PERINATAL BIOCHEMISTRY AND PHYSIOLOGY OF LONG-CHAIN POLYUNSATURATED FATTY ACIDS

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Docosahexaenoic acid (DHA) and arachidonic acid (ARA) are important structural components of the central nervous system. These fatty acids are transferred across the placenta, are present in human milk, and are accumulated in the brain and retina during fetal and infant development. The high concentrations of DHA in the retina and of DHA and ARA in brain gray matter suggests that these fatty acids have important roles in retinal and neural function. Animal studies have shown that depletion of DHA from the retina and brain results in reduced visual function and learning deficits. The latter effects may be explained by changes in the membrane bilayer that alter membrane-associated receptors and signal transduction systems, ion channel activity, or direct effects on gene expression. DHA can be formed in the liver from alpha linolenic acid, but it is unclear if the rate of DHA synthesis in humans is sufficient to support optimal brain and retinal development. Although there is no evidence that the ability to form ARA from linoleic acid is limiting, supplementation with DHA reduces tissue ARA, possibly creating a conditional need for ARA in infants with a dietary intake of DHA. The amount of DHA in human milk varies widely and is positively correlated with visual and language development in breast-fed infants. Advances in understanding essential fatty acid requirements will benefit from intervention studies that use functionally relevant tests to probe the deficiency or adequacy of physiologically important pools of DHA and ARA in developing infants. ***(J Pediatr 2003;143:S1-S8)***

Docosahexaenoic acid (DHA, 22:6n–3) and arachidonic acid (ARA, 20:4n–6) are important structural components of the highly specialized membranes lipids of the human central nervous system.[1,2] DHA is the major polyunsaturated fatty acid in the outer segments of the retina rods and cones, where it can constitute as much as 50% of the fatty acids in phosphatidylethanolamine (PE) and phosphatidylserine (PS), and as much as 80% of all the polyunsaturated fatty acids.[1] These membranes are specialized for the rapid transmission of light and contain 90% to 95% of the lipid as phospholipid. The phospholipids contain unusual PE, PS, and phosphatidylcholine (PC) species in which both acyl groups are DHA. Approximately 10% of the weight of the brain, and 50% of the dry weight, is lipid. About half of this lipid is phospholipid, with approximately 20% cholesterol, 15% to 20% cerebrosides, and smaller amounts of sulphatides and gangliosides.[2] The phospholipids of brain gray matter contain high proportions of DHA in PE and PS and high amounts of ARA in phosphatidylinositol (PI). ARA is also present in membrane phospholipids, particularly in PI throughout the body. Unlike other organs, the dietary essential fatty acid linoleic acid (LA, 18:2n–6) usually represents <1% of brain and retina fatty acids, and concentrations of α-linolenic acid (18:3n–3) are even lower.[2] These usual characteristics of brain and retina phospholipids suggest that specific mechanisms are available to allow the brain and retina to accumulate large amounts of DHA and ARA and that DHA has functional roles specific to visual and neural processes.

Studies over the last three decades have provided evidence that depletion of DHA from the developing retina and brain leads to abnormalities in electroretinogram and visual evoked potential (VEP) responses and learning behaviors.[3-8] Changes in cognitive

ARA	Arachidonic acid, 20:4n–6	PC	Phosphatidylcholine
CDI	Communicative developmental inventory	PE	Phosphatidylethanolamine
DHA	Docosahexaenoic acid, 22:6n–3	PI	Phosphatidylinositol
DPA	Docosapentaenoic acid, 22:5n–6	PS	Phosphatidylserine
EPA	Eicosapentaenoic acid, 20:5n–3	RBC	Red blood cell
LA	Linoleic acid, 18:2n–6	VEP	Visual evoked potential
LNA	α-Linolenic acid, 18:3n–3		

