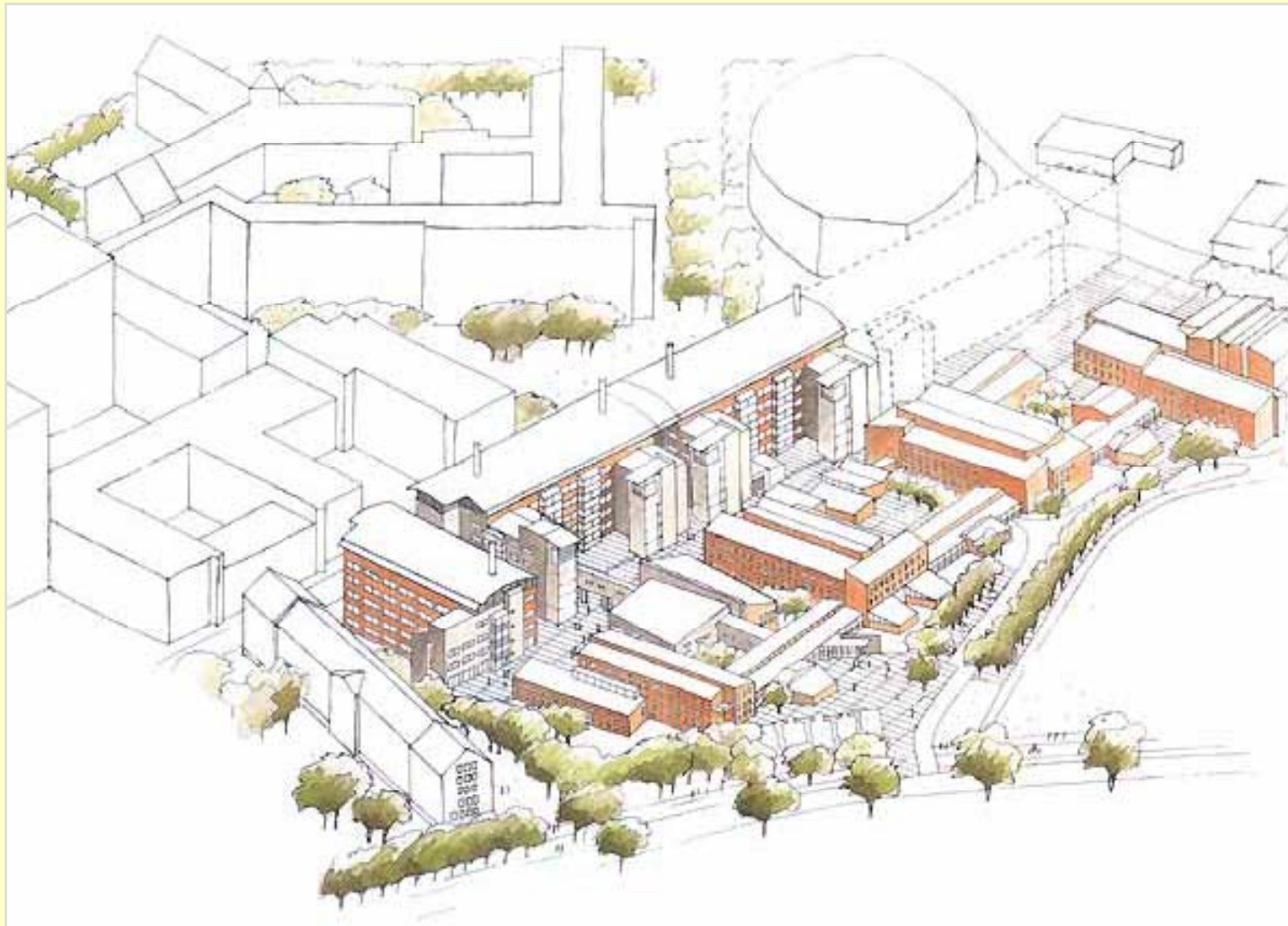


Polära mjölklipider som hälsomaterial

Åke Nilsson Avdelningen för Medicin, IKVL,
Lunds Universitet



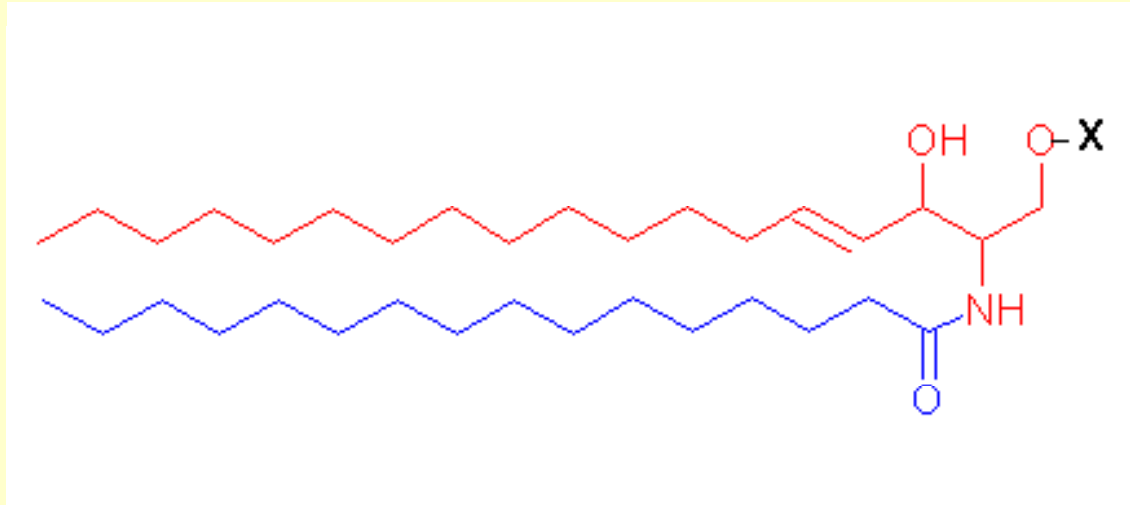
Polära mjölklipider med hälsopotential. BMC Lund.



The groups of polar lipids

- Glycerophospholipids
- Galactolipids
- Sphingolipids

Structure of sphingolipids



Headgroup X

Sphingolipid

H

Ceramide

Phosphocholine

Sphingomyelin

Glucose or galactose ...

Cerebroside

Glucose+oligosaccharide

Ganglioside

Exogenous sources of polar lipids

- Dietary intake 2,5-5 g/day
- About 300 mg sphingolipids/day
- Galactolipids in plants

Endogenous polar lipids

- 6-10 g/day secreted in bile, mainly PC.
- Amphiphilic component in mucus layer.
- Sloughing during cell turnover.

Absorption of polar lipids

- Pancreatic phospholipase A2 hydrolyzes both PC, PE and PI.
- Lysophospholipids and free fatty acids well absorbed.
- Galactolipids hydrolyzed by Pancreatic lipase related protein 2 (PLRP2).
- Sphingolipids slowly hydrolyzed by brush border enzymes.

Dietary polar lipids and medicine

- Blood lipids
- Gastric and duodenal ulcer.
- Inflammatory bowel disease.
- Gallstones
- Fatty liver and fibrosis.
- CNS functions.
- Infections of the GI tract.

Types of effects

- Protective in GI tract
- Effects on lipolysis
- Effects on sterol absorption
- Formation of lipid messengers
- Role in chylomicron formation
- Source of PUFAs and choline
- Antiinfectious effects

Choline as an essential nutrient

- Produced in the body by methylation of phosphatidylethanolamine.
- Demand modified by the methyl-exchange relationships between choline, methionine, folate, vitamin B₁₂.

Dietary sources of Sphingomyelin (SM)

