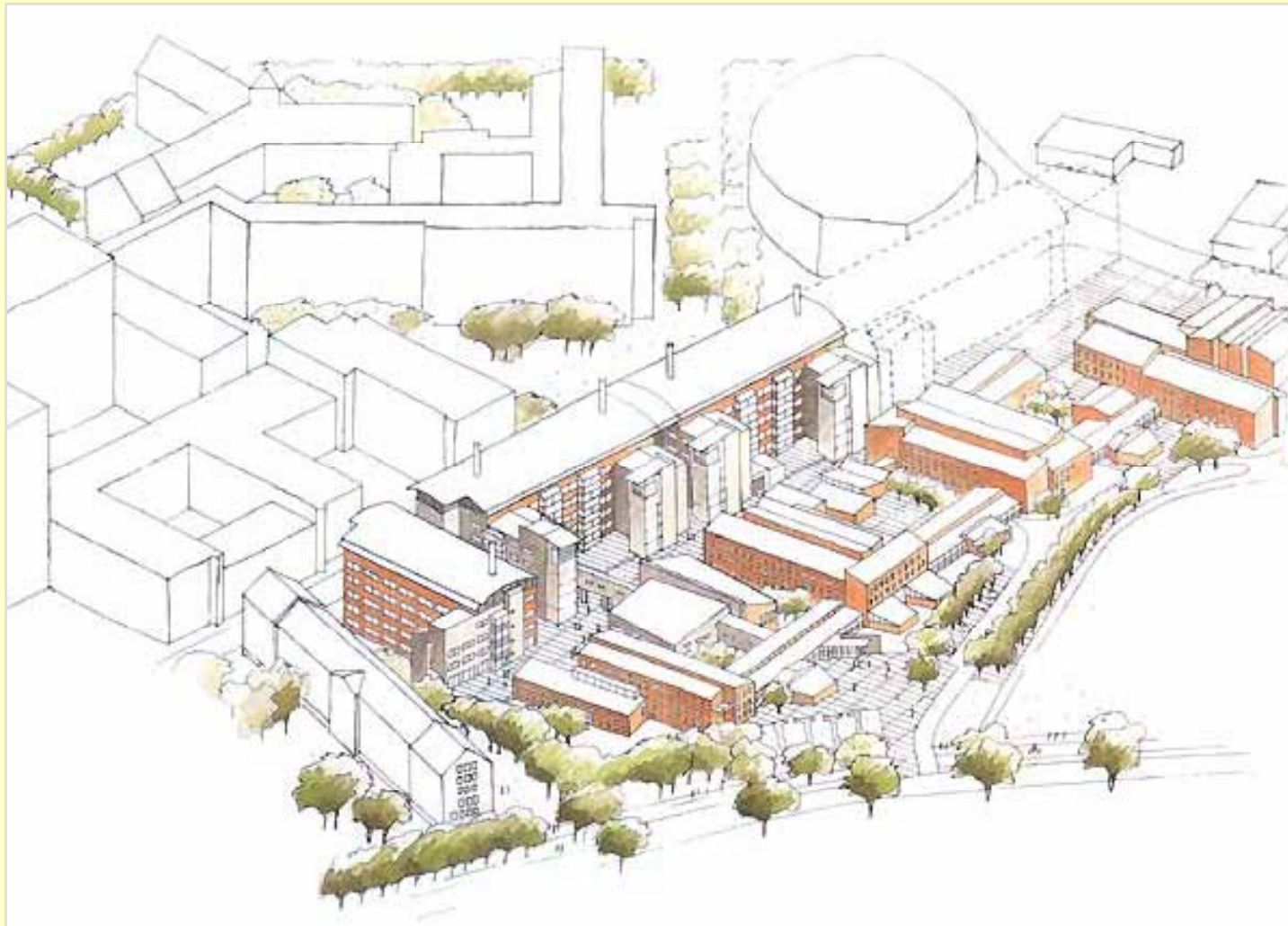


# Polära mjölklipider som hälsomaterial

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Lunds Universitet



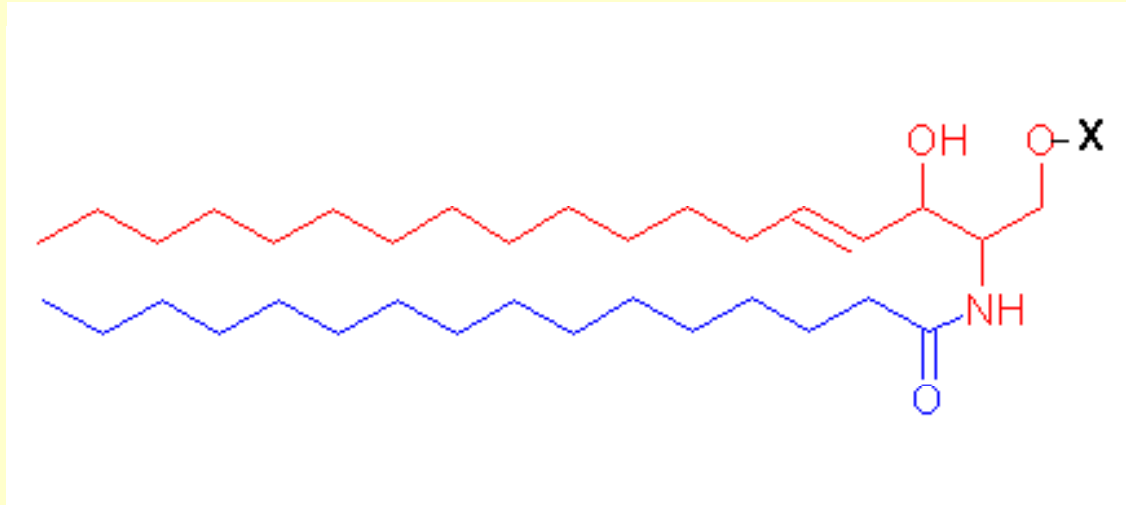
# Polära mjölklipider med hälsopotential. BMC Lund.



