Role of Sphingolipids in Infant Gut Health and Immunity

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Sphingomyelin (SM), glycosphingolipids, and gangliosides are important polar lipids in the milk fat globule membrane but are not found in standard milk replacement formulas. Because digestion and absorption of SM and glycosphingolipids generate the bioactive metabolites ceramide, sphingosine, and sphingosine-1-phosphate (S1P), and because intact gangliosides may have beneficial effects in the gut, this may be important for gut integrity and immune maturation in the neonate. The brush border enzymes that hydrolyze milk SM, alkaline sphingomyelinase (nucleotide phosphodiesterase pyrophosphatase 7), and neutral ceramidase are expressed at birth in both term and preterm infants. Released sphingosine is absorbed, phosphorylated to S1P, and converted to palmitic acid via S1P-lyase in the gut mucosa. Hypothetically, S1P also may be released from absorptive cells and exert important paracrine actions favoring epithelial integrity and renewal, as well as immune function, including secretory IgA production and migration of T lymphocyte subpopulations. Gluco-, galacto-, and lactosylceramide are hydrolyzed to ceramide by lactase-phlorizin hydrolase, which also hydrolyzes lactose. Gangliosides may adhere to the brush border and is internalized, modified, and possibly transported into blood, and may exert protective functions by their interactions with bacteria, bacterial toxins, and the brush border. *(J Pediatr 2016;173S:S53-9)*.

The milk fat globule membrane (MFGM) consists of amphiphilic lipids, cholesterol, and proteins. In addition to the major glycerophospholipids (PL), phosphatidylcholine (PC), and phosphatidylethanolamine, MFGM contains sphingomyelin (SM), glucosyl- and lactosylceramides, and gangliosides[1] (**Figure 1**). Thus, about one-half of the polar lipids in MFGM are sphingolipids (SL), but that is not the case in standard milk replacement formulas, which usually contain soy lecithin (ie, mainly PC as amphiphilic lipid emulgator). The polar lipids supply choline, ethanolamine, and fatty acids, which are needed for synthesis of cell membrane PL and acetylcholine during growth and expansion of tissue PL, pool in the neonate. In addition, MFGM SL have biological effects that could contribute to the beneficial effects of mothers' milk.

Digestion of SM, the major SL in milk, by nucleotide phosphodiesterase pyrophosphatase 7 (NPP7), a protease-resistant, bile salt-dependent brush border enzyme, generates ceramide, sphingosine, and sphingosine-1-phosphate (S1P).[3] These compounds are both metabolic intermediates during synthesis and degradation of SL, and bioactive compounds with numerous signaling functions mediated by intracellular pathways in the case of ceramide, and by well characterized plasma membrane G-protein coupled receptors in the case of S1P.[4] Because many of these effects are related to regulation of cell growth, differentiation, apoptosis, and immune cell migration, the question arises as to whether SL in milk may influence mucosal function and immune maturation in the gut.

NPP7 also has anti-inflammatory properties that may be related to its ability to inactivate the pro-inflammatory messenger platelet activating factor (PAF).[5] The sialic-acid-containing SL in milk (ie, the gangliosides) may have multiple effects including an influence on gut bacterial flora, interactions with pathogens, and effects on mucosal epithelial and immune functions.[2,6] This article summarizes current knowledge of the digestion and absorption of SL and how it may be related to biological effects in the neonatal gut. There are, however, few neonatal studies in this area. Some general aspects on SL metabolism in relation to gut inflammation and tumorigenesis are, therefore, also discussed.

SL in MFGM

The breastfed human infant ingests about 150 mg of SM per day,[7] which accounts for about 40% of the polar MFGM lipids. The MFGM also contains glucosylceramide, lactosylceramide, and gangliosides. In human milk, the content of glycosphingolipids is much lower than that of SM. Bovine milk MFGM contains more lactosylceramide than human milk.[8] The mucosal brush border contains significant amounts of SM, ceramides, glyco-SLs, and gangliosides, which are synthesized in the epithelium during differentiation along the crypt-villous axis.[9]

CRC	Colorectal cancer	NPP7	Nucleotide phosphodiesterase pyrophosphatase 7
DSS	Dextran sulphate sodium	PAF	Platelet activating factor
IBD	Inflammatory bowel disease	PC	Phosphatidylcholine
KO	Knockout	PL	Glycerophospholipids
MFGM	Milk fat globule membrane	S1P	Sphingosine-1-phosphate
NC	Neutral ceramidase	SL	Sphingolipids
NEC	Necrotizing enterocolitis	SM	Sphingomyelin

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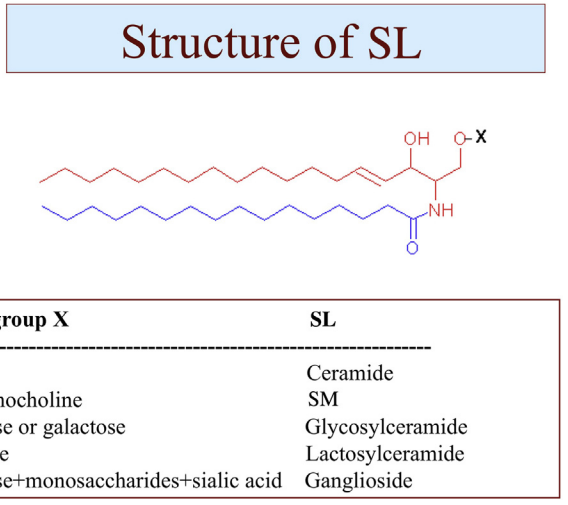

