ESSENTIAL FATTY ACIDS AND BRAIN DEVELOPMENT

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Summary

There is a need to determine whether there is a dietary requirement for docosahexaenoic acid (DHA, 22:6ω3) by term infants to achieve their full developmental potential. Studies of brain fatty acid composition have demonstrated that infants who were breast fed have greater levels of cerebral cortex DHA than infants who were formula fed, suggesting that DHA in the cerebrum is dependent on a supply in the diet. Some physiological studies report that electrophysiological and behavioural assessments of visual function are improved in breast fed infants relative to those fed formula and that this is related to the length of breast feeding. Randomised studies of DHA supplementation of infant formula demonstrate that the visual function of formula fed infants can be improved to breast fed levels by adding DHA to formula. Further work is necessary to establish if there are long term benefits of dietary DHA to the term infant.

I. INTRODUCTION

Breast milk is the perfect food for the young growing infant with all nutrients in an ideal balance (Neuringer et al. 1988; Clark et al. 1992; Makrides et al. 1993a; Van Aerde and Clandinin 1993; Gibson et al. 1994). Despite recommendations from health professionals and learned committees (Scientific Review Committee 1990; ESPGAN Committee on Nutrition 1991), only about 75% of Australian mothers are discharged from birth centres breastfeeding their infants. Difficulties in maintaining lactation in the home results in a rapid decline in breast feeding rates so that by six months less than 30% of those who start out, successfully maintain breast feeding their infants (Retallack et al. 1994).

Infant formulas are the only recommended alternative to breast milk. Since breast milk is a living tissue containing in addition to basic nutrients a range of cells and important immunoglobulins, it is not possible to exactly duplicate breast milk and provide it in an easily stored form (dry powder) that can be reconstituted at will. Approximations have been made by manufacturers that reflect the reality of stability, bioavailability and cost. Examples of the approximations made by manufacturers include the proteins, the mineral iron and fats. The composition of the constituent amino acids of skim milk protein varies significantly from human milk necessitating cows milk proteins being added at a higher level (≈1.5%) than the level found in human milk (≈1 %). Iron (Fe) is present in very low levels in human milk (≈l mg/L) but is extremely well absorbed (>50%). The only forms of iron that are stable in dry powder form tend to be poorly absorbed (< 10%) necessitating iron being added at many times (14 mg/L) the level found in human milk. The fats of human milk reflect those found in human plasma and provide a complex mixture of fatty acids including the essential 18 carbon polyunsaturates and many long chain (20 and 22 carbon) polyunsaturates (LCPUFA) that are proving to have important biological activity. In contrast, infant for

Despite the compromises made by manufacturers, infant formulas provide the growing infant with a basic level of nutrition that results in growth rates which are as good as or better than those observed in breast fed infants. It has only been since neuro-physiological end points have been used that deficiencies/limitations in the fat supply of formula fed infants has become apparent.

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In the past, dietary fat was considered mainly as a source of energy required by the baby to support rapid growth. It is now realised that the quality and composition of fat supplied to the infant has important effects on developing organs, especially the brain. Of particular interest are the results of research on the roles of two LCPUFA known as docosahexaenoic acid (DHA) and arachidonic acid (AA), which are leading to new concepts in the dietary fatty acid requirements of infants.

