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BRAIN RESEARCH

Review

Dietary omega 3 fatty acids and the developing brain

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ARTICLE INFO

Article history:
Accepted 22 August 2008
Available online 9 September 2008

Keywords:
Omega 3 fatty acid
Docosahexaenoic acid
Brain development
Dietary fatty acid
Maternal nutrition
Infant nutrition

ABSTRACT

The ω-3 fatty acids are essential dietary nutrients and one of their important roles is providing the fatty acid with 22 carbons and 6 double bonds known as docosahexaenoic acid (DHA) for nervous tissue growth and function. Inadequate intakes of ω-3 fatty acids decrease DHA and increase ω-6 fatty acids in the brain. Decreased DHA in the developing brain leads to deficits in neurogenesis, neurotransmitter metabolism, and altered learning and visual function in animals. Western diets are low in ω-3 fatty acids, including the 18 carbon ω-3 fatty acid alpha linolenic acid found mainly in plant oils, and DHA, which is found mainly in fish. The DHA status of the newborn and breast-fed infant depends on the maternal intake of DHA and varies widely. Epidemiological studies have linked low maternal DHA to increased risk of poor child neural development. Intervention studies have shown improving maternal DHA nutrition decreases the risk of poor infant and child visual and neural development. Thus, sufficient evidence is available to conclude that maternal fatty acid nutrition is important to DHA transfer to the infant before and after birth, with short and long-term implications for neural function. However, genetic variation in genes encoding fatty acid desaturases also influence essential fatty acid metabolism, and may increase requirements in some individuals. Consideration of ω-3 fatty acid to include brain development, optimizing ω-3 and ω-6 fatty acids in gestation and lactation, and in fatty acid nutrition support for intravenous and formula-fed neonates is important.

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doi:10.1016/j.brainres.2008.08.078

1. Introduction

The long chain ω-3 fatty acid with 22 carbons and 6 double bonds known as docosahexaenoic acid (DHA) is the most abundant ω-3 fatty acid in the mammalian central nervous system, and is specifically concentrated in membrane lipids of brain grey matter and the visual elements of the retina. The levels of DHA in the brain increase during development (Martinez 1992; Svennerholm 1968) and decrease with aging (Guisto et al., 2002; Rotstein et al., 1987; Soderberg et al., 1990), and both the retina and brain levels of DHA are altered by the dietary ω-3 and ω-6 fatty acid supply (Innis, 1991, 2005a). Epidemiological and intervention studies have linked low plasma and blood cell lipid DHA to increased risk of poor visual and neural development in infants and children (Bouwstra et al., 2003; Dunstan et al., 2006; Helland et al., 2003; Hibbeln et al., 2007; Innis and Friesen, 2008; Innis et al., 2001; Oken et al., 2005; Uauy and Danqour, 2006; Williams et al., 2001), and to an increased risk of dementia and cognitive decline in older individuals (Dullemeijer et al., 2007; Kalmijn et al., 2004; Morris et al., 2003; Nurk et al., 2007; Schaefer et al., 2006; Van Gelder et al., 2007). A growing body of information now provides cause to carefully weigh the possibility that dietary fatty acids, potentially influenced by genetic variation in fatty acid metabolism, contribute to poor central nervous system (CNS) functioning in infants and children, and do so with long-lasting sequelae. Understanding the importance of dietary ω-3 fatty acids in contributing to human CNS development, however, is challenging because of the complexity of fatty acid metabolism, and incomplete knowledge of the pathways of transfer and fatty acid uptake in the brain, and the functional roles of DHA. This review aims to provide a background on ω-3 fatty acids and current knowledge relating early fatty acid nutrition to cognitive and behavioral development.

