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NUTRITION

SureStart™ MFGM Lipid

Milk Fat Globule Membrane ingredients and brain development

April 2019

Introduction

Optimal brain development relies on both good nutrition and a caring and stimulating environment (Georgieff 2007; Delplanque et al. 2015).

Breastfeeding supports optimal cognitive outcomes which may be due to both the bonding experience and by providing the ideal nutrition in the first few months of life.

The composition of breastmilk is the gold standard reference for the development and improvement of infant formula products, for those who cannot or choose not to breastfeed. A recent area of interest for breastmilk composition and cognitive development is the milkfat globule membrane (MFGM). This paper will review the recent pre-clinical and clinical studies on MFGM and infant development.

WHAT IS THE MILK FAT GLOBULE MEMBRANE?

The MFGM is a trilayer of phospholipids, glycolipids, cholesterol and membrane proteins surrounding the triglyceride droplets in all mammalian milks (Figure 1). Traditionally MFGM was isolated by churning chilled cream into butter; the resulting aqueous phase, named buttermilk, contains broken MFGM fragments.

It is now possible to obtain at commercial scale ingredients more concentrated in MFGM. The components can be enriched into dairy ingredients through the manufacture of anhydrous milk fat (AMF) from concentrated cream to give MFGM-rich beta serum with 7-8% of phospholipids.

Another route is to harvest the MFGM components after cheese manufacture to give a higher fat-containing whey protein concentrate with enhanced MFGM content with 5-7% of phospholipids. The MFGM-rich beta-serum can replace some of the skim or whole milk powder in the formulation of infant formula, while the high fat whey protein concentrate can replace some of the other sources of whey proteins (Figure 2). These ingredients and derived fractions have been studied in pre-clinical and clinical trials for their ability to impact brain development, gut maturation, immunity and digestion.

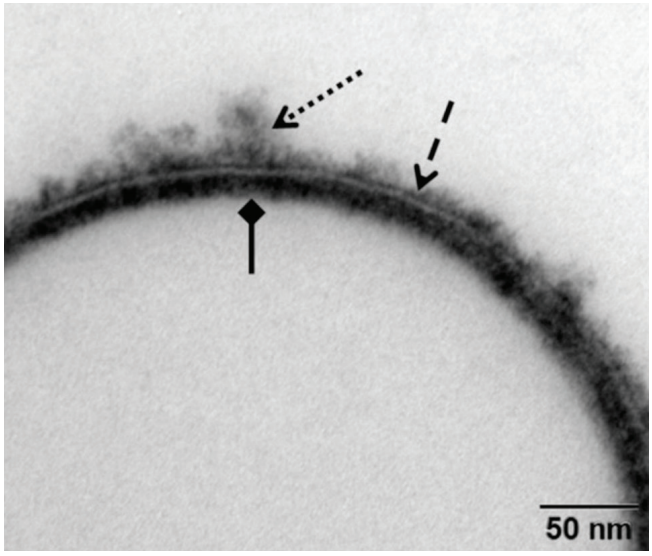

Figure 1: Transmission electron microscopy of the human MFGM. Adapted from Gallier et al (2015).

The evidence on MFGM and brain development – pre-clinical models

Research in neonatal models has shown improvements in learning and memory with increasing dose of MFGM components (Vickers et al 2009) and with different preparations of MFGM from beta serum (Guan et al 2015) or cheese whey (Mudd et al 2016).

Park et al (2005a and b) showed that a ganglioside-enriched diet increased ganglioside levels in the intestinal mucosa, plasma, brain and retina, and altered phospholipid metabolism in rats. This indicates that dietary gangliosides could play a role in gut, brain and retinal development in infancy.

Further studies have investigated the underlying mechanisms of action of MFGM components with findings of increased neuronal migration, neurite growth and branching in vitro, increased synaptic density in the hippocampus (Guillermo et al 2015), and upregulation of genes involved in brain functions in vivo (Brink and Lonnerdal 2018).

Infant formula enriched in milk phospholipids and fed to mice postnatally improved performance in short-term memory tasks, and in particular novelty exploration, in adolescence and adulthood (Schipper et al 2016).