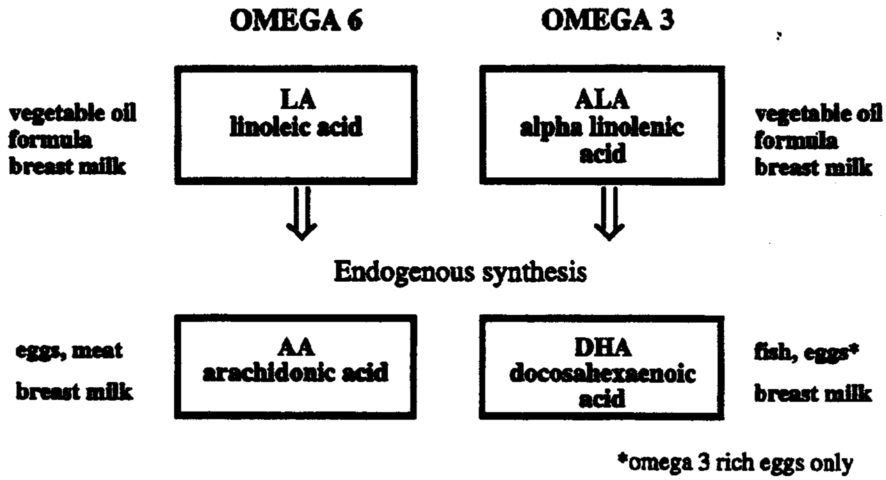

Figure 1. Sources of long chain polyunsaturated fatty acids in infant nutrition

II. THE ROLE OF LONG CHAIN POLYUNSATURATES

It has been known for many years that an adequate supply of the two essential fatty acids (EFA), alpha-linolenic acid (ALA) and linoleic acid (LA), are important in infant formula and all infant formulas in Australia contain vegetable oils that are rich in EFA. Health workers around the world came to assume that because most infant formulas contain levels of ALA and LA in excess of those found in breast milk and adequate growth rates were achieved, there was little to choose between breast milk and infant formulas. However, it is now realised that it is not enough to only measure growth - it is also important that a measure of mental and physical development is obtained to fully assess the well being of an infant.

a) Infant formulas containing only ALA and LA may not be nutritionally complete.

(i) Biochemical evidence Studies comparing breast and formula feeding indicate that formula fed infants have less DHA and less AA in their cells relative to breast fed infants (Clark et al. 1992). This was shown to be due in part to an imbalance in the ratio of the two EFA, ALA and LA. However, studies that have tried to increase the availability of ALA to formula fed infants demonstrate that it is only possible to increase DHA levels to 80% of those of breast fed infants (Clark et al. 1992). These results suggest that it is not completely possible to totally correct the balance of DHA and AA in formula fed infants by altering only the balance of vegetable oils in formula. In other words, supplies of DHA and AA are required to be present in formula.

(ii) Physiological evidence. We have examined the visual evoked potentials (VEP) of healthy term infants fed either breast milk or formula from birth. The VEP is a measure of the ability of the brain to respond to a visual stimulus - alternating checkerboard patterns of different sizes displayed on a video monitor. As VEP acuity improves with age, it is often used as an index of neural maturity of a baby. Formula fed infants were found to have low DHA levels and reduced visual acuity while breast fed infants had high DHA levels and better acuity (Makrides et al. 1993b). Thus babies who had received DHA from breast milk had more mature responses than those who had received formulas that do not contain LCPUFA.

We have recently investigated whether the differences between breast and formula fed term infants could be corrected by the addition of fish oil, (a source of DHA) to infant formula (Makrides et al. 1995). In a study involving over 70 term infants VEP acuity in breast fed and fish oil supplemented formula infants was better than in standard formula fed infants at both 16 and 30 weeks of age. Blood cell DHA in breast and fish oil-supplemented infants was maintained near birth levels for the entire 30 week study period, but was reduced in infants receiving standard formula. Furthermore VEP acuity was better in the infants getting the supplemented formula or breast milk. These results are supported by clinical studies in preterm babies carried out overseas (Uauy et al. 1990; Birch et al. 1992; Birch et al. 1992; Carlson et al. 1993).

Most importantly, our data established that VEP acuity was related to the length of breast feeding. Infants breast fed for less than 16 weeks had erythrocyte DHA levels intermediate between those fed breast milk continuously and those fed formula from birth when measured at 16 weeks of age (Figure 2). Furthermore, when infants were measured at 30 weeks of age only those who had