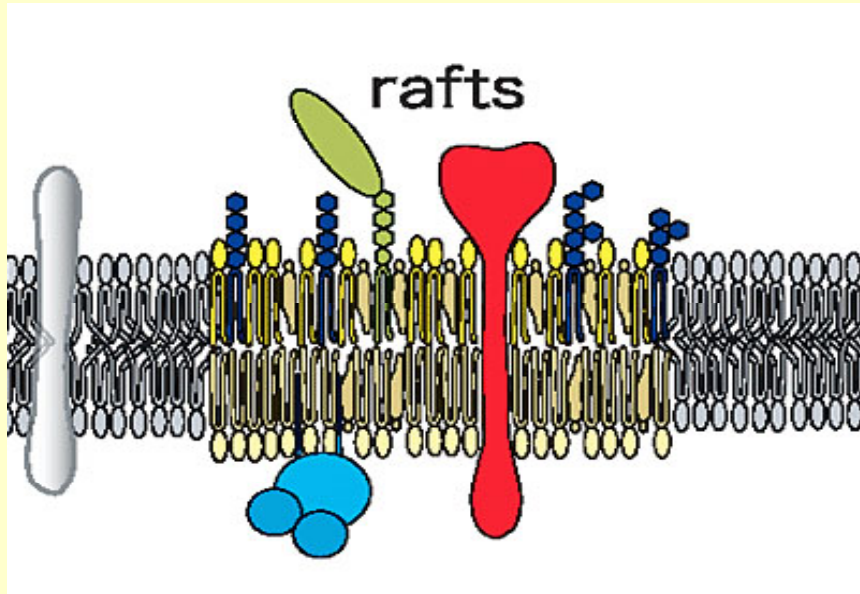


SM content mg/kg

Eggs	800
Butter	720
Cheese	500
Chicken	500
Fish	125
Milk	100

Sphingolipids in diet

- H Vesper et al. J Nutr 1999; 129:1239-50. Sphingolipids in food and the emerging importance of sphingolipids to nutrition.
- L Hellgren. 2001; 103:661-7. Occurrence of bioactive sphingolipids in meat and fish products. Eur J Lipid Sci Technol
- K Wehrmuller. Curr Nutr Food Sci 2007; 3:161-73. Occurrence and biological properties of sphingolipids – a review.



Sphingolipids in intestinal epithelium (mol/mol)

	Sphingolipids	Glycerophospholipids
Apical	38	29
Basolateral	19	56

Sphingomyelin in Diet

Dietary product	SM (mg/kg)
Human milk	130
Bovine milk (3.5% fat)	90
Cheese (28% fat)	350
Egg	800
Chicken	400
Turkey	290
Beef	290
Pork	260
Salmon	120
Catfish	80

Major sphingolipids in raw milk

(Rombaut et al J Dairy Sci 2005, 88:482-88)

- Sphingomyelin 82.6 mg/kg
- Lactosylceramide 19.1 mg/kg
- Glucosylceramide 8.0 mg/kg
- Gangliosides (GD3 and GM3)

Gangliosides in milk

(Sørensen et al 2006; Rapid Commun Mass Spectrom 20:3625-33)

- GD3 9.3 mg/l in Holstein and 17.5 mg/l in Jersey cow milk.
- GM3 0.1-0.2 mg/l.

Sphingolipids i plants

- Glucosylceramide.
- Ceramide phosphatidylinositol and its derivatives.
- Sphingoid base composition different than in mammalian sources.

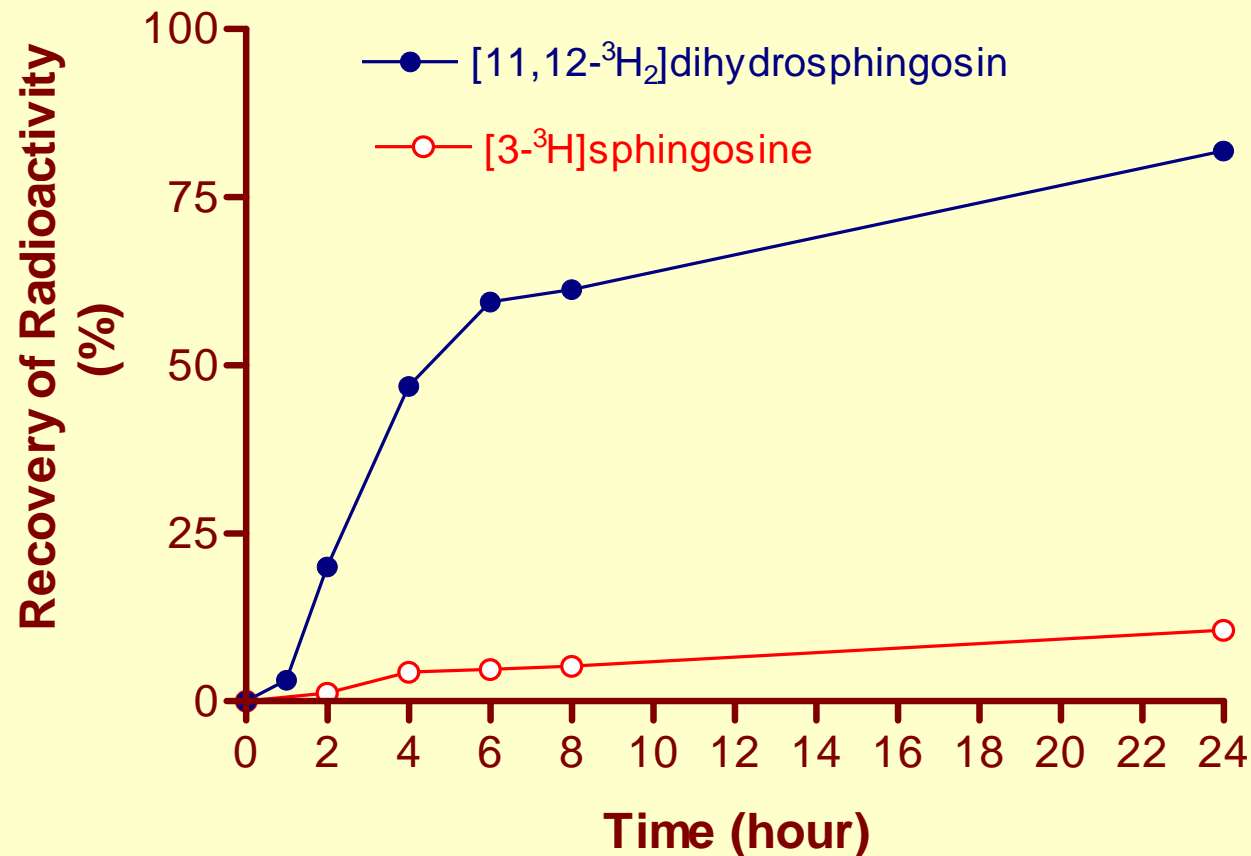
The early interest for sphingolipids in diet