In another study in rat pups, MFGM supplementation with or without prebiotics in infant formula reduced visceral sensitivity and improved cognitive performance (Waworuntu et al 2017). In addition, the MFGM + prebiotics supplementation regulated the response to early life stress.

A recent study (Moukarzel et al 2018) showed that dietary postnatal supplementation with a cheese whey MFGM ingredient improved reflex development and altered brain phospholipid and metabolite composition in rat pups.

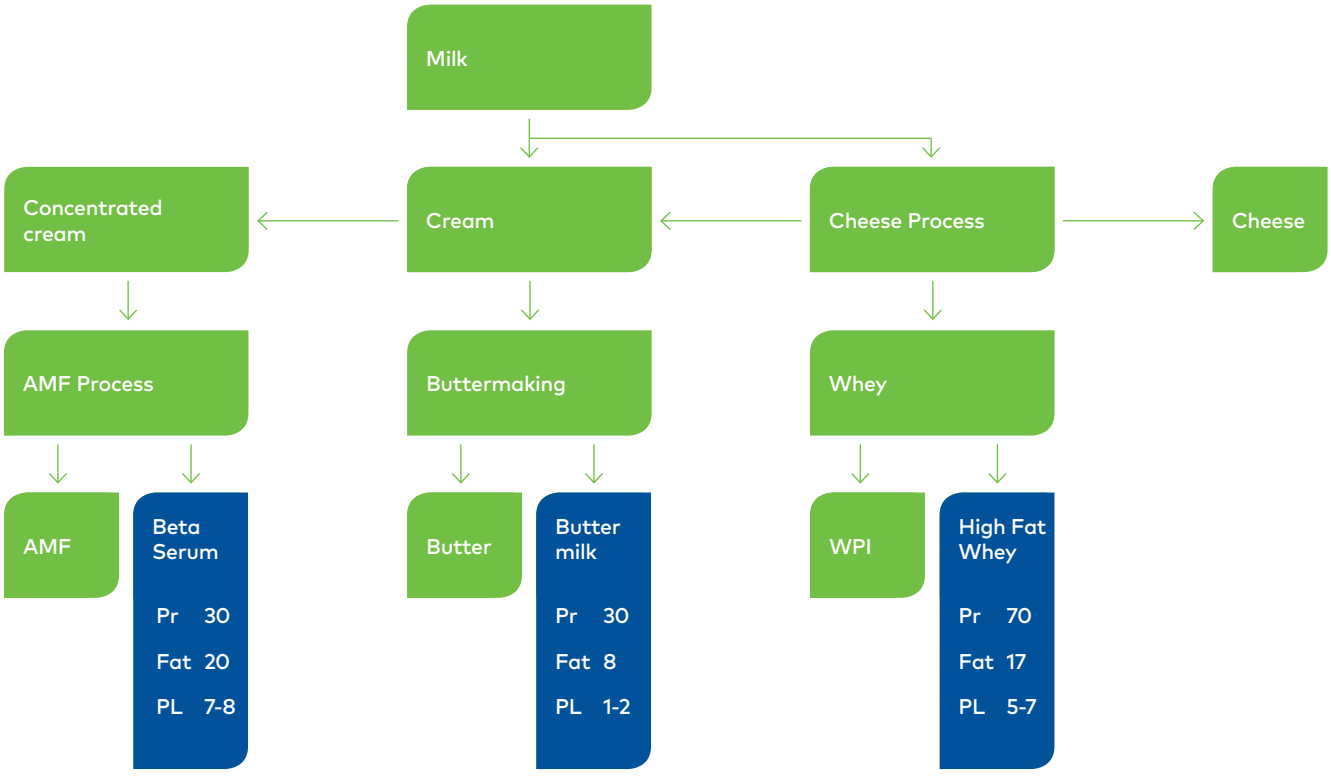

Figure 2: MFGM Lipid ingredient manufacture (Gallier et al 2018).