2. Dietary omega 3 fatty acids and their metabolism

Unsaturated fatty acids are classified by the position of the first double bond from the methyl end (ω) of the fatty acid carbon chain, while the desaturase enzymes are denoted by the carbon counting from the carboxyl end (Δ) at which hydrogen atoms are removed to create the carbon–carbon double bond (Fig. 1). Because animals lack a Δ-15 or Δ-12 desaturase, they are unable to form ω-3 or ω-6 fatty acids *de novo* and must obtain these fatty acids from their diet (Innis, 2003). Humans and other animals obtain DHA either as the 18 carbon chain precursor α-linolenic acid (18:3ω-3), or as DHA itself and intermediates between 18:3ω-3 and DHA, notably eicosapentaenoic acid (20:5ω-3), usually abbreviated as EPA (Fig. 2). However, DHA not 18:3ω-3 or 20:5ω-3, is the major ω-3 fatty acid esterified in the glycerophospholipids that form the structural matrix of brain grey matter and retinal membranes (Guisto et al., 2002; Sastry, 1985). DHA accumulation in the brain and retina, as in other organs, depends on the amount and types of ω-3 fatty acids in the diet, and on dietary intake of ω-6 fatty acids which interact and compete with ω-3 fatty acids in the fatty acid metabolic pathway (Arbuckle et al., 1994; Bourre et al., 1989, 1990; Galli et al., 1971; Hrboticky et al., 1990, 1991; Innis, 1991; Neuringer et al., 1986). Central questions in human nutrition are which and how much of the different ω-3 fatty acids are needed in the diet, and whether the current high intakes of ω-6 fatty acids, or low intakes of ω-3 fatty acids contribute to poor infant neural development and function.

Synthesis of DHA occurs in phytoplankton and animals, but not plants (Fig. 2). This means that DHA is absent from foods of plant origin, including vegetable fats and oils, grains, nuts and seeds. However, DHA is present in animal tissue lipids, with the richest dietary source being fatty fish (Chow, 2000). The meat and milk of ruminants also contain very low amounts of DHA. The 18 carbon ω-3 fatty acid 18:3ω-3 is also relatively sparsely distributed in foods, with higher levels in soybean, canola and flax seed oils, but common oils such as corn oil, safflower oil, sunflower oil and olive oil all contain<1% 18:3ω-3. The 18 carbon ω-6 fatty acid, linoleic acid (18:2ω-6) is the precursor of the ω-6 fatty acids and is abundant in modern food supplies, with over 50% of all the fatty acids in soybean, corn, safflower and sunflower oils being 18:2ω-6.

Once obtained from the diet, 18:3ω-3 can be further metabolized by Δ-6 desaturation, elongation and Δ-5 desaturation to 20:5ω-3, while 18:2ω-6 is metabolized using the same enzymes to the 20 carbon chain ω-6 fatty acid, arachidonic

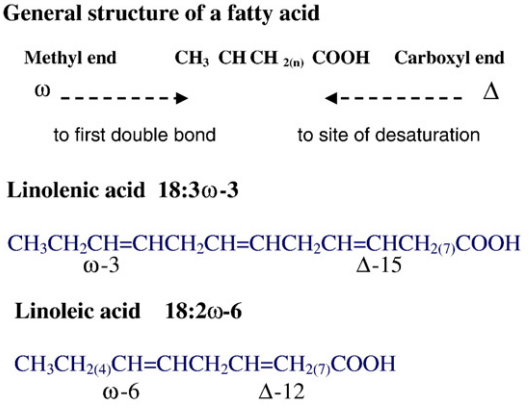

Fig. 1 – Schematic of the general structure and nomenclature of fatty acids. Fatty acids are denoted by the number of carbons:number of double bonds and position of the first double bond from the methyl end. Desaturase enzymes are denoted by the carbon at which they introduce double bonds from the carboxyl end. Humans and other animals lack Δ-15 and Δ-12 desaturase.

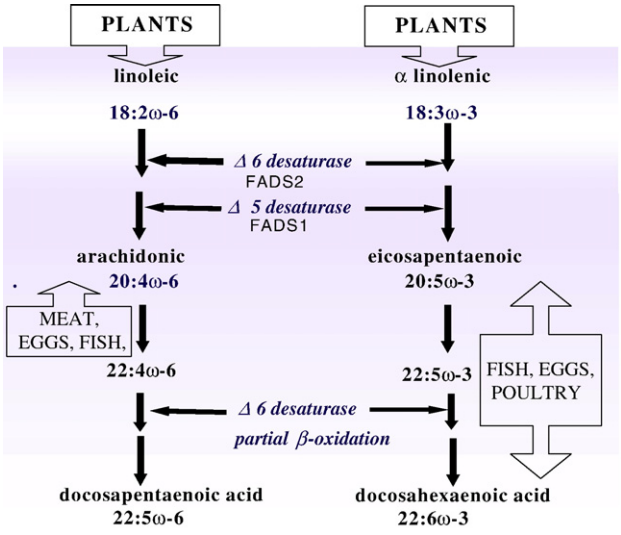

Fig. 2 – Schematic of the desaturation and elongation of essential fatty acids. The desaturase enzymes Δ-6 and Δ-5 desaturase introduce a double bond at carbon 6 or 5, respectively, from the carboxyl end of the fatty acid and are encoded by the genes FADS2 and FADS1, respectively. The major dietary source of the 18 carbon linoleic acid and α-linolenic acid is vegetable oils. The 20 and 22 carbon fatty acids including DHA are synthesized in animal tissues.