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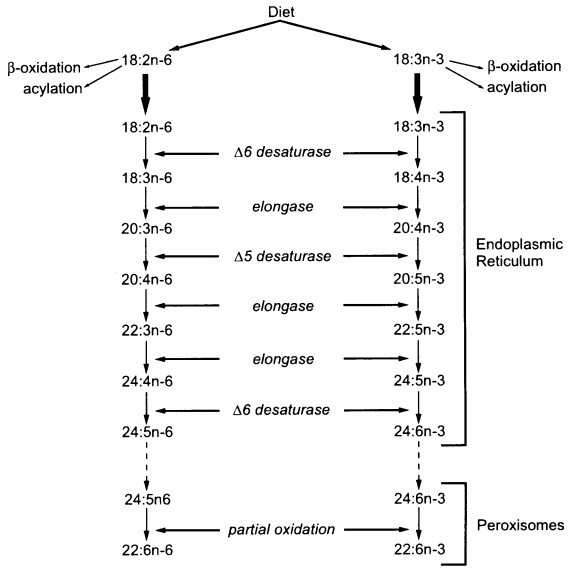

Fig 1. Schematic of n-6 and n-3 fatty acid desaturation and elongation.

performance and behavior and the transmission of visual and auditory information could involve the effects of DHA on neurotransmitter metabolism, ion channel activity, signaling pathways, or gene expression.[9-18] ARA is essential for normal growth and is critically important through its role in cell signaling and as a precursor to series 2 eicosanoids and series 3 leukotrienes, which also play a role in synaptic transmission.[19-21] The action of n–6 and n–3 fatty acids on metabolic and physiologic pathways may involve 3 general mechanisms: membrane phospholipid fatty acids influence the properties of the microenvironment of membrane bilayers and this in turn can effect the activity of membrane-associated proteins, receptors, transport systems, and ion channels; membrane phospholipids and their n–6 and n–3 fatty acids function as signal molecules and as precursors for eicosanoids; and finally, the n–6 and n–3 fatty acids have rapid and direct effects on gene expression through peroxisome proliferator activated receptor (PPAR)-dependent and PPAR-independent mechanisms.[12-19,22,23]

Deficiency of key components for normal growth and development, as illustrated for example by iron or iodine deficiency, during key stages of development can have long-term consequences for neural development in infants and children.[24,25] The difference in dietary intake of DHA and ARA among infants fed milk and formula diets[26] and their important role in visual and neural function has focused attention on the need to elucidate the ability of infants to form ARA and DHA from their LA and LNA precursors, respectively, the pathways by which these fatty acids are transferred to the developing brain and retina, and the effects of n–6 and n–3 fatty acid nutrition on infant growth and visual and neural development. This review explores recent understanding of polyunsaturated fatty acid metabolism in development, the supply of n–6 and n–3 fatty acids before and after birth, and the implications for neural development.

Polyunsaturated Fatty Acid Metabolism

ARA and DHA are formed from LA and LNA, respectively, in the liver by a series of alternating desaturation (addition of a double bond) and elongation (addition of a 2-carbon unit) reactions.[27-29] (Fig 1). Although LA and LNA are formed in plants, they cannot be formed in mammalian cells because of the absence of the Δ12 and 15 enzymes necessary to insert a double bond at the n (or ω) 6 or 3 position of a fatty acid carbon chain. LA and LNA are, therefore, considered essential dietary nutrients. Once obtained from the diet, LA and LNA are further metabolized by Δ6 desaturation, elongation, and Δ5 desaturation to form ARA and eicosapentaenoic acid (EPA, 20:5n–3), respectively (Fig 1). The Δ5 desaturase and subsequent steps in the pathway are found in animal but not in plant cells. Preformed ARA and DHA are present in the diet in meat, fish, and eggs but not in fruits, vegetables, nuts, grains, or their products.[30] Dairy products are also exceedingly low in DHA and ARA and in their precursors LA and LNA.