- SM is abundant in arteriosclerotic lesions.
- SM is an important phospholipid in plasma.
- The level correlates to plasma cholesterol, LDL and plasma triglycerides.
- Is SM absorbed intact?

Digestion and absorption of sphingolipids

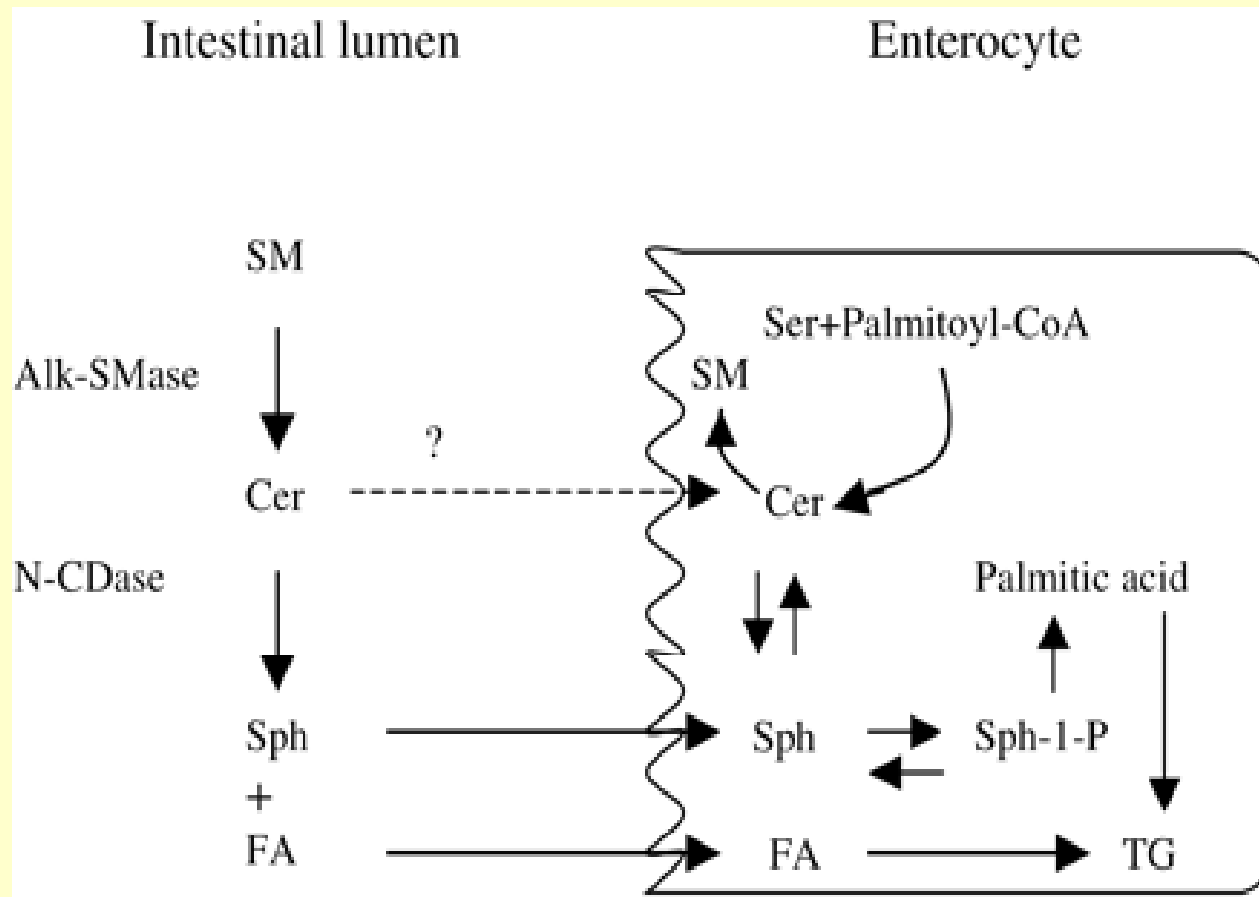
- Resistant to pancreatic lipases except that BSSL has some ceramidase activity
- SM hydrolyzed by mucosal alkaline sphingomyelinase
- Glycosylceramides hydrolyzed by lactase
- Ceramide hydrolyzed by mucosal neutral ceramidase 2

Recovery of radioactivity after feeding radiolabeled sphingosine and dihydrosphingosine in rats.