acid (20:4ω-6) (Innis, 2003, Fig. 2). The pathway generally accepted for metabolism of 20:5ω-3 to DHA involves elongation of the fatty acid carbon chain, then Δ-6 desaturation to form 24:6ω-3, which is then chain-shortened by 2 carbons to yield DHA, that is 22:6ω-3 (Sprecher et al., 1999). Metabolism of 18:2ω-6 via 20:4ω-6 to 22:5ω-6 uses the same enzymes as those required for the metabolism of ω-3 fatty acids. However, tissue levels of 22:5ω-6 are usually low, but show a characteristic increase in response to dietary ω-3 fatty acid deficiency (Arbuckle and Innis, 1992; Bourre et al., 1989; Galli et al., 1971; Hrboticky et al., 1989; Innis, 1991; Neuringer et al., 1986). In animals, an intake of 1% energy from 18:2ω-6, with an 18:2ω-6/18:3ω-3 ratio of 2:1 or lower, supports high levels of DHA in the developing brain (Bourre et al., 1990; Novak et al.,; Lands et al., 1990), However, high intakes of 18:2ω-6 inhibit desaturation of 18:3ω-3 to 20:5ω-3 and DHA and reduce accretion of DHA in the brain, retina and other organs (Arbuckle et al., 1994; Brenner and Peluffo, 1966; Bourre et al., 1990; Lands et al., 1990; Mohrhauer and Holman 1963; Novak et al., in press; Rahm and Holman, 1964). This means that dietary ω-3 fatty acids, both the amount and type (18:3ω-3 and DHA), and high 18:2ω-6 determine DHA accretion in the developing brain and retina.

Beginning in the 1980s, several studies reported that infants fed formula containing 18:2ω-6 and 18:3ω-3, but not DHA had lower blood levels of DHA and lower visual acuity (Carlson et al., 1996; Makrides et al., 1993; Ponder et al., 1992; Putnam et al., 1982) than breast-fed infants. Together with knowledge that DHA is high in brain lipid, and is present in human milk (Innis, 1992; Jensen, 1999), considerable research began to address whether inclusion of DHA in infant formula increases visual, mental and motor skill development in formula-fed infants (Fewtrell, 2006; Heird and Lapillone, 2005). Autopsy analyses to show lower brain cortex DHA in infants who had been fed formula with no DHA than in infants who had been breast-fed (Farquharson et al., 1995; Makrides et al., 1994) provided important information to show the human brain is not protected from deviations in fatty acid accretion when an inadequate diet is fed. The lower DHA in cortex ethanolamine phosphoglycerides (phosphatidylethanolamine plus ethanolamine plasmalogen, EPG) of formula-fed infants was accompanied by higher 22:4ω-6 and 22:5ω-6 (Farquharson et al., 1995), showing metabolic capacity for fatty acid desaturation, and a pattern of decreased DHA and increased ω-6 fatty acids similar to that in animals fed milk diets deficient in ω-3 fatty acids, or high in 18:2ω-6 (Arbuckle et al., 1994; Hrboticky et al., 1990; Novak et al.,). At that time, infant formulas had no DHA and had 8 to over 25% energy from 18:2ω-6 (Farquharson et al., 1995; Makrides et al., 1994; Ponder et al., 1992; Putnam et al., 1982). Formulas containing corn oil (which has over 50% 18:2ω-6 and less that 1% 18:3ω-3) led to marked deficits in DHA accretion in brain, brain synaptic membranes and retina of colostrum-deprived, formula-fed piglets (Hrboticky et al., 1989, 1990, 1991), and deficits in retinal function and visual acuity in infants (Birch et al., 1992). These studies show that lipid nutrition with very high ω-6 fatty acids and low in ω-3 fatty acids do not support biochemical and functional development of the central nervous system.