Early studies established that dietary deficiency of n–6 fatty acids results in growth failure and skin lesions, which are corrected by providing approximately 0.2% dietary energy as ARA or 2% to 3% dietary energy as LA.[19,20] LA has important functions in cholesterol metabolism and in specific skin lipids, and eicosatrienoic acid (20:3n–6) is an eicosanoid precursor.[19] LNA is not known to serve any essential functions other than as a precursor for EPA and DHA. A large proportion of LNA is β-oxidized to acetyl CoA, which is recycled into cholesterol and saturated and monounsaturated fatty acids, or further metabolized to CO_2.[31-35] Unlike LA, acylation of LNA into tissue lipids is very low. It is not yet known whether sufficient LNA enters the desaturation pathway to maintain optimal neural and retinal DHA in young infants. Elucidation of the regulation of partitioning of LA and LNA among their potential fates of direct esterification into tissue lipids, β-oxidation, and desaturation will be useful in addressing this.

For many years, it was assumed that fatty acid desaturation occurred in the endoplasmic reticulum and that the final steps in the synthesis of DHA and the n–6 DPA (22:5n–6) involved a Δ4 desaturation of 22:5n–3 to 22:6n–3 and 22:4n–6 to 22:5n–6. However, it is now known that the pathway involves synthesis of 24:5n–3 and 24:4n–6 by elongation of the 22 carbon chain products of Δ5 desaturase.[27-29] The 24:5n–3 and 24:4n–6 are desaturated at position 6 to yield 24:6n–3 and 24:6n–3, which are translocated to the peroxisomes where partial oxidation generates DHA (22:6n–3) and DPA (22:5n–6).[27] The elucidation of the final steps of DHA synthesis has important implications for the clinical treatment of infants with peroxisomal disorders such as Zellweger syndrome, who may benefit from supplementation with DHA.[36,37]

Dietary deficiency of LNA in developing animals results in decreased DHA with a reciprocal increase in n–6 fatty acids, particularly DPA in retina, whole brain, isolated brain membranes, and specific brain regions.[4,6,38-40] The decrease

in brain and retina DHA is accompanied by altered electroretinogram, decreased looking and VEP acuity, and changes in learning behaviors, including performance in maze tasks, habituation, exploratory activity in novel environments, and brightness discrimination and olfactory-based learning tasks.[3-8,41-43] Polydypsia and increased sterotypic (locomotor) activity have also been reported for monkeys fed diets very low in LNA.[44,45] The ability of developing animals to replace DHA with DPA indicates that the desaturase enzyme activity does not limit fatty acid desaturation and that DPA does not provide a functional substitute for DHA despite its similar carbon chain length.

Endogenous synthesis of DHA and ARA is believed to use the same Δ6 and Δ5 desaturase enzymes. This can result in competition between LA and LNA as well as inhibition of the enzyme pathway by products of the same and the opposing series of fatty acids.[5] For example, high dietary intakes of EPA or DHA result in decreased tissue ARA and decreased formation of ARA derived eicosanoids in favor of n–3 fatty acid derived eicosanoids.[46-48] Early clinical studies reported lower blood lipid ARA in preterm infants fed formulas containing fish oil (as a source of DHA) than in infants fed unsupplemented preterm formulas, lower growth, and an association between ARA status and growth.[49-52] Lower growth has not been reported in term infants fed formulas with DHA, although language development assessed with the MacArthur Communicative Developmental Inventory (CDI) at 14 months of age was lower in term infants fed formula with DHA and no ARA than in infants fed unsupplemented formula.[53] These clinical studies suggest that the balance of DHA or EPA+DHA to ARA may be important, but specific data to explain a mechanism of effect is lacking.

