomagnification process by placental anabolism.

**Table 3**

Percentage of 14C recovered over time in individual fatty acids in maternal, fetal, and placental tissue of pregnant guinea pigs fed [14C]-α-linolenic acid.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>18:3n–3</th>
<th>20:5n–3</th>
<th>22:5n–3</th>
<th>22:6n–3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal liver</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>65 ± 7.8</td>
<td>2.6 ± 0.6</td>
<td>1.1 ± 0.3</td>
<td>0.01</td>
</tr>
<tr>
<td>12</td>
<td>72 ± 7.7</td>
<td>3.5 ± 0.5</td>
<td>2.0 ± 0.3</td>
<td>0.03</td>
</tr>
<tr>
<td>24</td>
<td>48 ± 6.3</td>
<td>5.7 ± 0.9</td>
<td>1.6 ± 0.8</td>
<td>0.02</td>
</tr>
<tr>
<td>48</td>
<td>18 ± 2.3</td>
<td>4.3 ± 0.6</td>
<td>1.7 ± 0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>96</td>
<td>15 ± 2.0</td>
<td>9.2 ± 0.8</td>
<td>4.4 ± 0.8</td>
<td>1.8 ± 0.2</td>
</tr>
<tr>
<td>Placental tissue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>22 ± 2.7</td>
<td>38 ± 3.9</td>
<td>11 ± 2.0</td>
<td>9.0 ± 1.3</td>
</tr>
<tr>
<td>12</td>
<td>43 ± 5.6</td>
<td>28 ± 4.2</td>
<td>8.6 ± 1.2</td>
<td>7.1 ± 1.1</td>
</tr>
<tr>
<td>24</td>
<td>36 ± 4.1</td>
<td>26 ± 2.3</td>
<td>13 ± 1.5</td>
<td>8.6 ± 2.0</td>
</tr>
<tr>
<td>48</td>
<td>4.2 ± 0.7</td>
<td>12 ± 2.4</td>
<td>12 ± 1.4</td>
<td>14 ± 1.5</td>
</tr>
<tr>
<td>96</td>
<td>2.6 ± 0.4</td>
<td>12 ± 1.5</td>
<td>17 ± 1.9</td>
<td>20 ± 3.3</td>
</tr>
<tr>
<td>Whole fetus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3.8 ± 0.6</td>
<td>22 ± 2.8</td>
<td>12 ± 1.8</td>
<td>12 ± 1.4</td>
</tr>
<tr>
<td>12</td>
<td>12 ± 1.7</td>
<td>30 ± 3.3</td>
<td>14 ± 1.6</td>
<td>13 ± 1.5</td>
</tr>
<tr>
<td>24</td>
<td>4.5 ± 0.8</td>
<td>5.1 ± 0.7</td>
<td>22 ± 2.5</td>
<td>21 ± 4.7</td>
</tr>
<tr>
<td>48</td>
<td>2.3 ± 0.5</td>
<td>7.6 ± 1.1</td>
<td>24 ± 3.2</td>
<td>41 ± 5.1</td>
</tr>
<tr>
<td>96</td>
<td>0.8 ± 0.1</td>
<td>4.3 ± 1.0</td>
<td>28 ± 3.2</td>
<td>50 ± 6.1</td>
</tr>
</tbody>
</table>

\( \bar{x} \pm \text{SE}; n = 7 \). Data from reference 45.
Human placental perfusion studies

To validate the animal studies, we undertook a series of studies on human placental function (46). Isolated lobes were obtained from normal or cesarean deliveries. Once physiologic conditions had been established in the perfusion chamber, metabolism stabilized, and there was no maternal-fetal leak, \(^{14}\)C-LA and -AA were introduced bound to albumin or as a phosphoglyceride.

There is discrimination in favor of transporting AA rather than converting LA to AA, as shown in Figure 6. The \(^{14}\)C label from LA was barely detectable in the AA in the fetal circulation. However, AA labeled and administered as such crossed the placenta more readily (47). In our studies, it was the albumin-bound fatty acids that crossed the placenta. Labeled linoleyl choline phosphoglyceride did not act as a donor of either LA or AA under these perfusion conditions.