The evidence on MFGM and brain development – infant studies

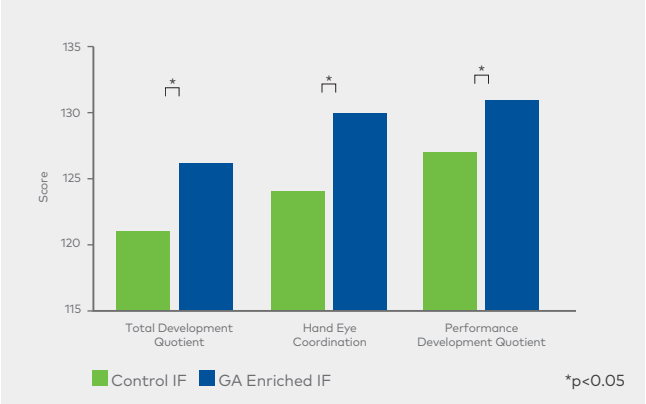

Figure 3: MFGM Ganglioside enriched infant formula vs standard infant formula supports improved development (Gurnida et al 2012).

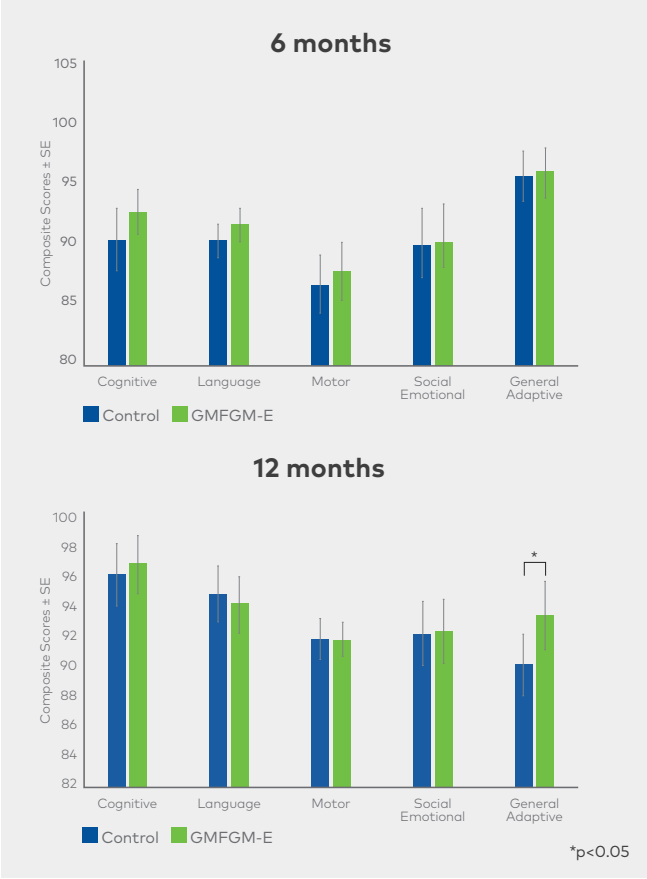

Figure 4a and b. Infant clinical feeding study using NZMP SureStart™ MFGM Lipid 100 fortified infant formula and a control formula from 1 to 12 months of age. Cognitive outcomes assessed at 6 months (a) and 12 months of age (b) using Bayley-III (Xia et al 2018).

A number of studies have now been published that show the potential benefits of MFGM containing ingredients for infant cognitive development (Table 1). Studies have included both types of MFGM ingredients –beta serum- and cheese whey-derived. Studies with MFGM preparations from beta serum (Figure 2) or from whey have demonstrated that the ingredients are well tolerated and support normal growth and development (Billeaud et al 2015, Gurnida et al 2012, Xia et al 2018; Wu et al, 2018).