Many studies have shown that plasma and red blood cell (RBC) DHA and ARA are lower in infants fed conventional formulas without DHA and ARA than in infants who are breast-fed.[54-58] Adding oils containing DHA and ARA to infant formulas in amounts approximating those in human milk results in "normalization" of the plasma and RBC DHA and ARA to levels within the range of those in breast-fed infants.[54-56] The increase in plasma and RBC DHA and ARA after an increase in dietary DHA and ARA intake is well-known from studies in adults.[59,60] However, the physiological significance of this with respect to the brain, which has specialized pathways for fatty acid uptake and conservation,[61,62] must be approached with caution. Studies in developing animals show that although n–3 fatty acid deficiency does result in low DHA concentrations in brain, the increase in DHA in brain, plasma, and RBC with increasing DHA intake is not linear.[63,64] Thus, tests of visual and neural function are needed to assess deficiency or adequacy of physiologically important pools of DHA in the brain of infants. These studies are likely to have greater sensitivity if based on advances in understanding of the role of DHA in neural function. Newer approaches to assessing infant development are discussed in other papers in this issue of The Journal.[65-68]

Until recently, much of the biochemical information gathered in studies with animals fed n–3 fatty acid-deficient diets was limited to descriptions of diet-related changes in fatty acids. In recent years, several studies have shown that n–3 fatty acid deficiency alters the metabolism of dopamine and serotonin in the brain of rodents and young piglets.[9-11,69-73] Particular interest has been given to the dopaminergic system because of the role of dopamine in the cognitive advances of early childhood, as a modulator of attention and motivation, and in the visual pathways.[74-77] The effects of DHA on dopamine metabolism are region-specific within the brain and involve changes in dopamine concentration, expression of the vesicular monoamine transporter 2 mRNA and dopamine D_2 receptor mRNA, and immunoreactivity of tyrosine hydroxylase (the rate-limiting enzyme in dopamine synthesis).[71-73] Although n–3 fatty acid deficiency results in reduced dopamine in frontal cortex, recent studies have shown concentrations of dopamine in the nucleus accumbens may be increased,[9-11,72,73] which suggests that the mesocorticolimbic area functions more and the mesocortical pathway is less active in chronically n–3 fatty acid-deprived animals.[11] Other recent studies have provided evidence that n–3 fatty acids regulate expression of genes involved in synaptic plasticity, cytoskeleton and membrane association, signal transduction, ion channel formation, energy metabolism, and the retinoid X receptor (RXR) in the brain.[17,18] EPA and DHA have also been shown to block the mitogenic effect of growth factors that act through receptor tyrosine kinase (such as platelet derived growth factor, fibroblast growth factor, epidermal growth factor, insulin-like growth factor) and G-protein–coupled receptors (such as bomberin, bradykinin, vasopressin, thrombin, serotonin, and thromboxane A2) signaling pathways.[12,13] Polyunsaturated fatty acids also regulate key genes related to hepatic lipid metabolism.[22,23] Whether the effects of n–3 or the n–3/n–6 fatty acid balance on neural function or other aspects of growth and development are mediated through regulatory effects on gene expression is an important area for further study.

Polyunsaturated Fatty Acid Metabolism in Development

Before birth, all of the n–6 and n–3 fatty acids accumulated by the fetus must originate from the maternal circulation through placental transfer, and after birth all must be derived from the milk or formula diet and later from complementary foods. The central question is the extent to which the developing fetus and infant is able to utilize LA and LNA or depends on exogenous ARA and DHA to meet the needs for optimal development. Delta 6 and Δ 5 desaturase activity has been shown in human fetal liver microsomes from as early as 17 weeks of gestation.[78,79] The activity of the pathway to DHA, however, is not known. Several tracer studies using stable isotopes of LA and LNA have shown that preterm and term human infants are able to convert LA to ARA and LNA to DHA.[80-84] Integrated area-under-the-curve estimates for the products of LNA metabolism suggest