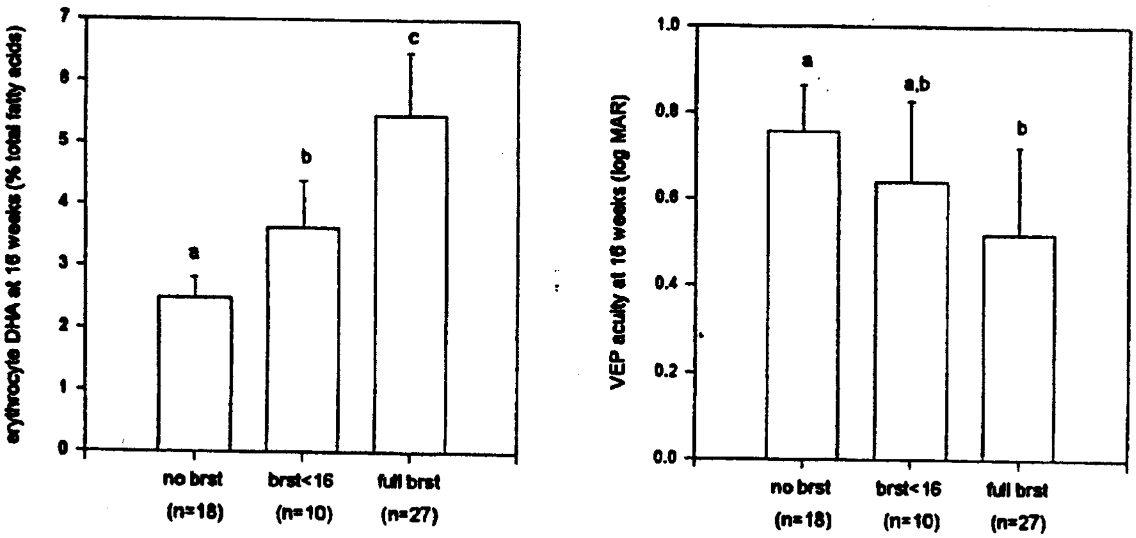

Figure 2: Effect of breast feeding duration on erythrocyte DHA ± SD (left) and VEP acuity ± SD (right) at 16 weeks of age. For erythrocyte DHA, values without a common superscript are significantly different at $P<0.0001$. VEP acuity is expressed as logMAR (log of the minimum angle of resolution) and values without common superscripts indicate significant differences at $P<0.0005$.

received DHA for at least 16 weeks had VEP acuity scores comparable to those who had been breast fed for the entire 30 weeks (Figure 3). The VEP acuity scores of those breast fed for less than 16 weeks were not different to those formula fed from birth (Figure 3). Taken together the data indicate a need for a continuous supply of LCPUFA from breast milk for at least the first four months of life.

The growth of all infants was similar. Erythrocyte AA in fish oil supplemented infants was reduced below standard formula levels and this was probably due to the high levels of some other fatty acids (such as eicosapentaenoic acid, EPA) found in the fish oil used. This is of some concern as other studies involving preterm infants suggest that AA is important to some aspects of neural function and growth.

Our results suggest that DHA levels and one aspect of neural performance of formula fed infants can be normalised to breast fed levels following supplementation with fish oil. However the suppression of erythrocyte AA levels associated with the use of fish oil as the ω3 supplement is undesirable. Thus there is a need for a blend of fatty acids in a similar balance to breast milk, that can be safely added to formulas.

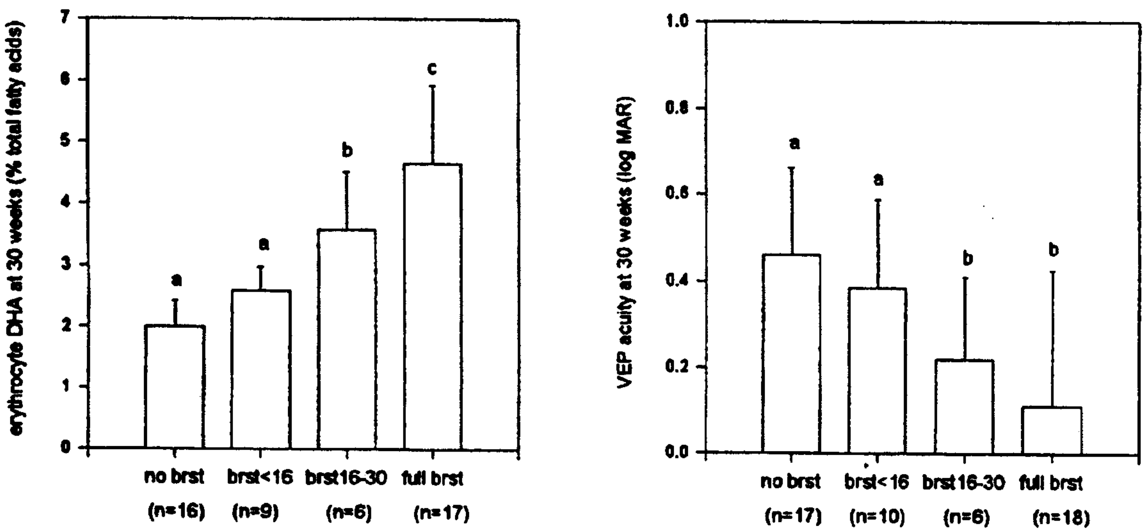

Figure 3: Effect of breast feeding duration on erythrocyte DHA ± SD (left) and VEP acuity ± SD (right) at 30 weeks of age. For erythrocyte DHA, values without a common superscript are significantly different at $P<0.0001$. VEP acuity is expressed as logMAR (log of the minimum angle of resolution) and values without common superscripts indicate significant differences at $P<0.001$.