DHA for brain growth and development is provided by placental transfer of ω-3 fatty acids before birth and in breast milk after birth (Innis, 2004, 2005b), meaning that consideration of the effect of the maternal diet and metabolism must be considered. Several studies have shown that conversion of stable-isotope-labeled 18:3ω-3 to DHA is low in adults and infants, with a possible increase in some pregnant women (Carnielli et al., 2007; Goyens et al., 2005; Pawlosky et al., 2001; Uauy et al., 2000; Williams and Burdge, 2006). However, supplementation with 18:3ω-3 during pregnancy does not increase DHA in maternal or newborn infant blood lipids (de Groot et al., 2004), and in lactation, has no measurable effect on the secretion of DHA in breast milk (Innis, 2004). Higher amounts of 18:3ω-3 in infant formula also fail to increase circulating levels of DHA in formula-fed infants (Ponder et al., 1992). DHA is required for membrane synthesis and turnover and dietary intakes of DHA, but not 18:3ω-3, are positively related to blood levels of DHA in pregnant women, to DHA levels in breast milk, and to DHA in the blood lipids of breast-fed infants (Gibson et al., 1997; Innis, 2005b; Innis et al., 1996; Jensen et al., 2005; Reddy et al., 1994; Sanders et al., 1978). However, extensive work over several decades on dietary 18:2ω-6 and 18:3ω-3 intakes and their metabolism in animals indicate that the fatty acid desaturation pathway is saturated when 18:2ω-6 intakes exceed 3% energy. Current western diets, human milk and infant formulas now provide more than 3% energy from 18:2ω-6, which suggests circulating and tissue levels of DHA will be low unless DHA is provided.

3. Dietary omega 3 fatty acids intakes

The types of fats in human diets has changed remarkably over the last century, driven in part by efforts to lower plasma

cholesterol by replacing dietary saturated fatty acids with vegetable oils rich in 18:2ω-6 (Kritchevsky, 1998). The implications of increasing ω-6 fatty acids on ω-3 fatty acid metabolism or neural function were not considered. Prior to the 1970s, fatty acid analyses were often limited to wide-bore chromatography columns, and little information is available on DHA. Extrapolation from the food supply and dietary intake data suggest 18:2ω-6 provided about 3% dietary energy at the beginning of the last century (Innis and Jacobson, 2007), with even lower intakes and a dietary ω-6 to ω-3 fatty acid ratio between 2:1 and 1:1 earlier in human history (Simopoulos, 1999). The current median intake of 18:2ω-6 is 5–7% dietary energy, with 0.5% energy from ω-3 fatty acids of which about 10% (0.05% energy) is 20:5ω-3 plus DHA and 90% is 18:3ω-3 (IOM/NAS 2002). Epidemiological studies have shown that high intakes of DHA and 20:5ω-3 (from fish and other sea-foods) are associated with decreased risk of poor child performance on standardized IQ tests (Hibbeln et al., 2006, 2007; Oken et al., 2005). However, other nutrients or lifestyle factors could be important in facilitating better neural development in children of women consuming diets rich in fish.

