Importance of arachidonic acid in infant health and development

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INTRODUCTION

The addition of long chain polyunsaturated fatty acids (LCPUFA) to infant formula began over a decade ago. These additions include docosahexaenoic acid (DHA 22:6, n-3) and arachidonic acid (ARA 20:4, n-6). Their inclusion was an important step toward bringing the health and development of formula-fed infants closer to that of their breastfed counterparts. LCPUFA are normal components of cells and are found in particularly high concentrations in nerve cell membranes, including those of the brain and retina (1). Both fatty acids can be formed from shorter chain precursors, but the efficiency of this conversion is highly variable and often inadequate (2-5). Both are rapidly accrued in the central nervous system and retina during the latter part of pregnancy and throughout the first years of life (1, 6).

These nutritionally important LCPUFA arise from two main fatty acid families, the n-3 and n-6 fatty acids. These two families are complex and intertwined both metabolically and functionally. Initially, the fatty acid of interest for infants was DHA and the important function it played in neurological and visual development. However, early research in this area showed that adding DHA alone to formula, particularly for premature infants, carried negative consequences (7-9). These early studies showed that adding DHA and eicosapentaenoic acid (EPA 20:5, n-3) without also adding ARA to infant formula was associated with sub-optimal growth in premature infants. Further research revealed that throughout infancy, blood levels of ARA decrease if formula feeding contains n-3 LCPUFA without ARA (10-13). The initial safety concerns regarding the supplementation of infant formula with n-3 LCPUFA without n-6 ARA caused future studies to focus on inclusion of ARA in any study with supplementation of DHA even though amounts and ratios varied.

ARACHIDONIC ACID: OVERVIEW DURING INFANCY

Human Milk Levels

Arachidonic acid is the primary n-6 LCPUFA in human milk (14). While the levels of DHA can vary widely according to maternal intake, ARA remains relatively constant. In fact, ARA appears to be a protected nutrient in human milk, indicating its importance for the developing infant (14). Breastfeeding of infants by well-nourished mothers is always considered the ideal for providing optimal nutrition. Provisions must be made, however, for infants who do not receive human milk. Therefore, formulation of infant feedings should be designed to provide nutrition as close to human milk as possible.

Blood and Tissue Levels

ARA is a component of all cell membranes, and is found at particularly high levels in neural membranes, including those of the brain. ARA accumulates rapidly in the central nervous system during the last intratriuterine trimester, continuing through the first few years of life. This fatty acid not only plays an essential structural role for neural membrane function, but is also metabolically essential for cells as a precursor and messenger for a variety of biological processes (1). Infants of all ages appear to have the capability to synthesize ARA. Studies using isotope tracers indicate that both preterm and term infants can synthesize ARA from its shorter chain dietary precursor, linoleic acid (2). This endogenous synthesis appears to be sub-optimal, however, and blood and tissue levels drop rapidly following birth unless dietary sources of preformed ARA are supplied (3, 5, 15). Plasma and red blood cell levels of ARA are significantly lower in infants fed formula lacking ARA than in those who are breastfed. Supplementation of formula with preformed ARA is required to achieve plasma and red blood cell levels that are equivalent to those of the breastfed infant (3, 5, 15, 16).

Importance for Growth

Human milk always contains DHA and ARA and healthy breastfed infants represent the standard for ideal growth. In infant formula, the combination of DHA and ARA is known to be safe in preterm and term infants. The combination also supports normal, but not excessive measures of growth including length, weight, and head circumference. A study in preterm infants which measured growth through the first 18 months of life (corrected age), showed that DHA+ARA-supplemented formula, but not unsupplemented formula, supported growth equal to that of breastfed infants (20). Recent meta-analyses of infant formula studies reinforced the safety of DHA+ARA-supplemented formula for growth in term and preterm infants (11, 21).

ARA is one of many nutrients associated with growth. In 1993, Carlson and others reported a significant correlation between the growth and arachidonic acid status in preterm infants (15). In 2002, Innis reported that the level of ARA in blood of preterm infants was positively correlated...
with weight gain prior to hospital discharge and with weight and length at 40, 48, and 57 weeks post-menstrual age (22). Concerns exist regarding the safety of n-3 LCPUFA-supplemented formula not containing ARA due to reports of inadequate growth. Several clinical studies have shown suboptimal growth in preterm infants fed formula containing fish oil with DHA and EPA but no ARA (7-9). While all age groups studied have shown decreases in circulating ARA levels with n-3 LCPUFA supplementation without ARA, preterm infants may be particularly susceptible to growth problems as a result.

In less vulnerable term infants, a meta-analysis of 14 randomized controlled trials failed to find a negative effect of DHA supplementation without ARA on growth (11). However, the study reports that plasma ARA levels decreased by approximately 25% in term infants fed n-3 LCPUFA formula lacking ARA compared to those fed unsupplemented formula. This reduction of plasma ARA in formula-fed term infants may impact processes which are more sensitive to ARA levels than growth, such as immunity and neural development.

Length, weight, and head circumference are the parameters used in the studies mentioned above as determinants of growth. They are standardized and represent the most frequently reported anthropometric measures in children. Bone growth is a less well defined but potentially important aspect of growth that is also affected by LCPUFA during the early life and throughout childhood. At age 4, children who received formula without LCPUFA as infants had poorer visual acuity and verbal IQ scores than those who received DHA and ARA. In fact, only those children who received DHA + ARA supplemented formula had verbal IQ scores equivalent to those who had been breastfed (25).