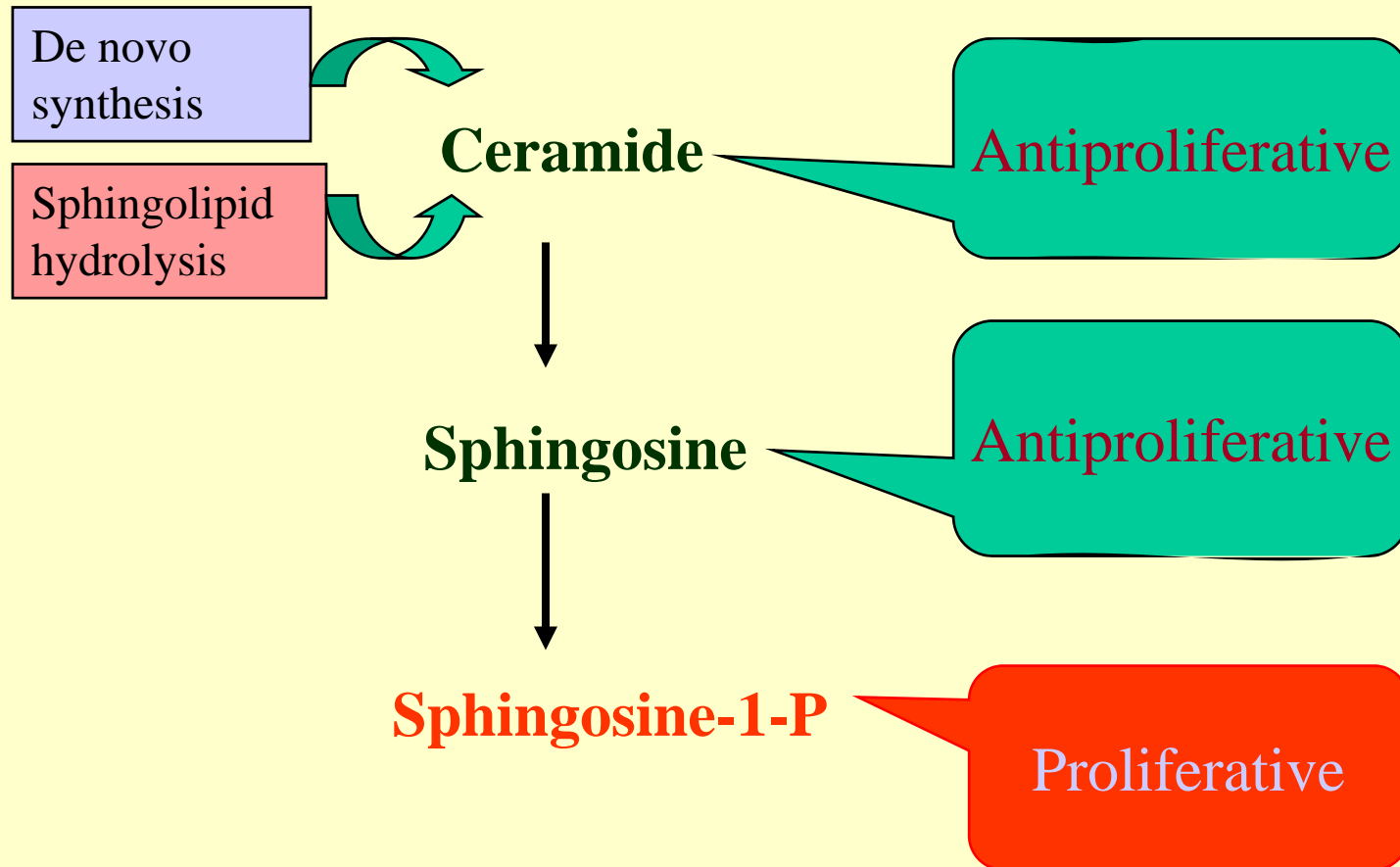


Scheme of sphingomyelin absorption.

