

Breastmilk composition and brain development

MFGM as a source of complex lipids to support the developing brain and cognitive function.

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Introduction

Nutrition in the first few years of life is critical to support optimal brain development and cognitive outcomes (Georgieff 2007; Delplanque et al. 2015). Breastmilk provides the best source of nutrition during the first 4-6 months and in combination with complementary foods thereafter.

Infant formula is the only suitable alternative to breastmilk for those who cannot or choose not to breastfeed; the composition of breastmilk is the gold standard reference for the development and improvement of infant nutrition products. Much is still to be discovered about the composition of breastmilk and how its unique components and structure contribute to infant development.

BREASTFEEDING AND BRAIN DEVELOPMENT



Exclusive breastfeeding for at least the first 4 to 6 months of life is thought to result in a child's optimal cognitive development (Birch et al 1998; 2007; Willats et al 1998; Hornstra 2000). A meta-analysis estimates an average of 2-3 IQ points higher for infants breastfed during the first 3-4 months of life, and even bigger gains for preterm infants (Anderson et al 1999). The benefits also appear to be long term; overall IQ and verbal IQ of infants breastfed for 8 months has been reported to be 6.2 and 10.2 points higher, respectively, at 7-8 years of age than for non-breastfed infants (Horwood et al. 2001). In a large study, the children of mothers in a breastfeeding promotion programme had higher IQ scores at follow up at around 6 years than those in a standard postnatal care group (Kramer et al 2008). In addition, prolonging breastfeeding after introduction of solid foods after 6 months of age resulted in improved psychomotor and mental developmental outcomes at 12 months of age (Agostoni et al 2001). It has been suggested that components in breastmilk, that are low or lacking in infant formula, may contribute to these observed outcomes in development (Innis 2014); in addition to essential nutrients such as protein and micronutrients, human breastmilk is higher in DHA and contains many bioactive components such as complex milk lipids from the milk fat globule membrane (MFGM), membrane proteins, oligosaccharides, lactoferrin and sialic acid that may also provide important building blocks for brain development and structure (Agostoni et al 2001; Delplanque et al 2015).

OPTIMAL NUTRITION AND BRAIN DEVELOPMENT

Infant formula products do not contain all the same components found in human breastmilk, and therefore may not provide optimised nutrition which could be required for infants to reach their developmental potential. The brain grows rapidly in the first 2 to 3 years of life and lipids play a key nutritional role in the development of brain composition and function. Over the last 30-40 years DHA has been added to infant formula to more closely match the levels found in breastmilk, principally due to its role in supporting cognitive development. However, there are a number of other compositional differences between breastmilk and standard infant formula that may also contribute to brain development. A current area of research interest is the role of complex milk lipids found in the MFGM present in breastmilk but largely absent in standard infant formula. The MFGM, the layer stabilizing fat globules in milk, contains a range of complex milk lipids, including glycerophospholipids, sphingomyelin, cholesterol, gangliosides (GA) and cerebroside. These components are also found in high concentrations in the brain (Figure 1, De Vries et al 1981).

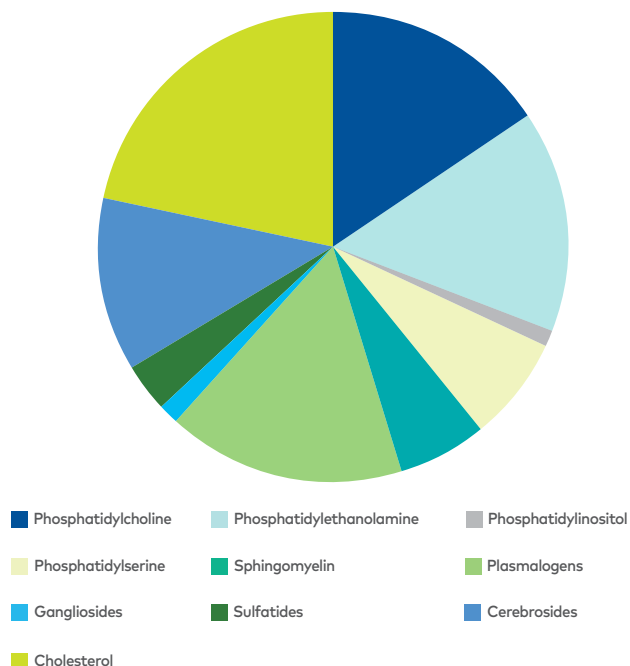


Figure 1. Composition of brain lipids (white matter and grey matter). Adapted from De Vries et al (1981).

