

Invited commentary

Modelling human infant requirements for long-chain polyunsaturated fatty acids

Linoleate (18:2 n -6) and α -linolenate (18:3 n -3) are generally recognized as essential nutrients in the mammalian diet. However, whether linoleate and α -linolenate are able to meet the requirement for long-chain polyunsaturated fatty acids during early postnatal development is currently under debate. Regulatory agencies in different countries have different views on whether the major long-chain polyunsaturates, arachidonate (20:4 n -6) and docosahexaenoate (22:6 n -3), should be included in milk formulas. Low tissue levels of docosahexaenoate are well recognized as impairing visual and neurological development. Low tissue levels of arachidonate are associated with retarded somatic development. A growing body of evidence indicates that, in particular, α -linolenate alone cannot adequately meet the requirement of human infants for docosahexaenoate.

Two general models have predominated in the development of the evidence concerning possible inclusion of long-chain polyunsaturates in infant formulas. One such general model employs human blood, milk or tissue samples while the other employs samples from various sub-human species; fewer samples, especially tissues, are available from humans but sub-human species do not always reliably model human development. Both general models have relied heavily on correctly interpreting fatty acid profiles as a measure of the adequacy of accumulation of arachidonate and docosahexaenoate in organs such as the human brain. The aim of this commentary is briefly to put these two models into perspective relative to the challenge of demonstrating adequacy or inadequacy of tissue accumulation of long-chain polyunsaturates as it relates to early human somatic and neurological development.

Quite a number of studies have reported plasma and/or erythrocyte fatty acid profiles obtained from human infants consuming breast milk or different formulas. In general, plasma or erythrocyte arachidonate and docosahexaenoate levels fall postnatally regardless of feeding type but they fall less on breast milk or on formulas containing arachidonate and docosahexaenoate than on formulas only providing linoleate and α -linolenate (Innis, 1992; Hamosh & Salem, 1998). By themselves, these differences and trends in blood fatty acid profiles do not necessarily prove that the tissue status of long-chain polyunsaturates is impaired when arachidonate and docosahexaenoate are not provided in the milk formula. Rather, this depends on demonstrating that tissue levels of these fatty acids are also proportionately low when docosahexaenoate and arachidonate are not provided in the diet. In fact, brain, liver and adipose tissue fatty acid profiles have been described for infants

consuming breast milk or formulas providing only linoleate and α -linolenate (Farquharson *et al.* 1992; Makrides *et al.* 1994). From this work, it seems clear that brain levels of docosahexaenoate found in breast-fed infants cannot be sustained in formula-fed infants under 6–12 months old unless pre-formed docosahexaenoate is provided. Interestingly, brain arachidonate levels are not as susceptible to depletion in the absence of dietary arachidonate. Despite this unique and valuable information from infant autopsy specimens, these were still two small studies that urgently need confirmation by other researchers.

Until more human tissue data are published, animal models will still provide important data regarding the link between dietary intake of long-chain polyunsaturates, tissue levels and behavioural and developmental measures. Recent studies, including the one by Rooke *et al.* (1999) in this issue of the Journal, indicate that plasma, umbilical cord and erythrocyte values for arachidonate and docosahexaenoate in newborn piglets and in more mature miniature swine are poorly correlated to those in the brain (Rioux *et al.* 1997; Berlin *et al.* 1998).

The study by Rooke *et al.* (1999) compared the effects of tuna and soyabean oil given during late pregnancy on fatty acid profiles of piglet organs at birth. Tuna oil increased brain weight at birth but did not affect body or other organ weights. In comparison with soyabean oil, tuna oil also increased long-chain n -3 polyunsaturates in various organs including brain. Nevertheless, the arachidonate and docosahexaenoate content of the brain was poorly correlated to umbilical cord or umbilical plasma values. However, erythrocyte levels of docosahexaenoate have been positively correlated to brain docosahexaenoate in human infants (Makrides *et al.* 1994). This lack of agreement between data from the human infant and the piglet model is disappointing from a modelling perspective. However, perhaps it is partly explained by the fact that docosahexaenoate accumulation in the brains of the formula-fed infants was impaired by 21% over 40 weeks postnatally, whereas the piglets in the study by Rooke *et al.* (1999) were studied at birth. One potential confounder in the piglet model is that piglet brain growth is relatively slow near term and in the first 2 weeks of postnatal life (Sweasey *et al.* 1976), a factor that probably influences the rate of brain fatty acid accumulation and, thus, the relationship to dietary or blood fatty acid profiles. Hence, it is not clear that studying the piglet very early postnatally actually gives useful information about the adequacy of brain levels of long-chain polyunsaturates in human infants on different intakes of polyunsaturates.