4. Dietary omega 3 and 6 fatty acids and placental transfer

Prior to birth, all of the ω-3 fatty acids required for fetal development must be provided by placental transfer from mother's circulation (Innis, 2005b). Transfer of DHA across the placenta involves fatty acid binding proteins, with release of DHA to the fetal circulation, followed by transport to liver where it is esterified and resecreted in lipoproteins. Although the proportions of DHA and 20:4ω-6 are higher, and 18:2ω-6 is lower in plasma phospholipids, triglycerides and cholesterol esters in fetal than maternal plasma, plasma levels of DHA vary widely among newborn infants, and are readily influenced by the maternal diet. In our studies, plasma phospholipid DHA had a range (mean) of 2.8–8.1 (5.0) and 4.4–11.7 (7.7), and plasma triglyceride DHA varied from 0.2–1.4 (0.8) and 0.5–5.9 (2.8) g/100 g fatty acids in the 58 pregnant women and their newborn infants, respectively (Elias and Innis, 2001). The ω-6 fatty acid 18:2ω-6 also varied widely, with a range in plasma triglycerides of 7.8–26.0 and 2.9–17.0, and in phospholipids of 13.6–27.2 and 5.0–17.0 g/100 g fatty acids in the maternal and newborn infant plasma, respectively (Elias and Innis, 2001). Circulating levels of DHA, 18:2ω-6 and other unsaturated fatty acids in maternal and fetal plasma are significant and positively correlated (Elias and Innis, 2001). These studies show DHA is higher and 18:2ω-6 is lower in the fetus (newborn) than mother, but DHA and 18:2ω-6 varies widely with the maternal fatty acid status directly affecting that of the infant before birth. Furthermore, 18:2ω-6 was inversely related to DHA in pregnant women and young children (Elias and Innis, 2001; Innis et al., 2004), raising the possibility that high 18:2ω-6 may contribute to low circulating levels of DHA. To summarize, placental fatty acid transfer shows considerable dependence on maternal plasma fatty acids, and is not regulated to protect the fetus from high maternal ω-6 fatty acids, or low DHA. In our centre, supplementation of pregnant women with 400 mg/day DHA beginning at 16 weeks of gestation increased the maternal erythrocyte EPG DHA by 32% at 36 weeks gestation, and prevented the increase in 22:4ω-6 and 22:5ω-6 in women given a placebo (Innis and Friesen, 2008). The increase in circulating 22:4ω-6 and 22:5ω-6 in some pregnant women could be explained by inadequate intakes of ω-3 fatty acids or excessive intakes of 18:2ω-6, both of which are practically overcome by dietary DHA.

5. Dietary omega 3 fatty acids intake and human milk

After birth, breast milk provides the sole source of ω-3 fatty acids, as well as the ω-6 fatty acids to support the growth and development of the breast-fed infant, continuing for much of the first year of life when low fat cereals, fruits and vegetables are added to the infant diet (Innis, 2004). DHA, other ω-3 fatty acids and 18:2ω-6 vary widely in human milk, a variability explained largely by differences in the maternal dietary fat intake. Human milk fat DHA varies among and within populations, from <0.1% to over 1.0% DHA, explained largely by differences in the intake of preformed DHA, usually from fish and other sea-foods. Women following vegan and vegetarian diets usually have 0.1% or less DHA in their milk fat (Sanders et al., 1978), and in our centre, human milk DHA decreased by 50% to less than 0.2% milk fat over the last 3 decades (Innis, 2003). The amount of DHA in human milk is increased by increasing the maternal intake of DHA (Innis, 2004). Human milk 18:2ω-6 also varies, typically from 6 to 30% milk fatty acids, depending on the maternal intake of 18:2ω-6 (Innis and King, 1999, Jensen, 1999). In the 1970s, human milk had an average of 7% 18:2ω-6 compared the current average of 12 to 16% 18:2ω-6, an increase explained by the increased consumption of 18:2ω-6 rich vegetable oils (Innis, 2004). Fat provides about 50% of the energy in human milk, which means that breast-fed infants now consume a milk diet high in 18:2ω-6, but low in ω-3 fatty acids. To summarize, as for placental transfer, the secretion of DHA and 18:2ω-6 in human milk is strongly influenced on the mother's fat intake, with mammary gland appearing to lack mechanisms to protect the breast-fed infants from maternal dietary deficiency or excessive intakes of unsaturated fatty acids.

6. Dietary omega 3 fatty acids deficiency and brain development in animals

High proportions of DHA in brain EPG and phosphatidylserine (PS), reaching as high as 35% of fatty acids in synaptic membranes, is characteristic of the mammalian brain (Innis, 2005a). This is found even in herbivores that consume no DHA and have low plasma and liver DHA. Important knowledge on the physiological roles of DHA arose from studies on bovine retina rod outer segments, in which DHA is also high in phosphatidylcholine (PC) (Guisto et al., 2002; Louie et al., 1991), notable since cows consume a diet lacking DHA. In the brain, DHA is found esterified in EPG and PS, but is low in PC, and both DHA and EPG increase, while PC decreases with brain development. (Tam and Innis, 2006; Sastry, 1985; Svennerholm, 1968).