BREASTMILK LIPID COMPONENTS

Breastmilk lipid content increases over lactation; mature milk contains 3.2–3.6 % lipids (Jensen, 1996; Gidrewicz and Fenton, 2014). Breast milk lipids are present as milk fat globules. Over the first 4 postnatal days, the size of the human milk fat globules decreases significantly, however their size increases again after 1 month postpartum (Michalski et al 2005).

MFGM phospholipids include phosphatidylcholine (PC), phosphatidylserine (PS), phosphatidylethanolamine (PE), phosphatidylinositol (PI) and sphingomyelin (SM), and the main glycosphingolipids are GA and cerebroside. Reported levels of these bioactive components in human breastmilk vary greatly from one individual to another, from country to country and during lactation (Ma et al 2017a, Ma et al 2017b, Ma et al 2015; Guiffreda et al 2016). With growing evidence of the potential benefits of MFGM components, understanding their concentration and variability is important to optimize their level in infant formula products.

Using modern techniques of HPLC-MS, more robust quantitation of these minor components has been reported in different population groups and throughout lactation (Figure 2).

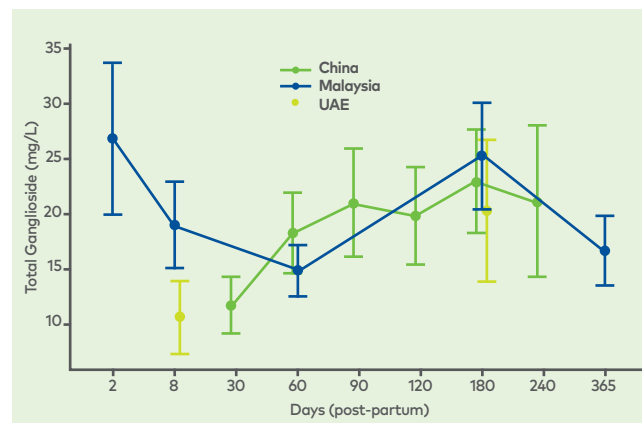


Figure 2. Changes in human milk ganglioside content in different ethnic groups and throughout lactation (adapted from Ma et al 2017a)

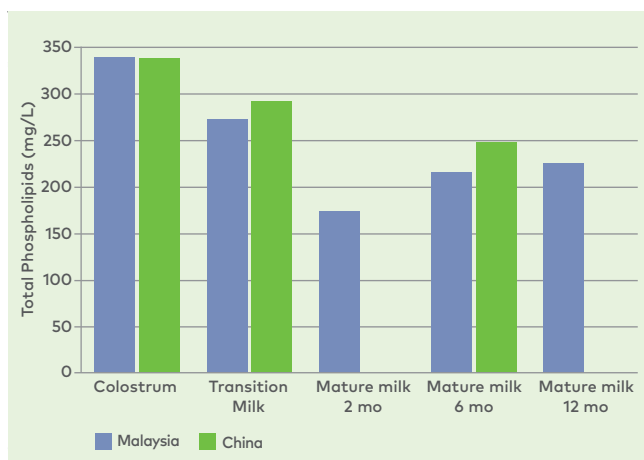


Figure 3. Changes in human milk phospholipid content in different ethnic groups and throughout lactation (adapted from Ma et al 2017b and Giuffrida et al 2016).