# 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 B<sub>12</sub>.

# Dietary sources of Sphingomyelin (SM)

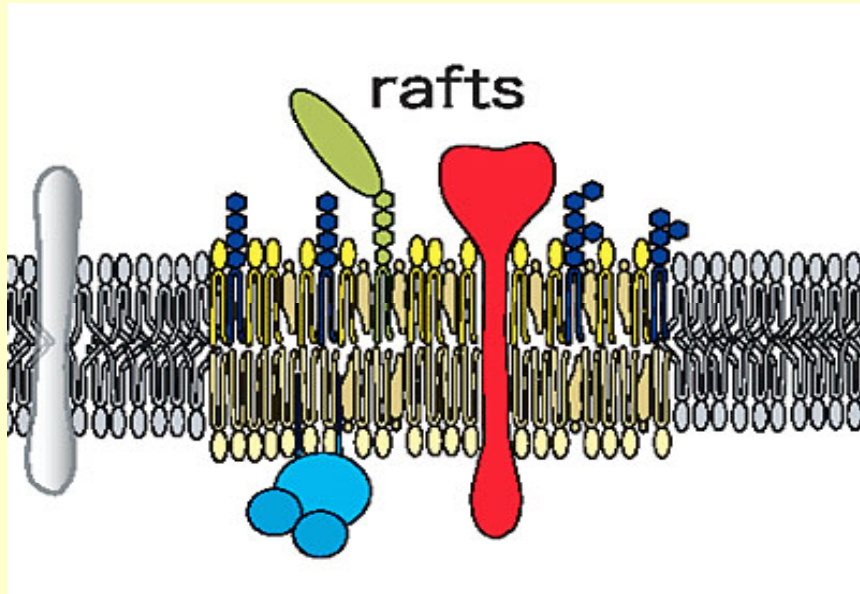


SM content mg/kg

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.