Nilsson and Duan, J Lipid Res 2006; 47:154-71



Lipid messengers derived from sphingolipids



Effects of SM on cholesterol absorption

- L Nyberg et al J Nutr Biochem 2000; 11:244-9. A mutual inhibitory effect on absorption of sphingomyelin and cholesterol.
- Milk SM lowered cholesterol absorption much more than hydrogenated soy PC.

SM inhibition of cholesterol absorption

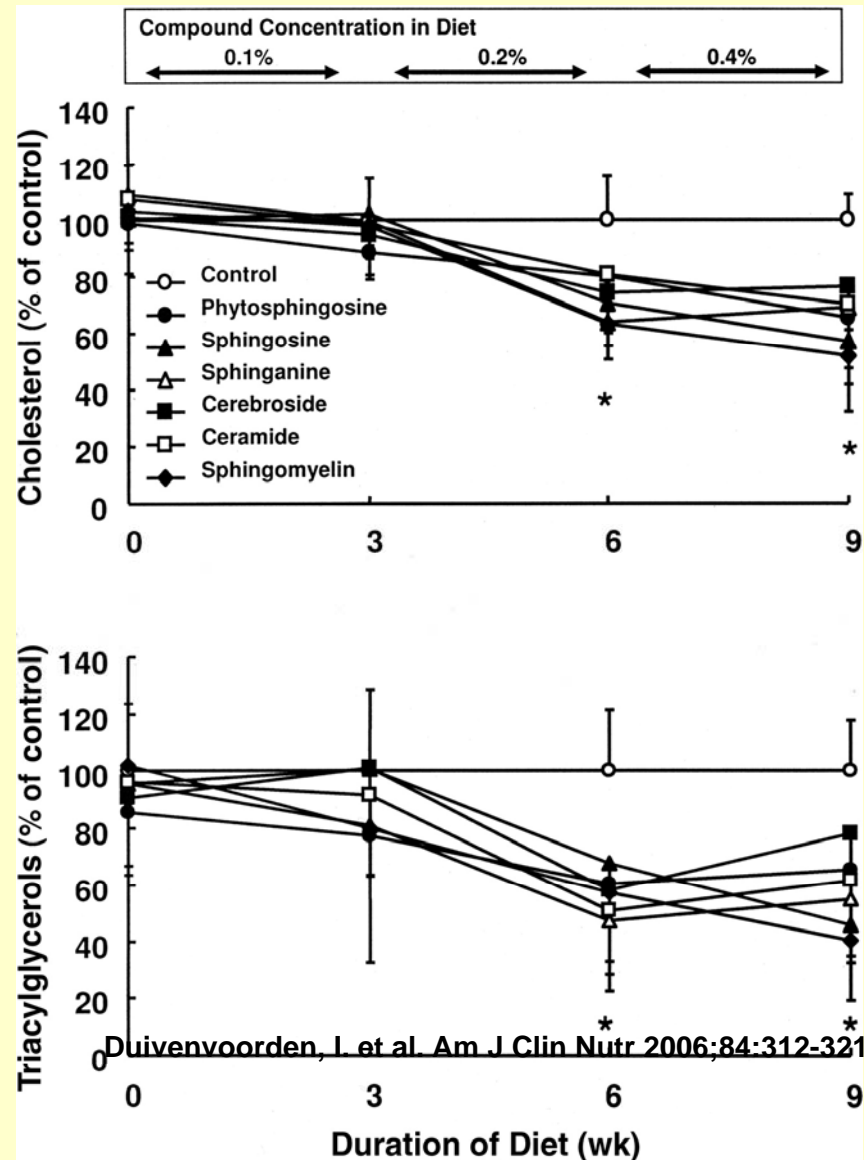
- SK Noh and SI Koo. J Nutr 2004; 134:2611-6.

Milk sphingomyelin is more effective than egg sphingomyelin in inhibiting intestinal absorption of cholesterol and fat in rats.

SM inhibits in vitro lipolysis

Patton, J. S., and M. C. Carey. 1981.
Inhibition of human pancreatic lipase-
colipase activity by mixed bile salt-
phospholipid micelles. *Am. J. Physiol.*
241: G328–G336.