COMPLEX LIPIDS IN THE BRAIN

In addition to the essential nutrients known to be important for brain development, many other dietary components such as DHA and arachidonic acid, GA, sialic acid, choline, sphingomyelin, phosphatidylserine and ceramides, have been shown to play relevant roles in brain development, structure and function pre- and post-natally (Cutler and Mattson, 2001; Mendez-Otero et al., 2013 Ryan et al 2013; Glade and Smith 2015). Many of these components are abundant in the brain and are involved in the growth and maturation of brain structures (McJarrow et al 2009; Mudd et al. 2016). An increase in ganglioside levels in brain tissue are particularly noted in the late pre-natal and early post-natal periods (Figure 4). The MFGM GA and phospholipids may also be important for normal growth and development of the neonatal gut, immune system, visual and cognitive performance (Park et al 2005; Guan et al 2015; Anderson et al 2018).

Gangliosides are complex glycosphingolipids which contain sialic acid and make up approximately 10% of the total mass of brain lipids (McJarrow et al 2009). Gangliosides play a role in the formation of synapses between neural cells and also in their function during the process of neural transmission. Gangliosides facilitate the transmission of nerve signals across the synaptic membranes (Rahmann 1995). They also contribute to neural growth, modulate neural functions and are involved in neuritogenesis, information storage and the process of memory formation (McJarrow et al 2009; Rahmann 1995). Gangliosides are also presumed to act as substrates for neural layer formation which generates higher cognitive functions in the brain (Rosner 2003).

The total GA (GD3 + GM3) content of breastmilk from Chinese and Malaysian mothers increased throughout lactation in mature milk, after an initial decline from colostrum levels (Figure 2). The maximum total ganglioside concentration in breastmilk was around 25 mg/L for Chinese and Malaysian mothers, which was slightly higher than a single timepoint measurement for UAE mothers (Ma et al 2017a, Ma et al 2017b, Ma et al 2015). The average total phospholipid concentration also increased gradually over the lactational period for the Malaysian mothers, but remained relatively stable in Chinese mothers from 201 mg/L to 216 mg/L (Figure 3). The dominant PL class in mature breastmilk from Malaysian mothers was sphingomyelin (Ma et al 2017b), as has been reported in other studies (Jensen, 1996).

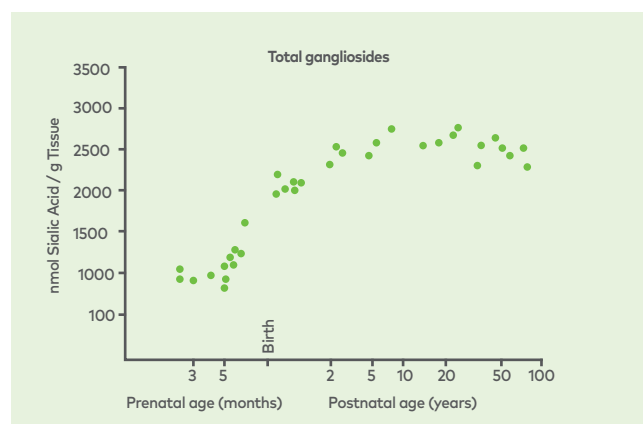


Figure 4. Increase in concentration of gangliosides in brain tissue (redrawn with permission; Svennerholm et al 1989)

Phospholipids are found in the bilayer of cell membranes and provide structural fluidity and permeability in the membrane, anchor membrane proteins, and supply precursors for neurotransmitter production (Figure 5). DHA is the main fatty acid in the brain cell membrane phospholipids – mainly associated with phosphatidylserine and phosphatidylethanolamine, making up around 35% of the fatty acids (Innis 2007). Milk phospholipids were recently shown to have a neurotrophic effect on cortical neurite outgrowth in vitro (Barry et al 2018). The addition of long-chain polyunsaturated fatty acids (PUFAs) enhances this effect on outgrowth of cortical neurons (Matsuo, 2016). PUFAs play key roles such as precursors of membrane lipids, antioxidants and ligands to transcription factors (Innis 2007). PUFAs also activate cell signalling pathways and affect the functions of membrane proteins (Matsuo, 2016).