The effect of feeding of diets severely restricted in 18:3ω-3 (with no DHA) to the pregnant and lactating animals on brain fatty acids in the offspring has been extensively described, and these changes include a decrease in DHA, with a reciprocal increase in 22:4ω-6 and particularly 22:5ω-6 (Coti-Bertrand et al., 2006; Innis, 1991; Innis and de la Presa Owens, 2001; Neuringer et al., 1986). Changes in the embryonic and fetal brain DHA occur readily when the pregnant animal is fed 10% by weight or more as fat, with high 18:2ω-6 and low 18:3ω-3 (Coti-Bertrand et al., 2006; Innis and de la Presa Owens, 2001). Feeding the newborn animal with milk formulas low in 18:3ω-3 reduces DHA and increases 22:4ω-6 and 22:5ω-6 in the brain, brain synaptic membranes and retina (Arbuckle and Innis, 1992; Hrboticky et al., 1989, 1990, 1991; Ward et al., 1998). Inclusion of DHA in the maternal diet increases DHA in the embryonic brain in gestation and infant brain during nursing (Arbuckle and Innis, 1993; Coti-Bertrand et al., 2006; Innis and de la Presa Owens, 2001), with the increase in DHA showing a curvilinear dose–response to DHA intake (Arbuckle et al., 1991;Ward et al., 1998). Studies comparing the efficacy of dietary 18:3ω-3 and DHA as sources of DHA for the developing brain have shown the superiority of DHA, probably explained by β-oxidation of large amounts of dietary 18:3ω-3 for energy rather than quantitative desaturation to DHA (Arbuckle et al., 1991, 1992; Greiner et al., 1997; Innis, 2005a), Fig. 2.

The decreased DHA in the brain of animals fed an 18:3ω-3 deficient diet in development is accompanied by altered metabolism of several neurotransmitters, including dopamine and serotonin, and membrane-associated enzyme and receptor activities (Innis, 2007). Deficits in behavioral tasks of learning, and increased stereotyped behavior in non-human primates raised on ω-3 fatty acid deficient diets show that diet-induced perturbations in brain fatty acids have functional consequence (Bourre et al., 1989; Lim et al., 2005; Neuringer et al., 1986; Reisbick et al., 1986, 1994; Wainwright, 2002).

The potential for adverse effects of inadequate fatty acid nutrition during development to have lasting effects on neural functions, and the nature of those effects will depend on the stage in development, duration and severity of the dietary insult. Prolonged, and even permanent deficits in neural function are usually considered most likely when nutrient deficiency impairs processes such as neurogenesis, dendritic arborization, synapotogenesis, selective pruning, and myelination (Georgieff and Innis, 2005). The large membrane surface areas of neuronal cells, astrocytes, oligodendrites and microglia, with extensive branching of dendrites that continuously change shape and length during development and learning (Muller et al., 2002), and the integral role of DHA in membrane lipids raise the possibility that inadequate DHA alters brain development through effects related to membrane structures. However, in addition to a structure–function role, membrane glycerophospholipids provide a reservoir for regulated release of 20:4ω-6 and bioactive molecules, such as anandamides. Prostaglandins synthesized from 20:4ω-6 play pivotal roles in regulation of brain development, synaptic plasticity, long-term potentiation, and spatial learning (Bazan, 2003), relevant because DHA may regulate 20:4ω-6 release from neural membranes, thus influencing prostaglandin synthesis (Bazan, 2006; Chen and Bazan, 2005; Corey et al 1983; Ferritti and Flanagan, 1990; Strokin et al 2007; Tassoni et al., 2008). Diet-induced changes in the piglet brain fatty acids was accompanied by corresponding changes in arachidonyl and docosahexaenoyl containing anandamides (Berger et al., 2001), although the functional implications are not yet known.