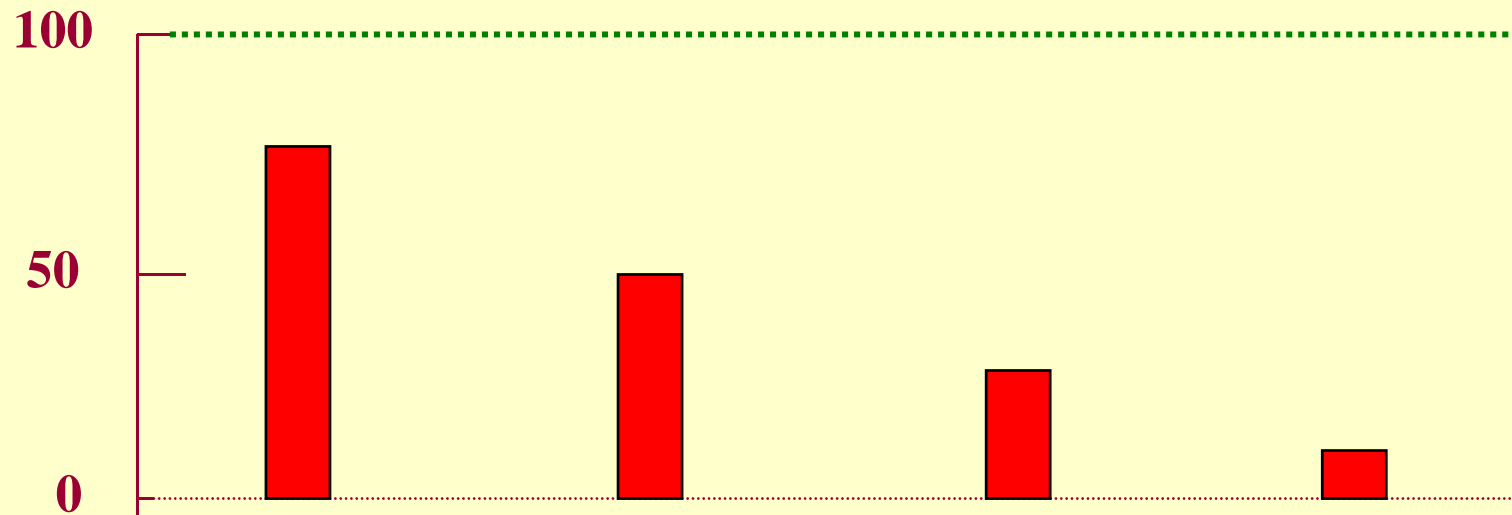
FIGURE 2. Mean (\pm SD) plasma cholesterol and triacylglycerol concentrations in APOE*3Leiden mice after food deprivation for 4 h



Effects of sphingolipids on colon cancer.

- DL Dillehay et al, Dietary sphingomyelin inhibits 1,2-dimethylhydrazine-induced colon cancer in CF1 mice. *J Nutr* 1994, 124:615-20.
- EM Schmelz, Sphingolipids in the chemoprevention of colon cancer. *Front Biosci* 2004; 9:2632-9.
- RD Duan, Anticancer compounds and sphingolipid metabolism in the colon. *In vivo* 2005; 19:293-300.

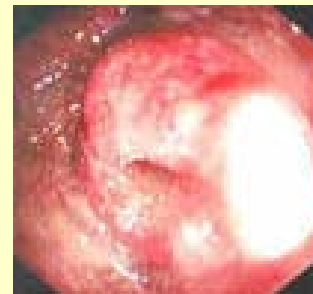
Changes of Alkaline SMase in Human Biopsy Samples of Colonic Diseases (% of normal)



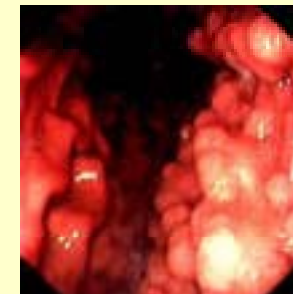
Ulcerative
Colitis



Sporadic
Adenoma



Colonic
Carcinoma



Adenomatous
Polyposis

Hertervig E et al Cancer 79:448, 1997. Hertervig et al Br J Cancer 81:232, 1999. Sjöqvist U et al Inflamm Bowel Dis 8:258, 2002