Beta-serum derived MFGM ingredients have been shown to support cognitive development in infants and young children. A concentrated form of the MFGM lipids, G600, improved indices of hand eye coordination, performance and overall development at 6 months measured using the Griffiths scale (Figure 3; Gurnida et al 2012). Higher cognitive scores at 6 months (Figure 4a) and higher general adaptive behaviour scores at 12 months (Figure 4b) measured using the Bayley Scales of Infant and Toddler Development – 3rd Edition (Bayley III) were observed in infants fed an infant formula with beta-serum derived MFGM from birth to 12 months of age compared with infants fed a standard formula (Xia et al 2018). Other studies using the whey-derived MFGM ingredient, in combination with reduced protein content in infant formula or with lactoferrin, have also reported improvements in cognitive, language and/or motor scores measured using the Bayley III (Timby et al 2014, Li et al 2018). While most studies have focused on MFGM supplementation during the first year of life, one study showed that MFGM supplementation in school children reduced the number of febrile episodes and improved behavioural regulation, using the Achenbach System of Empirically Based Assessment (Veereman-Wauters et al 2012).

The different preparations of the MFGM ingredients used in the studies to date vary in composition but are generally similar in complex lipid profile. Whether specific components are responsible for the observed effects or the benefits are due to the overall mix is yet to be determined. Studies using more concentrated sources of MFGM components contributes some insights. Fortification of milk with cow's milk sphingomyelin improved neurodevelopment of preterm infants at 18 months of age measured using the Behaviour Rating Scale of the BSID-II, the Fagan test, the latency of visual evoked potential, and sustained attention test (Tanaka et al 2013). Cow's milk gangliosides may also play a role with support from a clinical study of children with GM3 synthase deficiency due to a genetic mutation. Slight improvements in growth and parents report of engagement were noted when these children received an oral supplement enriched in MFGM GA (Wang, et al 2018).

Some studies looked at other outcomes in addition to cognitive development in infancy. For example, Timby et al (2015), as part of the same study looking at cognitive outcomes (Timby et al 2014), reported a reduction in the risk of acute otitis media and use of antipyretics and immunomodulatory effects on humoral response against pneumococcus vaccine in infants fed the MFGM-supplemented formula with lower calorie and protein levels.

In addition, the supplementation with MFGM modulated the plasma and erythrocyte membrane lipidomes, in particular the concentrations of sphingomyelin, phosphatidylcholine and ceramides, and sphingomyelin, phosphatidylethanolamine and phosphatidylcholine, respectively, at the end of the supplementation period (6 months of age) (Grip et al 2018).

The lipidomic changes may be reflected in the lipidomes of the membranes of immune cells and cells in other tissues. Furthermore, Rueda et al (1998) showed that ganglioside supplementation in infant formula resulted in lower relative content of Escherichia Coli and higher bifidobacterial counts in stools of preterm infants. The accumulating evidence of the role of MFGM components on the gut and brain development highlights the potential impact of the MFGM on the gut-brain axis early in life.

Study	Source of MFGM	Number of participants (completed)	Age at start	Intervention period	Outcomes (scores) (intervention vs control)
Gurnida et al 2012	Fonterra G600 – achieved ~12ug/ml GA	~30 per group	2-8 wks	Until 6 mo of age	At 6 mo of age – significant improvement in hand eye coordination, performance, overall DQ – (Griffiths scale)
Veereman-Wauters et al 2012	InPulse – 2.5% gave 500mgPL/day	~90 per group	2-6 years	4 mo	Significant improvement in parent reported behaviour regulation (Achenbach)
Tanaka et al 2013	200mg PL/100g milk – 20% = SM	12 per group	Preterm ~10 weeks (<1500g)	8 weeks	At 18 mo of age significant improvement in behaviour (Bayley-II)
Timby et al 2014	Arla Lacprodan MFGM-10 (± 40mg/ 100ml) ~5% addition rate	~70 per group	~45 days	Until 6 mo of age	At 12 mo of age significant improvement in cognitive (Bayley-III)
Li et al 2018 (poster)	Arla Lacprodan MFGM-10 0.74 g/100 kcal ~4% addition rate	~145 per group	10-14 days	IF to 6 mo of age, FO to 12 mo of age	At 12 mo of age significant improvement in motor, language & cognitive (Bayley-III)
Xia et al 2018 (poster)	SureStart™ MFGM Lipid100 ~4% addition rate	~80-90 per group	Up to 2 weeks	IF to 6 mo of age, FO to 12 mo of age	At 12 mo of age significant improvement in general adaptive (Bayley-III)

Table 1: Summary of infant intervention studies using MFGM fortified infant formula and effects on neurodevelopment, cognition and behavior.