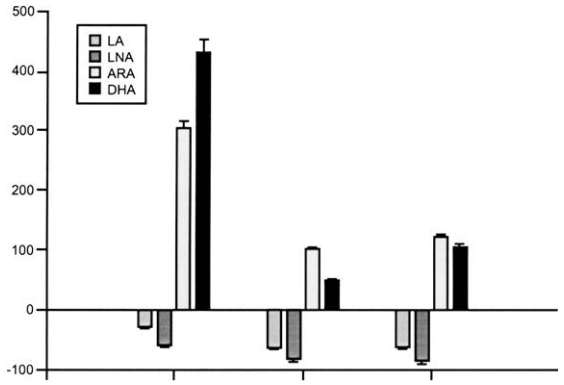

Fig 2. Fatty acid enrichment in fetal compared with maternal plasma. Relative enrichment of LA, LNA, ARA, and DHA in fetal compared with maternal plasma was calculated for each mother-fetal cord plasma pair as the difference in the given fatty acid in the maternal compared to fetal plasma/maternal plasma × 100%. Values shown are mean ± SEM, n = 55. Adapted from data published in Reference 89.

that preterm infants are as capable as term infants, and perhaps more so, in converting LNA to DHA.[84] Conversion of LNA to DHA appears to be highly variable among individual infants. The reasons for this variability are not known. Although these tracer studies have provided important demonstrations that conversion of LNA and LA occurs in human infants, further developments are needed to allow quantitative estimates of ARA and DHA accumulation at the level of the tissues.

Tracer methodology has also been used to show that DHA is transferred across the baboon placenta.[85] and that fetal baboons can form DHA from an intravenous dose of [U^{-13}C]-LNA.[86] In the latter studies, approximately 0.6% of the LNA administered was recovered in brain DHA, whereas 4.6% of a dose of DHA was recovered in brain. In contrast to the studies with baboons, no apparent synthesis of DHA from [U^{-13}C] LNA was found in liver of fetal piglets at 70 to 72 or 110 to 112 days' gestation (term, 115 days).[87] Synthesis was limited at EPA. Synthesis of DHA, however, increased rapidly over the first 14 days after birth. Concentrations of DHA and ARA are high in fetal plasma,[88,89] which suggests that fetal desaturase enzymes may be decreased secondary to preferential transfer of DHA and ARA from the maternal circulation.

Autopsy analyses have shown lower DHA but not ARA in the brain of infants who had been fed formula without DHA and ARA rather than breast-fed.[90-92] The decrease in DHA in frontal cortex PE of infants fed formula with 1.5% LNA or 0.4% LNA was accompanied by increased ARA, 22:4n–6 and DPA,[90] which is consistent with the increase in n–6 fatty acid desaturation that accompanies an inadequate supply of n–3 fatty acids.[5] Although this could be interpreted as evidence that dietary DHA is important for "optimal" DHA assimilation in developing human brain, reduced brain DHA also results from inadequate dietary LNA or high LA/LNA ratios.[4-6,39,40,93]

Placental Transfer of Polyunsaturated Fatty Acids

Although it is clear that all of the n–6 and n–3 fatty acids accumulated in the fetus must ultimately be derived from the mother by placental transfer, the process involved in this transfer remains incompletely understood. The concentrations of DHA and ARA are 300- to 400-fold higher in fetal compared with maternal plasma phospholipids, whereas the their LA and LNA precursors are lower (Fig 2).[89] Delta 6 and Δ5 desaturase are both present in placenta, and in ovine placenta Δ6 desaturase activity increases near term.[94,95] The higher DHA and ARA in fetal than maternal plasma may involve selective placental transfer, synthesis in placental or fetal tissues, or selective fetal retention. Current research suggests selective placental transfer of ARA and DHA that involves a multistep process of uptake by membrane-associated proteins with higher affinity and binding capacity for ARA and DHA than for other fatty acids and intracellular translocation by specific cytosolic fatty acid-binding proteins.[96-99] However, despite selectivity in placental n–6 and n–3 fatty acid transport, women with higher plasma ARA and DHA during gestation give birth to infants with higher ARA and DHA, respectively.[89,100,101] This is important because in addition to potential positive effects on fetal growth and neural development,[89,100] a higher n–6 and n–3 fatty acid status at birth does result in higher blood levels of ARA and DHA for several weeks after birth in the infant.[102,103]