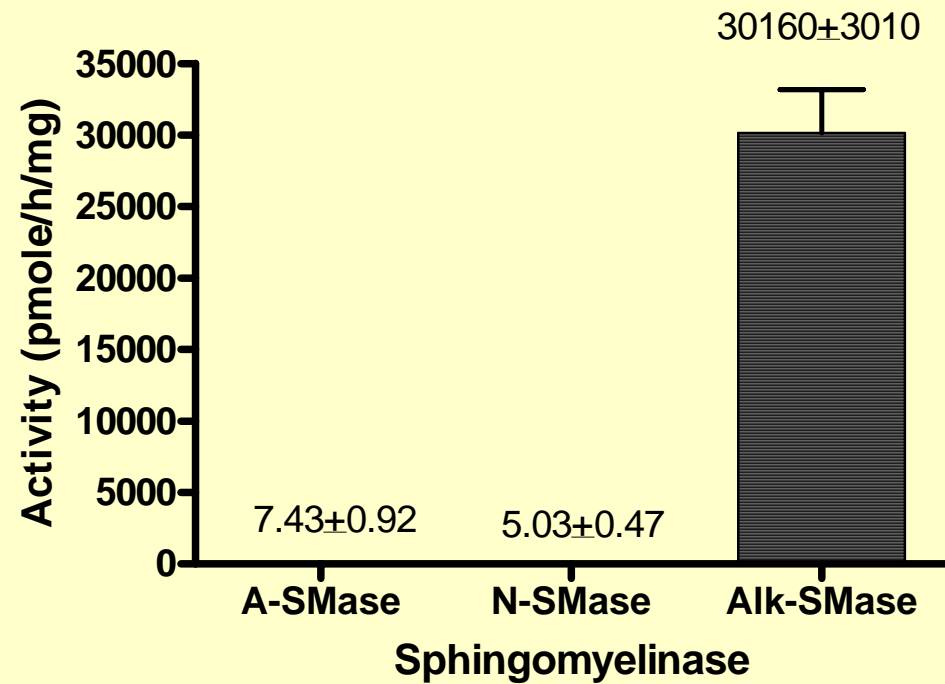
Do sphingolipids have biological effects in the neonate?

- Motouri et al. J Pediatr Gastroenterol Nutr
Seven day old rats fed intragastrically with 0.5% SM or 0.5% PC for seven days.
- Lactase lower and Auerbach plexus more developed in SM group. Vacuolated cells in ileum only in villus tips.

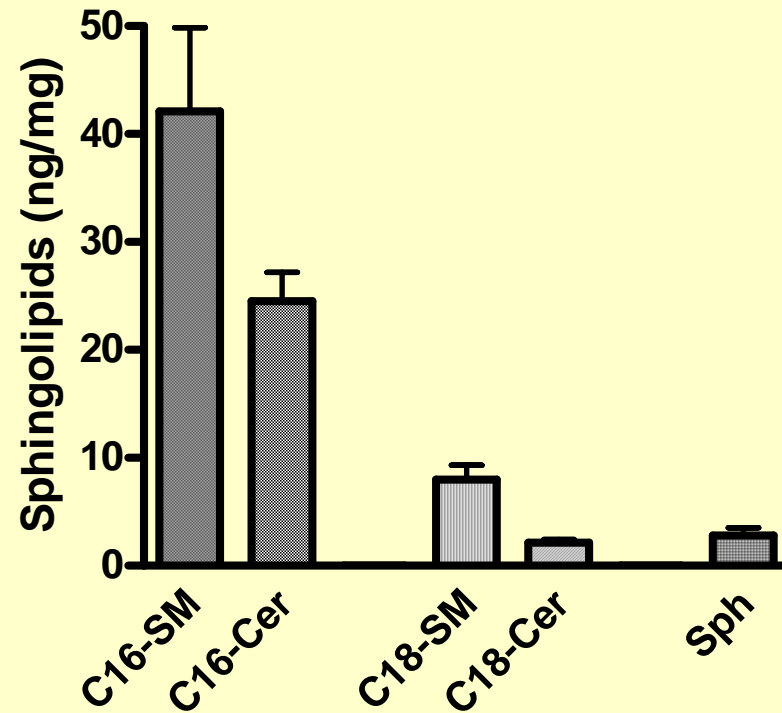
Gut sphingomyelinases in fetus and newborns

- Lillienau et al Lipids 2003; 38:545-9.
- Intestinal alkaline SMase increases promptly at day 20-22.
- Thus, alk-SMase appears just in time to digest milk SM.

Sphingomyelinases in meconium



Sphingolipid metabolites in meconium



Effects of dietary gangliosides

- Decreased adhesion of cholera toxin.
- Influence of adhesion and growth of E coli species.
- Increase in bifidobacteriae species and decrease in E coli.
- Counteract GiardiaLlamblia infections.
- Influence on polyunsaturated fatty acid metabolism.

Can sphingolipids have adverse effects?

- Increase in atherogenic lipoproteins under some circumstances?
- Enhancing tumour growth or inflammation under some circumstances, by stimulating S1p-formation?

Conclusions from neonatal studies

- Neonates ingest significant amounts of sphingolipids during suckling.
- They are able to digest them.
- The importance of this needs further study.

General conclusions

- Sphingolipids may have lipid lowering effects by inhibiting cholesterol absorption as well as other mechanisms.
- They may counteract colon cancer and gut inflammation.
- Effects in the neonate need further characterization.
- Humans studies are necessary.

Even more general conclusions

- Potential targets for dietary effects of sphingolipids have been identified.
- What can be achieved in humans by using these targets we still don't know.

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