Growth of neural cell membranes requires synthesis of lipids which are then added to the growing membrane through fusion of lipid transport vesicles with the plasma membrane, involving soluble *N*-ethylmaleimide-sensitive fusion protein attachment receptor (SNARE) proteins in a similar process to that involved in release of neurotransmitters from their storage vesicles (Darios and Davletov, 2006; Wojcik and Brose, 2007). Recent studies suggest the fast fusion of storage vesicles is spatially restricted and depends on the membrane ω-6 and ω-3 fatty acids, including DHA (Darios and Davletov, 2006). In our work, ω-3 fatty acid deprivation during brain development decreased brain DHA and increased membrane-bound SNARE protein complexes in the hippocampus, suggesting that DHA deficiency slows membrane fusion, or SNARE protein dissociation and recycling (Pongrac et al., 2007). We also demonstrated that maternal ω-3 fatty acid deficiency decreased the embryonic brain growth cone membrane DHA (de la Presa Owens and Innis, 1999), with under-development of the hippocampus in a pattern suggesting impaired post-mitotic cell migration (Coti-Bertrand et al., 2006). Together these studies demonstrate that even short-term ω-3 fatty acid restriction is sufficient to cause early morphological and biochemical changes in the embryonic brain. Other studies have shown that ω-3 fatty acid deficiency decreases the mean cell body size of neurons in the hippocampus, hypothalamus and parietal cortex, and decreases the complexity of cortical dendritic arborization (Ahmad et al., 2002; Wainwright et al., 1998). Current evidence suggests that most brain DHA originates by uptake from plasma (Innis, 2007), with an apparent absence of selectivity for DHA over 22:5ω-6 (Novak et al.,). Significant amounts of 22:5ω-6 are present in the developing human brain, and 22:5ω-6 concentrations are increased in the brain of infants fed formula (Svennerholm, 1968). However, DHA but not 22:5ω-6 enhances neurite outgrowth and the formation of secondary neurites (Calderon and Kim, 2004; Cao et al., 2005; Kawakita et al., 2006; Novak et al.,), showing 22:5ω-6 does not substitute for DHA in morphological processes that may predispose to lasting deficits in neural function (Georgieff and Innis, 2005).

7. DHA in early human brain development

As described in the preceding sections, the wide variability in ω-3 fatty acid nutrition among women in gestation and lactation leads to large differences in circulating DHA among infants at birth and among breast-fed infants. Information on the functional importance of DHA in infant development is available from studies on effects of feeding formulas without and with DHA, often with 20:4ω-6, with the most robust benefits of DHA for visual, mental and motor skill development in preterm infants (Fewtrell, 2006; Heird and Lapillone, 2005). However, circulating levels of DHA vary among breast-fed infants, with the lower end of distribution of DHA in

breast-fed infants overlapping that in infants fed formula without DHA (Innis et al., 1996; Sanders et al., 1978). This raises the question of whether inadequate maternal ω-3 fatty acid nutrition is present among women and has implications for infant neural development. To begin to address this question, we used a longitudinal, prospective study to gather evidence of whether the variability in breast milk DHA and circulating levels of DHA among breast-fed infants is related to infant visual and neural development (Innis, 2003; Innis et al., 2001). Infants fed breast milk with 0.17% DHA had lower erythrocyte DHA at 60 days of age, and lower visual acuity and language development during the first 14 months after birth than infants fed breast milk with 0.34% DHA (Innis, 2003; Innis et al., 2001). However, these studies could not dissociate effects of the DHA supply from breast milk from differences in maternal DHA supplies in gestation, and provided only associative data to link maternal diets low in DHA with lower infant developmental test scores. To address whether DHA status in pregnant women is so low as to contribute to poor infant development, we used a randomized intervention with 400 mg/day DHA or a placebo from 16 weeks of gestation until term infant delivery (Innis and Friesen, 2008). Because an increased intake of an essential nutrient cannot have benefit in individuals with an intake above their needs, women without deficiency cannot benefit from additional DHA. This means that there will be non-responders in the DHA intervention group, and women in the placebo group with DHA sufficient to meet needs. Adding complexity, infant development has a distribution, not as single value, in which the developmental potential of an individual infant is unknown. To overcome these problems, we considered that DHA deficiency, if present, would be evident by a shift in the distribution of developmental test scores, decreasing the risk of low scores, indicating correction of deficiency (Innis and Friesen, 2008). Multivariate analyses showed infant visual acuity at 60 days of age was related to infant gender, with visual acuity higher in girls than boys (β, SE, and odds ratio = 0.660, 0.93, 1.93, respectively), and to the intervention (β, SE, and odds ratio = 1.215, 1.64, 3.37, respectively, with DHA intervention higher than the placebo) (Innis and Friesen, 2008). This work showed that the risk of low infant visual acuity was decreased by improving maternal DHA status in pregnancy. We found that the maternal 22:4ω-6 was a better predictor of visual acuity in infant boys, Rho −0.37, $P<0.05$, and girls, Rho −0.48, $P<0.01$ than DHA (Innis and Friesen, 2008), which suggests high ω-6 fatty acids and low DHA, but not necessarily low DHA alone, contributes to poor infant neural development.