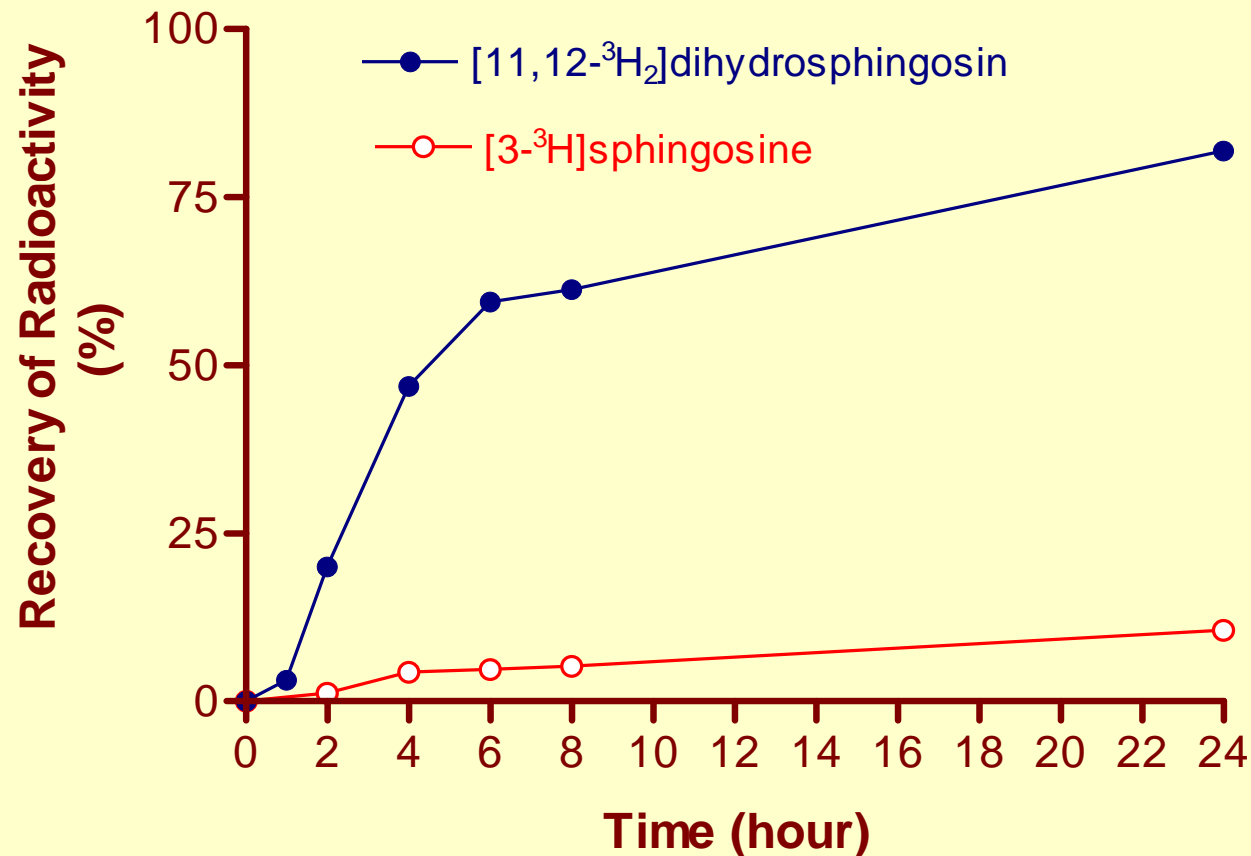
## **The early interest for sphingolipids in diet**

- 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

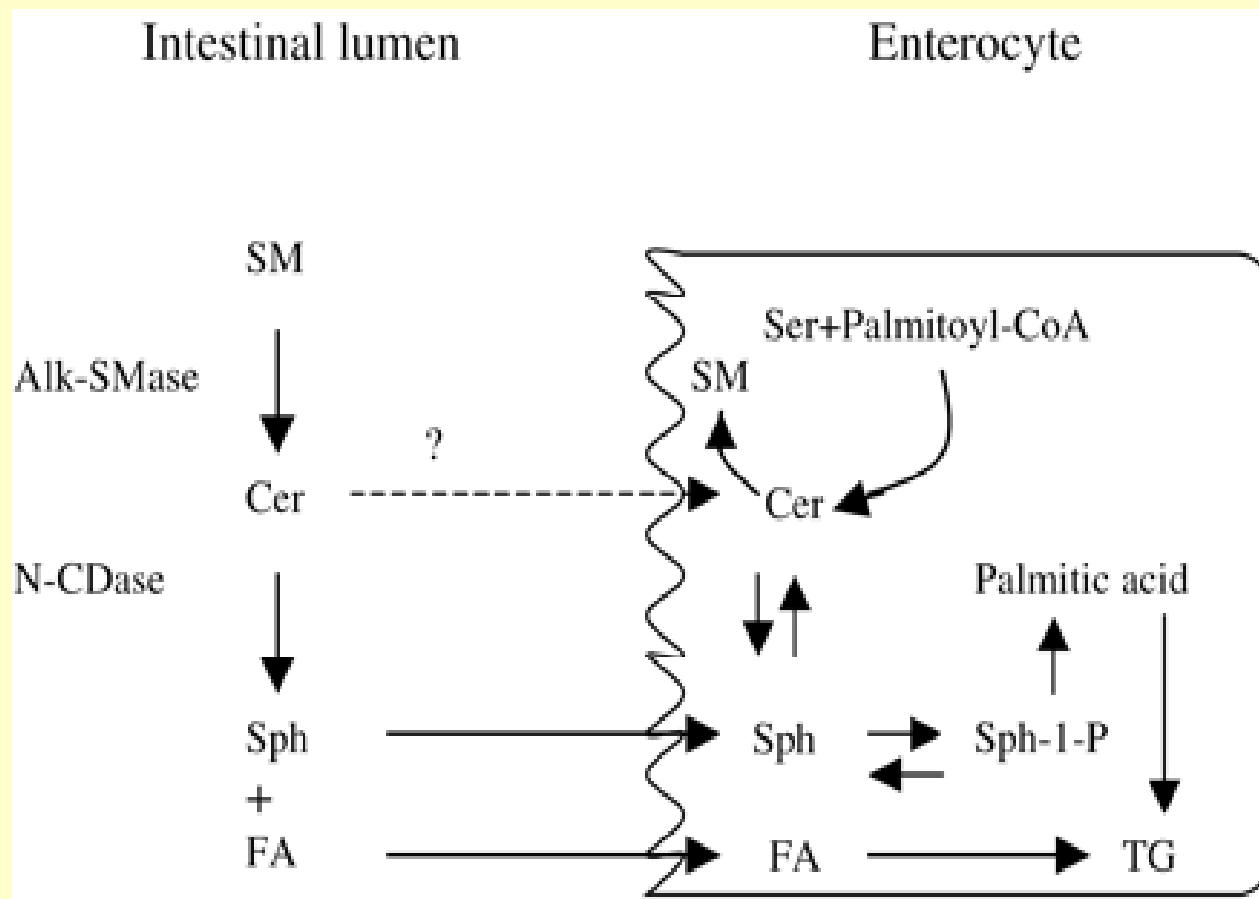
- Resistant to pancreatic lipases except that BSSL has some ceramidase activity
- SM hydrolyzed by mucosal alkaline sphingomyelinase
- Glycosylceramides hydrolyzed by lactase
- Ceramide hydrolyzed by mucosal neutral ceramidase 2