This returns us to the initial predicament of how best to determine the degree to which an infant's requirement for polyunsaturated fatty acids is being met. It may indeed still be possible to choose an animal model that mimics human infants and determine the relationship between dietary, blood and brain fatty acid profiles relative to appropriate developmental indices. However, better human data rather than more animal data are likely to be more persuasive for convincing regulatory agencies to include arachidonate and docosahexaenoate in human milk formulas. A scattered literature on infant growth rate, organ weights, and organ and milk fatty acid concentrations and profiles does exist but needs updating and more complete information from individual infants.

We have collected this information together with the aim of estimating docosahexaenoate accumulation and apparent requirement during early postnatal life. We have reported in preliminary form that the whole human infant accumulates about 10 mg/d of docosahexaenoate during the first 6 months of life. Accounting for obligatory losses, this rate of accumulation would require a docosahexaenoate intake of about 20 mg/d (Cunnane *et al.* 1999), an amount that appears to be easily met by breast milk containing docosahexaenoate at least 0.2% of fatty acids (which is the case in the majority of reports thus far; Hamosh & Salem, 1998). However, to achieve that rate of docosahexaenoate synthesis in infants not receiving pre-formed docosahexaenoate would require about a 5% conversion rate of dietary α -linolenate, a rate that markedly exceeds anything reported for humans, rats or primates. The apparent inability to synthesize sufficient amounts of docosahexaenoate from α -linolenate probably accounts for the low brain accumulation of docosahexaenoate in infants not given dietary docosahexaenoate, regardless of either docosahexaenoate stores in body fat at birth, or α -linolenate intake.

In conclusion, some countries have accepted that sufficient evidence already exists for listing arachidonate and docosahexaenoate as conditionally essential nutrients and including them in infant formulas. To make this argument more persuasively in countries that have not yet adopted this position, I believe that more comprehensive human infant autopsy data and fatty acid profiles will provide the necessary evidence to remove any residual doubts about the need

for inclusion of arachidonate and docosahexaenoate in infant formulas.

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References

- Berlin E, Bhathena SJ, McClure D & Peters RC (1998) Dietary menhaden and corn oils and the red cell membrane lipid composition and fluidity in hyper- and normocholesterolemic miniature swine. *Journal of Nutrition* **128**, 1421–1428.
- Cunnane SC, Francescutti V, Brenna JT & Crawford MA (1999) Whole body fatty acid accumulation data suggest that without pre-formed dietary docosahexaenoate, the formula-fed infant cannot meet its docosahexaenoate requirement. *Proceedings of the Nutrition Society* (In the Press).
- Farquharson J, Cockburn F, Patrick WA, Jamieson EC & Logan RW (1992) Infant cerebral cortex phospholipid fatty acid composition and diet. *Lancet* **340**, 810–813.
- Hamosh M & Salem N (1998) Long chain polyunsaturated fatty acids. *Biology of the Neonate* **74**, 106–120.
- Innis SM (1992) Plasma and red blood cell fatty acid values as indexes of essential fatty acids in the developing organs of infants fed with milk or formulas. *Journal of Pediatrics* **120**, S78–S86.
- Makrides M, Neumann MA, Byard RW, Simmer K & Gibson RA (1994) Fatty acid composition of brain, retina and erythrocytes in breast- and formula-fed infants. *American Journal of Clinical Nutrition* **60**, 189–194.
- Rioux FM, Innis SM, Dyer R & MacKinnon M (1997) Diet-induced changes in liver and bile but not brain can be predicted from differences in plasma phospholipid fatty acids in formula- and milk-fed piglets. *Journal of Nutrition* **127**, 370–377.
- Rooke JA, Bland IM & Edwards SA (1999) Relationships between fatty acid status of sow plasma and that of umbilical cord, plasma and tissues of newborn piglets when sows were fed on diets containing tuna oil or soyabean oil in late pregnancy. *British Journal of Nutrition* **82**, 213–221.
- Sweasey D, Patterson DSP & Glancy EM (1976) Biphasic myelination and the fatty acid composition of cerebroside and cholesterol esters in the developing central nervous system of the domestic pig. *Journal of Neurochemistry* **27**, 375–380.