Summary

The role of MFGM for infant brain development, cognition and behaviour is an area of growing research interest for infant development. Other potential benefits include immune protection and gut maturation. Further research investigating the role of human MFGM and the advantages of fortifying infant formula with cow's milk-sourced MFGM will support its use to improve the composition of infant formula to be closer to that of breastmilk.

REFERENCES

Billeaud et al. Safety and Tolerance Evaluation of Milk Fat Globule Membrane-Enriched Infant Formulas: A Randomized Controlled Multicenter Non-Inferiority Trial in Healthy Term Infants. Clinical Medicine Insights: Pediatrics 2014:8 51–60 doi: 10.4137/CMPed.S16962.

Brink LR, Lonnerdal B. The role of milk fat globule membrane in behaviour and cognitive function using a suckling rat pup supplementation model. J Nutr Biochem 2018 58:131-7.

Delplanque B, Gibson R, Koletzko B, Lapillionne A, Strandvik B. Lipid quality in infant nutrition: Current knowledge and future opportunities. JPGN 2015; 61: 8-17.

Gallier S, MacGibbon A, McJarrow P. Milk fat globule membrane (MFGM) supplementation and cognition. Agro Food Industry Hi Tech 2018; 29(5): 4-6.

Gallier S, Vocking K, Post JA, Van de Heijning B, Acton D, Van der Beek E, Van Baalen T. A novel infant milk formula concept: Mimicking the human milk fatglobule structure. Colloids and Surfaces B: Biointerfaces 2015; 136: 329–39.

Georgieff MK. Nutrition and the developing brain: nutrient priorities and measurement. Am J Clin Nutr 2007;85(suppl):614S-20S.

Grip T, Dyrlund TS, Ahonen L, Domellof M, Hernell O, Hyotylainen T, Knip M, Lonnerdal B, Oresic M, Timby N. Serum, plasma and erythrocyte membrane lipidomes in infants fed formula supplemented with bovine milk fat globule membranes. Paediatric Research (2018), https://doi.org/10.1038/s41390-018-0130-9.

Guan J, MacGibbon A, Fong B, Zhang R, Liu K, Rowan A, McJarrow P. Long-Term Supplementation with Beta Serum Concentrate (BSC), a Complex of Milk Lipids, during Post-Natal Brain Development Improves Memory in Rats. Nutrients 2015;, 7(6): 4526-4541; doi:10.3390/nu7064526.

Guillermo RB, Yang P, Vickers MH, McJarrow P, Guan J. Supplementation with complex lipids during brain development promotes neuroplasticity without altering myelination of vascular density. Food and Nutrition Research 2015 59:25765-74.

Gurnida D, Rowan AM, Idjradinata P, Muchtadi D, Sekarwana N. Association of complex lipids containing gangliosides with cognitive development of 6-month-old infants. Early Human Development, 2012, 88:595-601. DOI 10.1016/j.earlhumdev.2012.01.003

Li F, Wu SS, Bersen CL, Harris CL, Colombo J, Liu B, Rudolph C, Cleghorn G. (2018) The cognitive and immune effects of feeding an infant formula enriched with milk fat globule membrane (MFGM) and lactoferrin in a population of Chinese infants. ESPGHAN 2018 poster P-043.

Moukarzel S, Dyer RA, Garcia C, Wiedeman AM, Boyce G, Weinberg J, Keller BO, Elango R, Innis SM. Milk fat globule membrane supplementation in formula-fed rat pups improves reflex development and may alter brain lipid composition. Scientific Reports (2018) 8:15277.

Mudd AT, Alexander LS, Berding K, Waworuntu RV, Berg BM, Donovan SM, and Dilger RN. Dietary prebiotics, milk fat globule membrane, and lactoferrin affects structural neurodevelopment in the Young Piglet. Frontiers in Pediatrics 2016; 4:4. doi: 10.3389/fped.2016.00004.