From a pulse dose of \(^{14}\)C-LA and -AA, maximum transfer was achieved rapidly in <2 min (Figure 7; 47). The LA, which did cross the placenta, was largely incorporated into plasma triacylglycerols, whereas AA was incorporated preferentially into the structural lipid, namely the plasma choline phosphoglycerides (Figure 7B). When the neonate's red cells were included in the fetal perfusate of the human placental perfusion chamber, the red cell phosphoglycerides rapidly took up the AA injected into the maternal circulation, providing evidence that the exchange protein in the fetal red cell membrane is active on the fetal side of the placenta (Figure 7C).

**FIGURE 4.** Reductase activity in maternal liver, placental, and fetal liver microsomes of pregnant guinea pigs just before parturition (n = 6). ■, NADH cytochrome c reductase; □, NADH ferricyanide; △, B5 reductase (in pmol activity/mg). Maternal liver activity was significantly different from placental and fetal liver activity (two-tailed Student's t test), P < 0.001.

**FIGURE 5.** Desaturation of 18:2n−3 to 18:3n−6 in maternal, placental, and fetal tissues in guinea pigs (n = 7) at midterm. Relatively little desaturation occurred in the placenta compared with the fetal and maternal livers. Because the proportion of arachidonic acid doubled across the placenta, it is unlikely that this biomagnification is achieved by biosynthesis in the liver.
Little is known about the actual mechanism of transfer. It may well involve free fatty acid release and reesterification with preferential incorporation of the long-chain polyunsaturated fatty acids, a hypothesis favored by the preferential transfer of albumin-bound fatty acid over choline phosphoglyceride. On the other hand, there is little AA and DHA in the free fatty acid pool. However, a study of maternal and umbilical arterial and venous data gave evidence from which it was concluded that maternal red cells were acting as a source of AA and DHA (48). Our data on the red blood cell uptake of AA support this hypothesis in that it shows the converse, namely the avid uptake of AA by fetal red cells, showing that red blood cells are not inactive in fatty acid transfer and destination.

There is good evidence of selective uptake by the placenta, rather like that of the brain, of AA and DHA (49). The similarity between the fatty acid composition of the choline phosphoglycerides in the umbilical vein and the ethanolamine phosphoglyceride in maternal red cells is also striking. It may be that an exchange protein performs the switch in the placental circulation with the driving force being the selective transfer of free AA and DHA out of the maternal-placental circulation. A mechanism for the transport of AA and DHA across the placenta has been proposed (50). The placental phosphoglycerides themselves have probably the highest content of AA of any cell system, so are concentrating AA from the maternal circulation, in which the red blood cells are the richest source.

**POSTNATAL CONDITIONS**

**Peroxidation**

It is clear from the above evidence that some preterm neonates experience a degree of malnourishment, possibly related to poor placental development or dysfunction. Postnatal conditions could arguably either compensate or exacerbate this condition. One of the factors that is physiologically unexpected in preterm birth is the need to breathe air, hence the suggested risk of peroxidation.

Several mechanisms exist to protect against peroxidative damage. Postnatal conditions could arguably either compensate or exacerbate this condition. One of the factors that is physiologically unexpected in preterm birth is the need to breathe air, hence the suggested risk of peroxidation.

Several mechanisms exist to protect against peroxidative damage. As endogenous enzyme systems in the cytosol and embedded in the cell membrane. Exogenous vitamins (E, A, and C) protect against peroxidative damage. The endogenous systems are the metalloenzymes Cu/Zn superoxide dismutase, Mn superoxide dismutase, Fe catalase, and Se glutathione peroxidase.