Several other studies have considered the effects of enhanced maternal DHA supplementation in pregnancy on infant development (Colombo et al., 2004; Helland et al., 2001, 2003; Malcolm et al., 2003; Lauritzen et al., 2004). A consistent pattern emerges in which the maternal or infant circulating levels of DHA at birth is associated with better infant neural and visual development (Colombo et al., 2004; Helland et al., 2001; Malcolm et al., 2003; Lauritzen et al., 2004), although as in our studies (Innis and Friesen, 2008) mean test scores were not higher in DHA supplemented than non-supplemented groups, reasonably explained by the overlap in DHA status between the DHA intervention and placebo groups. Emerging data from follow-up studies suggests DHA nutrition in gestation and lactation has long-term benefits to mental and motor skill development in early childhood (Helland et al., 2003), consistent with epidemiological evidence to link maternal ω-3 fatty acid intakes in pregnancy to decreased risk of poorer IQ scores in young children (Hibbeln et al., 2007; Oken et al., 2005).

Fatty acid desaturase (FADS)1 and FADS2 encode for the rate limiting enzymes, Δ 5 desaturase and Δ 6 desaturase, respectively which regulate the synthesis of 20:4ω-6, 20:5ω-3 and DHA (Fig. 2). FADS1 and FADS2 are localized as a cluster, with FADS1 and FADS2 oriented head to head, with exon 1 of the genes separated by an 11 kb region, on chromosome 11 (11q12–q13.1). Recent studies have shown that single nucleotide polymorphisms (SNP) in the FADS1 FADS2 cluster contribute to variability in plasma phospholipid and erythrocyte 20:4ω-6 (Malerba et al., 2008; Schaeffer et al., 2006). Furthermore, in recent epidemiological studies involving large cohorts of children, breast-fed children carrying the rs174575 C allele of FADS2 had higher scores on IQ tests than children carrying the GG allele (Caspi et al., 2007). In recent studies, we genotyped rs174553, rs99780, rs174575, and rs174583 in the FADS1 FADS2 gene cluster, and showed that minor allele homozygotes of rs174553(GG), rs99780(TT) and rs174583(TT) had lower 20:4ω-6, but higher 18:2ω-6 in plasma and erythrocyte lipids in pregnancy, and lower 20:4ω-6 and 20:5ω-3 in breast milk during lactation (Xie and Innis, in press). Breast milk of women with the minor allele (GG) of rs174575 had lower 20:5ω-3, DHA and 20:4ω-6 in their milk than major allele carriers. The ratio of the Δ-6 and Δ-5 desaturase products to their 18:2ω-6 or 18:3ω-3 precursors showed a robust effect with lower fatty acid product/precursor ratios in minor allele homozygotes. This new knowledge shows that genetic variation in FADS1 and FADS2 contributes to variability in circulating ω-6 and ω-3 fatty acids in pregnancy and in breast milk. Understanding the interaction of genetic variation in the FADS1 FADS2 gene cluster and dietary fatty acid intakes is the next critical step needed to elucidate whether genetic variations influence dietary ω-3 and ω-6 fatty acids requirements, or confer a particular vulnerability to poor infant neural development, as well as some neurological disorders and aging-related cognitive declines in some individuals with low intakes of preformed DHA.

8. Summary

In conclusion, while there is no doubt that DHA is a critical component of brain membrane lipids, the possibility that western diets poor in ω-3 fatty acids and rich in ω-6 fatty acids contribute to poor CNS development and function is becoming increasingly recognized. The evidence to show low rates of conversion of 18:3ω-3 to DHA in individuals following western diets, and the demonstrated dependence of maternal-to-infant transfer of DHA and ω-6 fatty acids on the maternal polyunsaturated fat intake provides strong reason for dietary recommendations for omega 3 fatty acids that include consideration of brain development and function. Recent research to show genetic variations in the fatty acid desaturase pathway influences circulating and human milk essential fatty acids also raise the need to understand whether gene polymorphisms alter the requirements for particular ω-3 fatty

acids, and if diet-gene interactions increase risk of poor neural development or disease in some individuals.

Acknowledgment

Research in the author's laboratory is supported by grants from the Canadian Institutes of Health Research (CIHR).

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