Park E.J., Suh M., Clandinin T. (2005a). Dietary ganglioside and long-chain polyunsaturated fatty acids increase ganglioside GD3 content and alter the phospholipid profile in neonatal rat retina. Invest. Ophthalmol. Vis. Sci. 2005; 46(7): 2571-2575.

Park E.J., Suh M., Ramanujam K., Steiner K., Begg D., Clandinin M.T. (2005b). Diet-induced changes in membrane gangliosides in rat intestinal mucosa, plasma and brain. J. Pediatr. Gastroenterol. Nutr. 2005; 40: 487-495.

Rueda R, Sabatel JL, Maldonado J, Molina-Font JA, Gil A. Addition of gangliosides to an adapted milk formula modifies levels of fecal Escherichia coli in preterm newborn infants. J Pediatr. 1998 Jul;133(1):90-4.

Schipper L., van Dijk G., Broersen L.M., Loos M., Bartke N., Scheurink A.J.W., van der Beek E.M. A Postnatal Diet Containing Phospholipids, Processed to Yield Large, Phospholipid-Coated Lipid Droplets, Affects Specific Cognitive Behaviors in Healthy Male Mice J. Nutr. 2016; 146 (6) 1155-1161.

Tanaka K et al. The pilot study: Sphingomyelin-fortified milk has a positive association with the neurobehavioural development of very low birth weight infants during infancy, randomized control trial. Brain & Development 2013; 35: 45–52

Timby K, Domellof E, Hernell O, Lonnerdal B, Domellof M. Neurodevelopment, nutrition, and growth until 12 mo of age in infants fed a low-energy, low-protein formula supplemented with bovine milkfat globule membranes: a randomized controlled trial. Am J Clin Nutr, 2014; 99, 860–8.

Timby N., Hernell O., Vaarala O., Melin M., Lönnerdal B., Domellöf M. Infections in infants fed formula supplemented with bovine milk fat globule membranes. A randomized controlled trial. J. Pediatr. Gastroenterol. Nutr. 2015; 60(3): 384-389.

Veereman-Wauters G, Staelens S, Rombaut R, Dewettinck K, Deboutte D, Brummer RJ, Boone M, Le Ruyet P. Milk fat globule membrane (INPULSE) enriched formula milk decreases febrile episodes and may improve behavioural regulation in young children. Nutrition 2012 28:749-52.

Vickers MH, Guan J, Gustavsson M, Krägeloh CU, Breier BH, Davison M, Fong B, Norris C, McJarrow P, Hodgkinson SC. Supplementation with a mixture of complex lipids derived from milk to growing rats results in improvements in parameters related to growth and cognition. Nutr Res 2009; 29:426–35.

Wang H, Sency V, McJarrow P, Bright A, Huang Q, Cechner K, Szekely J, Brace J, Wang A, Liu D, Rowan A, Wiznitzer M, Zhou A, Xin B. Oral ganglioside supplement improves growth and development in patients with ganglioside GM3 synthase deficiency. Journal of Inherited Metabolic Disease 2018, Sept 13 DOI: 10.1007/s10545-018-0220-1

Waworuntu R.V., Hanania T., Boikess S.R., Rex C.S., Berg B.M. Early life diet containing prebiotics and bioactive whey protein fractions increased dendritic spine density of rat hippocampal neurons. Int. J. Devl. Neuroscience. 2016; 55: 28-33.

Wu SS, Yeiser M, Harris CL, Wampler JL. Milk fat globule membrane (MFGM) and adjustments in protein, arachidonic acid, and iron in routine infant formula is well-tolerated and supports normal growth and normal iron status at one year of age. ESPGHAN 2018 poster N-P-138.

Xia Y, Gallier S, Rowan A, Wang B, Complex Lipids in Neurodevelopment and Growth (CLING) Study Group. (2018) Milk fat globule membrane as a source of gangliosides and phospholipids in infancy to support brain development and healthy growth. ESPGHAN 2018 poster N-eP-022.

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