Sphingolipids, which include GAs and SM, are abundant in the brain and essential for the development and maintenance of nervous system functions. GAs are particularly found in the grey matter and neurons, while SM, sulfatides and galactosylceramides are mainly enriched in oligodendrocytes and myelin (Olsen and Færgeman, 2017). The concentration of SM and galactolipids increases during the development of myelin in the brain early in life (Olsen and Færgeman,

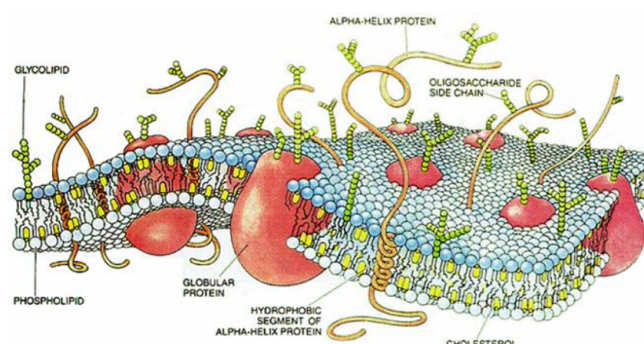


Figure 5. Cell membrane structure adapted from Singer and Nicolson 1972

2017). In human and cow's milk MFGM (Gallier et al 2015) and similarly in the plasma membrane of cells in the nervous system (Olsen and Færgeman, 2017), SM (and other sphingolipids) and cholesterol form microdomains affecting the local properties of the membrane. Sphingolipids, in particular the formation of microdomains, help develop and maintain normal neuronal physiology (Olsen and Færgeman, 2017).

PROVIDING COMPLEX LIPIDS IN EARLY LIFE

As brain growth starts in utero, infants born preterm are at higher risk of cognitive delay (Tanaka et al 2013). It is plausible that, if there was a lack of the basic building blocks such as DHA, phospholipids and gangliosides during the rapid period of brain growth and development in utero and the first 2-3 years of life, that cognitive development may not reach its potential.

Modern infant formula products are still commonly formulated with vegetable oils and proteins to form a milky emulsion. This results in an infant formula with little to no MFGM components. Human and cow's milk phospholipids share some similarities in the phospholipid class profile, which also happens to be similar to the profile in human brain phospholipids (Figure 6). Cow's milk phospholipids appear as the most suitable source of phospholipids to add to infant formula to provide building blocks for brain cell membranes, compared with other common sources of phospholipids (Figure 6).

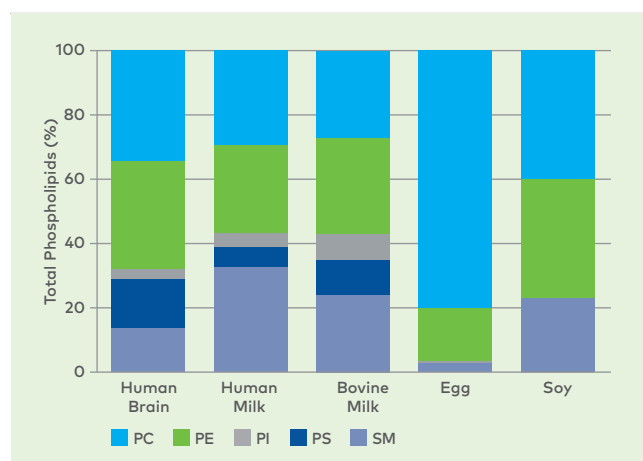


Figure 6. Phospholipid profile of brain tissue, human milk, bovine milk and egg and soy lecithins (Ansell and Hawthorne 1964; DeVries et al 1981; Christie 1995; Wang 2002).

Summary

Breastmilk contains many interesting minor lipid components in the MFGM. These are more abundant in breastmilk than in standard infant formula. The profile of phospholipids and other complex lipids such as gangliosides is similar in human milk, cow's milk and the brain. There is increasing evidence that MFGM complex

lipids may play important roles in brain development, gut maturity and immune protection and therefore using cow's milk MFGM ingredients in infant formula to more closely match the composition of human milk presents an important opportunity in infant formula innovation.

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