III. DIETARY DHA ALTERS BRAIN COMPOSITION

Levels of LCPUFA in brains of young animals can be dramatically raised or lowered by feeding diets with a surplus or a deficiency of dietary fish oil (Neuringer et al. 1991). The relationship between brain fatty acids and diet in human infancy has also been studied. Breast fed infants (receiving DHA and AA) have a greater proportion of DHA in their brain cortex relative to those fed formula and this is largely an effect of length of feeding (Makrides et al. 1994). These new observations indicate that there is a real effect of diet on brain DHA composition and most importantly, the evidence suggests that if it is provided, DHA can accumulate for at least the first year of life. These results generally support the functional studies described above. In contrast, there are no differences in the level of brain AA between breast and formula fed infants. This suggests that either AA is aggressively conserved in brain tissue or that the amount of AA produced from the precursor (LA) in formula is sufficient to meet the AA requirements of the rapidly growing brain.

IV. LONG TERM OUTCOME

There are some tantalising clues that suggest that early nutrition is related to long term outcome. Barker's group have reported that nutritional stress before the baby is born can be a determinant in adult cardiovascular disease (Barker 1993; Fall et al. 1995) and the work of Lucas suggests that breast milk consumption by preterm infants for the first four weeks of life is related to improvements in IQ at 7-8 years (Lucas et al. 1992). In the absence of additional information, it must be assumed that a supply of LCPUFA such as DHA and AA are important since they accumulate in the brain when provided and they are present in the food that was designed by nature for babies - breast milk.

V. INDUSTRY RESPONSE

To date, two formula manufacturers have released formulas containing long chain polyunsaturates. The Milupa company (Germany) has released both a preterm and term formula containing the long chain polyunsaturates AA and DHA while Nestle (Switzerland) has released a formula containing a mixture of AA and DHA in a preterm formula. Both companies have used a phospholipid fraction isolated from egg yolks as a source of AA and DHA. However, the AA and DHA of breast milk fats is in the form of triglycerides (oils), so although these formulas contain LCPUFA in about the amounts found in breast milk they are in a different form. They are apparently stable to oxidation in powder form but increase the level of phosphorus and choline (from the phospholipid) in the formula. Experimental batches of formulas with fish oils as sources of long chain polyunsaturates have proven to be unstable in dry powder form.

The addition of long chain polyunsaturates to formulas has been recommended by authorities in Europe (ESPGAN Committee on Nutrition 1991), Canada (Scientific Review Committee 1990) and are to be included in the new R7-Infant Formula guidelines currently being rewritten by the National Food Authority. The question to be addressed is whether there are proven benefits of long chain polyunsaturates in the diet or whether there is a sufficient body of evidence supporting their inclusion in the diet of infants.

VI. CONCLUSIONS

Despite numerous papers in support of the relative advantages of breast feeding over formula feeding, there is no direct proof (Lanting et al. 1994; Temboury et al. 1994), nor is there direct proof of the advantages of long chain polyunsaturates in the diets of infants whether they are supplied in the form of breast milk or formulas supplemented with various fats. However, the case for the advantages of diets containing long chain polyunsaturates (breast milk, supplemented formula) over diets devoid of these compounds is strong and can be summarised as follows:

1. Long term follow-up studies have demonstrated neurological and intellectual advantages for infants who received breast milk early in life over those who received standard formula (Lanting et al. 1994; Temboury et al. 1994).
2. Better neuro-physiological functions such as electro-retinogram (ERG), visual evoked potential (VEP) and behavioural visual acuity (Forced Choice Preferential Looking) and the Bayley Developmental Test have been consistently reported for infants receiving long chain polyunsaturates such as DHA (Uauy et al. 1990; Birch et al. 1992; Birch et al. 1992; Carlson et al. 1993; Makrides et al. 1993c). These results are confirmed by primate studies (Quackenbush et al. 1942; Neuringer et al. 1991).
3. The brains of infants fed long chain polyunsaturates (breast milk) contain higher levels of DHA than infants fed standard unsupplemented formulas (Makrides et al. 1994).
4. No ill effects or growth problems were reported in an Australian clinical trial involving healthy term infants receiving long chain polyunsaturates in the form of a blend of fish oil and evening primrose oil (Makrides et al. 1995) or in a group of preterms supplemented with fish oil (Uauy et al. 1994).

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