In an earlier study by Scott and others, negative findings were associated with a formula supplemented with DHA and EPA from fish (tuna) oil without ARA (30). In that study, infants fed the fish oil formula not containing ARA had significantly lower scores on the Vocabulary Production Subscale of the MacArthur Communicative Development Inventories at 14 months compared to infants fed an unsupplemented control formula. The majority of studies examining the effects of LCPUFA on visual and cognitive development utilized formulas supplemented with both ARA and DHA. Many, although not all, showed a benefit of including DHA and ARA in infant formula on visual and neural development. In fact, many now show long-term benefits as the result of including LCPUFA during the early months of life (20, 24, 25, 31). There is, however, very little research available showing long-term effects of LCPUFA formula without added ARA.

**Importance for Neurological Development**

Incorporation of ARA and DHA in neural membranes is important for the developing brain. Numerous studies, although not all, show a difference between LCPUFA-supplemented and unsupplemented formula on neurocognitive development (21). These studies show a positive effect of the combination of DHA and ARA intake on neural development through improved scores on visual, mental, and psychomotor tests (20, 24-28). Although few in number, studies that examined the effect of formula supplemented with DHA without ARA show a negative effect on neural development. In a study by Birch and others, term infants were given test formulas exclusively for the first 17 weeks of life (29). The infants were fed either formula lacking LCPUFA; formula supplemented with DHA only; or formula supplemented with DHA + ARA. Groups were compared to infants who were exclusively breastfed. At 18 months, the authors found a significant increase in scores on the Bayley Mental Development Index (MDI) in infants fed a formula containing DHA + ARA compared to those fed unsupplemented formula. The infants who had been fed DHA-only formula had MDI scores that were greater than control but lower than the DHA + ARA group, although not statistically different from either. Furthermore, the MDI score of infants fed DHA + ARA formula were equivalent to those of breastfed infants. Most important, the benefits of DHA+ARA supplementation continued beyond the initial period of supplementation into childhood. At age 4, children who received formula without LCPUFA as infants had poorer visual acuity and verbal IQ scores than those who received DHA and ARA. In fact, only those children who received DHA + ARA supplemented formula had verbal IQ scores equivalent to those who had been breastfed (25).

In two studies by Field and others (34, 35), the authors found that adding DHA and ARA to preterm formula resulted in immune outcomes more similar to and consistent with those of breastfed infants. A separate lab reported a lower incidence of respiratory illness in infants supplemented with LCPUFA as compared to controls (36).

**Recommendations for Infant Formula**

Expert groups and authoritative bodies who have evaluated the literature for LCPUFA requirements during infancy recommend the addition of ARA to formula whenever DHA or other LCPUFA are added. They also recommend a balance of n-6 to n-3 fatty acids overall. The International Expert Group representing the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommend that whenever DHA is added to an infant formula, ARA also be added in at least an equal amount (37). The latest version of the Codex Committee on Nutrition and Foods for Special Dietary Uses defines, in its standards for infant formula, the addition of ARA should reach at least the same concentration as DHA when added to infant formula (38). The recently published European Commission Directive on Infant Formula and Follow-on Formula also requires the addition of n-6 LCPUFA (ARA) in at least an equal amount as DHA (39).

**SUMMARY**

DHA and ARA are considered conditionally essential nutrients during early life and are related to cognitive, visual and immune development during infancy and throughout childhood. Human milk always contains both DHA and ARA. DHA + ARA- supplemented formula raises plasma and red blood cell concentrations of DHA and ARA in infants to levels comparable to those of breastfed infants. The consequences of supplementation of infant formula with DHA alone include suboptimal growth in preterm infants, and lower neurocognitive scores in term infants and beyond. As a precursor for eicosanoids and cell messengers, ARA plays an important role in immune development. The addition of ARA to...
Nucleotides in infant nutrition: an update

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ABSTRACT

Infants are at higher risk for morbidity resulting from infectious diseases, due in part to immaturity of their immune system. Immune modulators in human milk explain some of the protective effects of mother milk. One of those is Nucleotides (NT). NT and their related products play key roles in many biological processes. They play a role in the development, maintenance and function of the gastrointestinal and immune systems. Studies of compromised or normal term and preterm babies, fortified by NT, showed beneficial effect on cellular and humoral immunity and morbidity. It seems that there is a clinical dose response effect and mainly the disadvantaged infants benefit the most. NT provide scientific evidence to justify their addition to breast milk substitutes.

INTRODUCTION

Nucleotides (NT) are ubiquitous component in human milk and are crucially important to fundamental cellular metabolism and functions. When the body needs are greater than the amounts of NT synthesized or salvaged, the term semiessential or conditionally essential nutrients can be applied. Rapid growth, certain disease states, low nutrient intake or disturbed endogenous synthesis represent such conditions. Infant formulas are continuously modified as new scientific evidence about nutrient needs of the baby become available. The field of immunonutrition is expanding and NT is only one on the list. In the last years, several infant manufacturers

LCP(U)A-supplemented formula is recommended by most expert and authoritative bodies in an effort to ensure that commercially available infant formula provides health benefits closer to those of breast milk.

REFERENCES AND NOTES