Polyunsaturated Fatty Acids in Human Milk

It is well appreciated that fat is the most variable macronutrient in human milk and that the composition of the component fatty acids is also exceedingly variable.[104] Human milk contains more than 150 different fatty acids, of which LA, LNA, ARA, DHA, and several other n–6 and n–3 fatty acids typically make up 15% to 20% of all the fatty acids present. Studies published in the last 5 years show that human milk from women who follow Western diets generally has 10% to 17% LA, 0.8% to 1.4% LNA, 0.3% to 0.7% ARA, and 0.1% to 0.5% DHA.[100,105-112] Studies from other areas of the world show concentrations of DHA as high as 2.8% in human milk in Zhangzi, China,[113] and 1% ARA and 1.1% DHA in the milk of women in Japan,[114] probably explained by a higher intake of 22:6n–3 from fish and seafood among these populations than in North America. Regression analyses and calculation of Pearson correlation coefficients of the change in DHA and ARA in mature human milk from predominantly white women in Vancouver show that DHA has decreased by 50% from 0.4% to 0.2% ($P < .001$), whereas ARA has declined from 0.7% to 0.4% ($P < .001$) over the period from 1988 to 1998 in this segment of the population (Fig 4). A similar decline in human milk DHA in Australia has been reported.[115] Whether this is explained by a decrease in DHA and ARA intake from meat, eggs, and/or fish is not known; current mean intakes among pregnant women in Vancouver are 160 mg/d DHA and 120 mg/d ARA (Fig 3).[116] The maternal plasma phospholipid DHA is significantly and

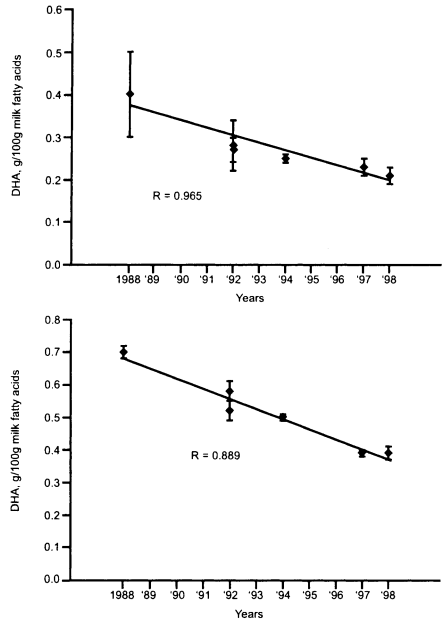

Fig 3. Change in DHA and ARA in mature human milk from predominantly white women who followed North American diets in Vancouver from 1988 to 1998. Data shown are mean ± SEM data for 6 individual studies, representing 240 women. Decrease in DHA and ARA is statistically significant, $P < .001$.

positively correlated with the intake of DHA[116] and with the amount of DHA in human milk.[100,108,109] Higher amounts of DHA in human milk, as can be expected to result in higher plasma and RBC DHA in the breast-fed infant.[100,108,111] Our recent prospective studies have addressed whether the variability in human milk DHA is important for infant visual and neural development. Visual acuity, at 2 and 12 months but not 4 and 6 months, was significantly related to blood lipid DHA at 2 months of age among term breast-fed infants.[117] Infants in the lowest tertile of RBC PE DHA who received milk with 0.17% DHA had significantly lower visual acuity than infants in the highest tertile of RBC DHA who received milk with 0.31% DHA (Fig 4). No relation was found between the infants' ARA or DHA status and scores on the Bayley II mental or motor developmental indexes, novelty preference assessed by the Fagan test, or on a standardized object search task (Piaget A not B). However, the infants' DHA status at 2 months of age was significantly related to the ability to discriminate a nonnative (Hindi) retroflex and dental phonetic contrast at 9 months of age and to language production and comprehension assessed with the CDI at 14 and 18 months of age, after adjusting for confounding variables.[117,118] The RBC PE, RBC PC, and the plasma phospholipid DHA at 2 months of age were all significantly related to the vocabulary comprehension ($r = 0.326$, $P = .01$; $r = 0.359$, $P = .005$; $r = 0.342$, $P = .007$, respectively) and to vocabulary production ($r = 0.367$, $P = .004$; $r = 0.410$, $P = .001$; $r = 0.23$, $P = .05$, respectively) at 18 months of age. A significant association between sweep VEP acuity and human milk DHA was also recently reported in a cross-sectional study of breast-fed infants in Denmark.[110] These