Headgroup X	SL
H	Ceramide
Phosphocholine	SM
Glucose or galactose	Glycosylceramide
Lactose	Lactosylceramide
Glucose+monosaccharides+sialic acid	Ganglioside

Figure 1. Sphingosine is a hydrophobic amino alcohol with 18 carbons and a terminal hydroxy-group at position 1. At position 2, an amino group forms an amide bond with a long chain fatty acid in ceramide. The OH group at position 1 forms an ester with phosphocholine in SM and a glycosidic bond with glucose or galactose in glycosylceramide. In lactosylceramide, the bond is formed with lactose, and in gangliosides, with a sialic acid-containing carbohydrate. For nomenclature of individual gangliosides, see Rueda.[2]

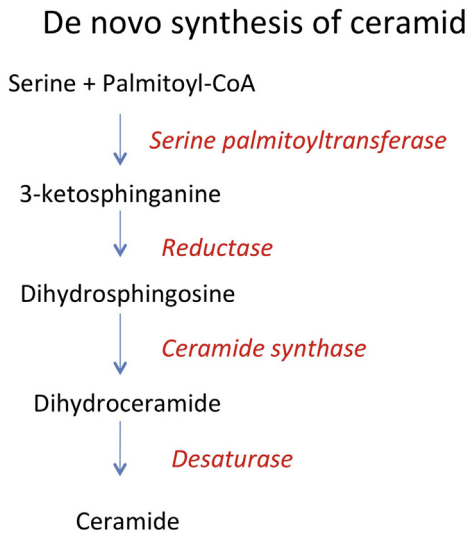

Figure 2. SM is not digested by any pancreatic enzyme but by the brush border enzyme NPP7, which generates ceramide and then is hydrolyzed to sphingosine and free fatty acids. Sphingosine is phosphorylated to S1P by sphingosine kinase and converted to palmitic acid and ethanolamine phosphate by S1P lyase, which is highly expressed in the gut. The fatty acids formed are incorporated mainly into chylomicron triglycerides. *CoA*, Coenzyme A.

Digestion of SM and Glycosylceramides

As previously reviewed,[3] dietary SM is sequentially hydrolyzed by NPP7 and a neutral ceramidase (NC) acting at the brush border of the intestinal epithelium and in the gut lumen. In contrast to SM and ceramide, sphingosine is rapidly absorbed and most is converted to palmitic acid in the mucosa and transported in chyle triacylglycerol[10] (Figure 2). Digestion and absorption of glucosylceramide exhibit similar features. The digestion of SM in the rat is extended throughout the gut; in humans with an ileostomy, most SM is digested and absorbed.[11]

In rodents, NPP7 occurs only in the gut, but in humans, it is also expressed in the liver and secreted in bile.[12] It has been purified, cloned, and identified as a novel member of the NPP family.[13] In the gut, levels of NPP7 are highest in the jejunum and ileum, and are lower in the colon. Studies in NPP7-/- mice confirmed its central role in SM digestion.[14] NPP7 was also shown to have some phospholipase C activity against PC and lyso-PC and against the pro-inflammatory lipid messenger PAF (1-alken-2-acetyl-glycerophosphocholine).[5] PAF can be produced by epithelial and immunocompetent cells in the gut and has been ascribed a pathogenic role in both inflammatory bowel disease (IBD) and in neonatal necrotizing enterocolitis (NEC).[15]

Gut NC from rats and humans has been purified,[16] and studies in NC knockout (KO) mice confirmed its role in ceramide digestion.[17] Interestingly, NC KO mice exhibit normal growth and phenotype. Bile-salt stimulated lipase hydrolyzes ceramide,[18] but the physiological importance of this is uncertain. Both NPP7 and NC are protease resistant and remain active in the gut lumen. They are released by bile salts, and in the case of NPP7, by tryptic cleavage as well. These features make it possible to use NPP7 and NC meconium levels to measure neonatal expression.[19]

Similar to SM, glucosyl- and galactosylceramide are not hydrolyzed by pancreatic enzymes but degraded in the gut to ceramide and sphingosine.[20] The brush border enzyme lactase-phlorizin hydrolase, which hydrolyzes the lactose in milk, also hydrolyzes glycosylceramides to ceramide.[21] The absorption of gangliosides is not well characterized. Studies in Caco2 cells indicate that the intact molecule can be associated with the brush border side and converted to other gangliosides by glycosyltransferases. A transcellular transport and intracellular degradation may also occur.[22] In rats fed ganglioside GD3, levels of this ganglioside increased in lipid rafts from the brush border and in plasma.[23]

Metabolism of Sphingoid Bases in Epithelial Cells

Released sphingosine is absorbed and most is converted to S1P by sphingosine kinases. S1P is converted to hexadecanal and ethanolamine phosphate by S1P lyase. Hexadecanal is oxidized to palmitic acid, which is incorporated into chylomicron triacylglycerols[10] (Figure 3). Some

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