Red blood cell Cu/Zn superoxide dismutase activity in infants born <32 wk gestational age was about half that expected at term (51). Birth concentrations of plasma vitamin A also correlated with birth weight (52). Hence, in preterm neonates both prenatal nutritional consideration and the degree of physiologic maturation may need to be taken into account. Peroxidation of cell membrane AA and DHA has important physiologic consequences that are variously interpreted as good or bad. AA and DHA are considered to be susceptible to peroxidation because of their high degree of unsaturation. Paradoxically, they are oxidized at a quarter of the rate of LA and ALA (33, 34). The idea of AA and DHA being dangerous because of peroxidation is curious because they are major structural and functional components of the systems that demand the highest oxygen inputs, ie, mitochondria and neuronal cells. The current thought is that a cell membrane that is appropriately constructed with proper proportions of the right fatty acids for its configuration and function will be the most resistant to peroxidation. Because this configuration requires the incorporation of highly unsaturated fatty acids, this apparently contradictory situation has been referred to as the peroxidation paradox (53). Stability is conferred by appropriate membrane composition.

On the other hand, a deficiency of AA and DHA in cell membranes classically results in leaking, loss of integrity, and membrane rupture. The consequent release of free AA from attack by lysosomal phospholipase results in peroxidation of the free AA to a well-characterized set of physiologically active hydroperoxides and eicosanoids, which stimulate platelet aggregation and adhesion, vasoconstriction, white cell activation, inflammation, loosening of endothelial cell junctions, chemokinesis and chemotaxis, cell infiltration, and cytokine activation (54). Indeed, cytokine activity has been associated with morbidity in preterm infants (55).
FIGURE 7. Placental perfusion of linoleic (LA) and arachidonic (AA) acids. Fetal uptake of isotopically labeled bolus doses of fatty acids in the maternal circulation. A, Fetal plasma uptake of [14C]LA; B, fetal plasma uptake of [14C]AA; C, fetal red blood cell uptake of [14C]AA. FFA, free fatty acid; TG, triacylglycerol; PL, total red blood cell phospholipid. Data from reference 47.
The data suggest that some preterm infants will have had a reduced provision of AA and DHA in utero. Consequently, they may be born at a nutritional disadvantage. No treatment is available to make good such deficits or to make up for the subsequent loss of the placental input of AA and DHA. Hence, preterm infants are exposed postnatally to an even greater loss. In view of the priority given to fetal brain development, it may be that this loss is in part responsible for the major complications of prematurity in which both the brain and blood vessels are intimately involved.

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FIGURE 8. Postnatal essential fatty acid concentrations in preterm infants. Data lines for placental arachidonic acid (AA) and linoleic acid (LA) represent the starting concentrations at birth and what the infant would have received during the same period had it remained a fetus fed by the placenta. Data from references 23 and 24.

Etiology

Although peroxidation has attracted attention mostly as an explanation of morbidity, it has also led to the hypothesis that the complications of premature birth are “facets of one disease” (56). This concept fits with our evidence of reduced superoxide dismutase activity in conjunction with reduced birth concentrations of plasma AA and DHA and umbilical signs of essential fatty acid deficits, making the case for a degree of prenatal undernourishment of AA and DHA (57). Postnatally, plasma AA and DHA plummet to one-third of what the placenta would have provided within 2–3 wk after birth. This fall in AA occurs regardless of the fact that the proportions of its precursor, LA, rise to 3–4 times the intraterine concentrations at birth (Figure 8).

The idea that severe damage, ie, cerebral palsy, is a combination of pre- and postnatal conditions (16) fits glove-like with this evidence. The obliteration of blood vessels in the retina, leaking blood vessels in the lungs, intraventricular rupture, and periventricular leukomalacia can be explained by the simple devaluation of endothelial cell membrane integrity caused by reduced AA and DHA in the membranes with the expected leakage, fragility, and rupture leading to the eicosanoid and cytokine response. Added to this scenario is additional damage in the brain expected through the reperfusion peroxidation of nitric oxide accumulated during the ischemia to peroxynitrite (57), which would finally set the stage for neural cell death. This is not to say that the fatty acid story explains cerebral palsy or other forms of damage, but given the likelihood of associated infection, stress, blood pressure changes, and other physiologic disturbances that preterm neonates may experience before, during, or after birth, impoverished cell membranes probably do not help to maintain biological stability.

CONCLUSION

REFERENCES

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