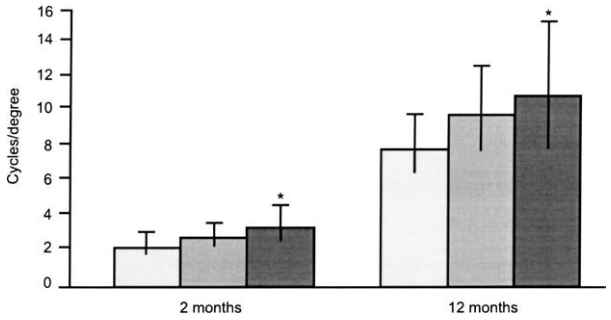

Fig 4. The infants were divided into tertiles of RBC PE DHA (g/100 g fatty acids) at 2 months of age: 6.30 to 8. 54, 8.55 to 10.78, and 10.79 to 13.0. Mean concentration of DHA in mothers' milk for infants in the tertiles was 0.17, 0.22, and 0.31 g/100 g milk fatty acids, respectively. *Visual acuity at 2 and 12 months of age was significantly higher ($P < .05$) among infants in the highest compared with lowest tertile of RBC PE DHA at 2 months of age, when all infants were breast-fed. Adapted from Reference 117.

associations between DHA and visual and neural development in breast-fed infants should not be confused with demonstration of causality; this requires dietary intervention that modifies the intake of DHA but not other nutrients. However, the evidence to show dependence of the fetal and infant DHA on the maternal intake of DHA does raise important questions on the n–3 fatty acid requirements of pregnant and lactating women with respect to supporting optimal visual and neural development in the infant.

Approaches to Assessing Requirement

The rate of nutrient accretion in fetal and infant tissues or the amounts provided by human milk can be used as a guide to estimating nutrient requirements of the preterm infants and term infants 0 to 6 months, respectively. The mean concentrations of DHA in human milk varies >10-fold, and concentrations of ARA vary >3-fold among different populations of women; the variability in milk DHA and ARA among individual women is even greater.[104-115] This raises important questions on how to use information on the composition of human milk fatty acids to estimate fatty acid requirements for infants unless they are accompanied by functional measures of infant development. The fatty acid content of the third trimester human fetus has been estimated from fatty acid analysis of autopsy tissue, data on the weight of the human brain and cerebellum at different stages of development, and tissue weights and fat contents obtained by dissection.[119,120] Accretion, estimated as the mean ±2 SEM, was 67 mg/d n–3 fatty acids, which was mostly DHA, and 552 mg/d n–6 fatty acids.[120] Assuming the preterm infant has an intake of 150 mL/kg per day of milk with 3.7g fat/dL, then the milk fat will need to contain 1.2% DHA and 10% n–6 fatty acids to provide 67 mg DHA and 552 mg n–6 fatty acids to a 1-kg infant. This suggests that preterm infants have high needs for n–6 and n–3 fatty acids, which for n–3 fatty acids could exceed that typically provided by human milk.

In summary, it will be apparent to the reader that progress in the understanding of polyunsaturated fatty acid requirements during growth and development will not be

achieved by descriptive analysis of the variable amounts of n–6 and n–3 fatty acids in human milk, blood, or other tissue lipids. Rather, future advances will benefit from a marriage of new knowledge on the functional roles of DHA and ARA with the application of sensitive tests of neural and retinal function to probe the physiologically important pools of DHA and ARA in developing infants.

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