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

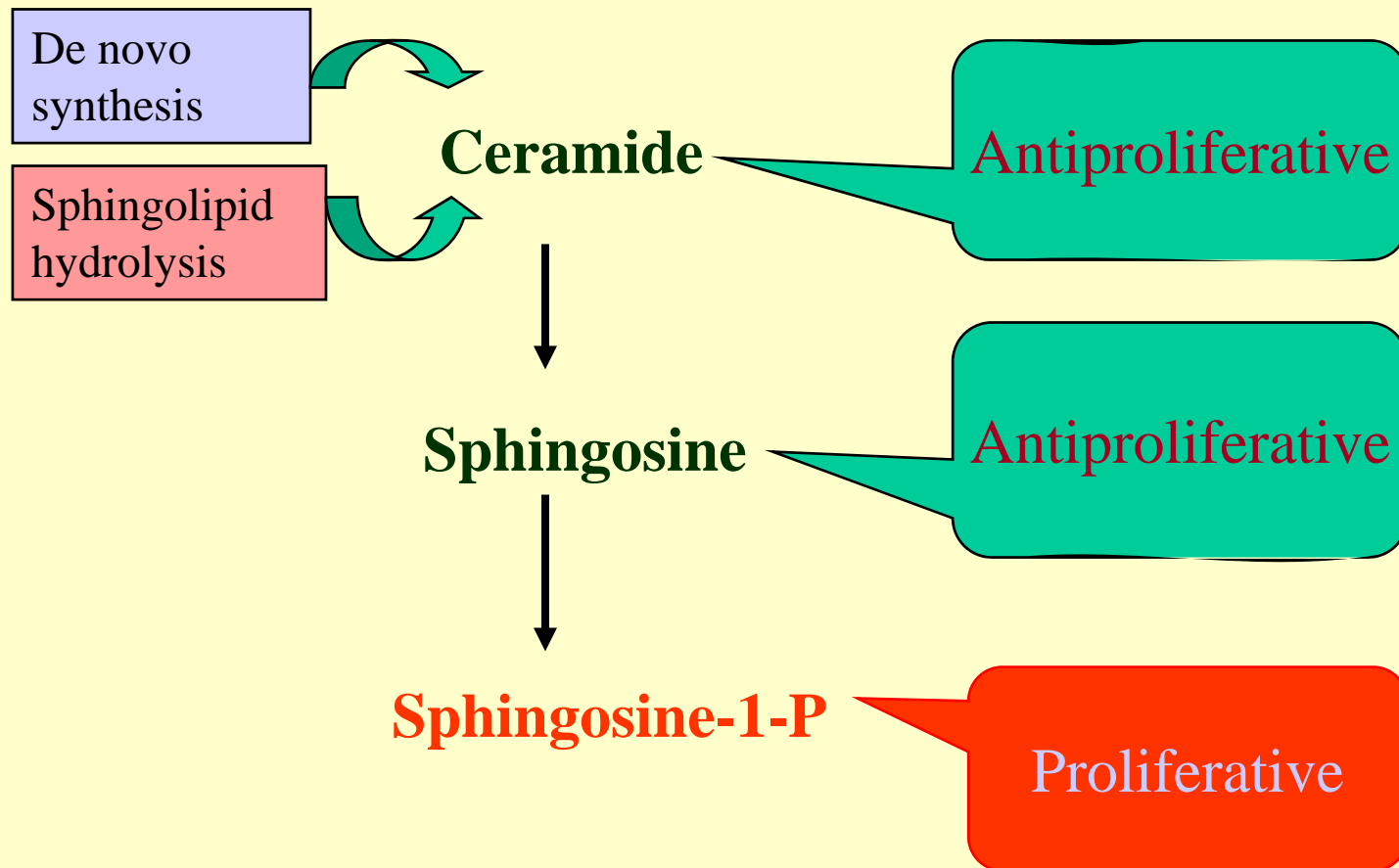


# Scheme of sphingomyelin absorption.

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

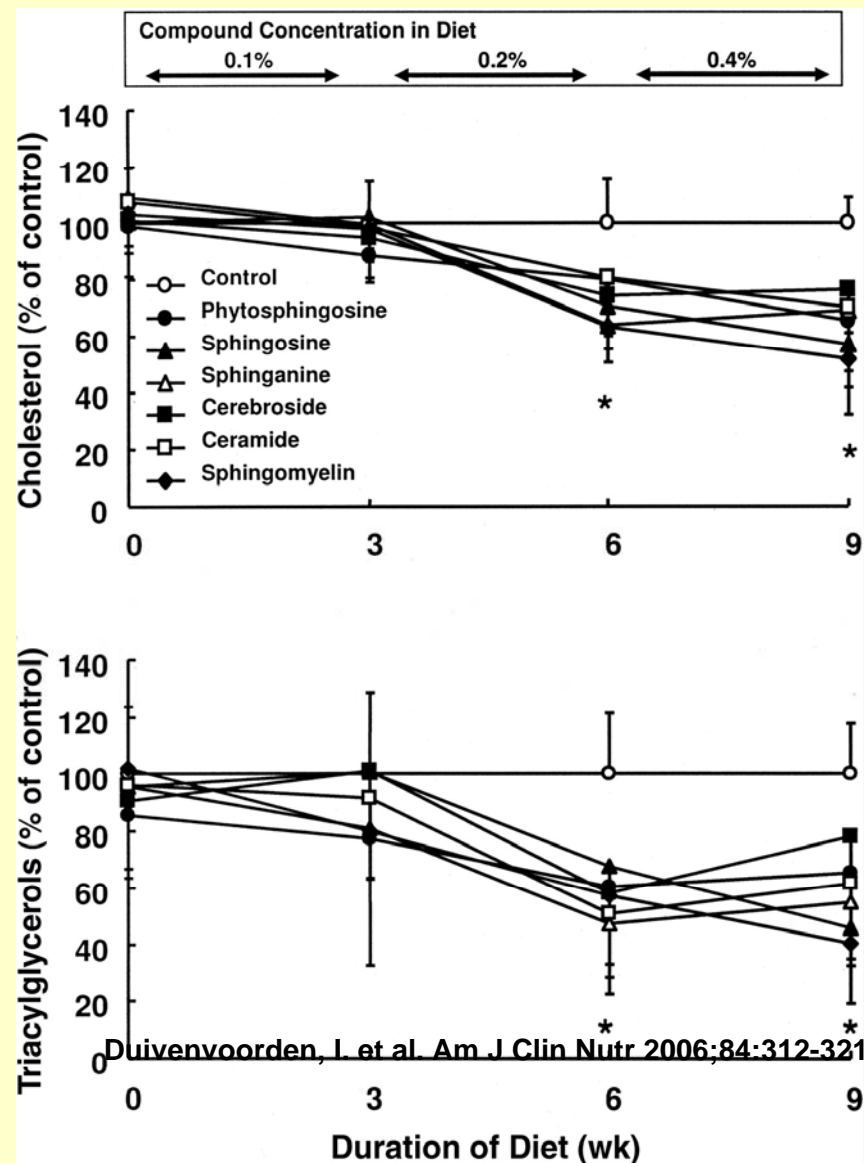
- SK Noh and SI Koo. J Nutr 2004; 134:2611-6.

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.

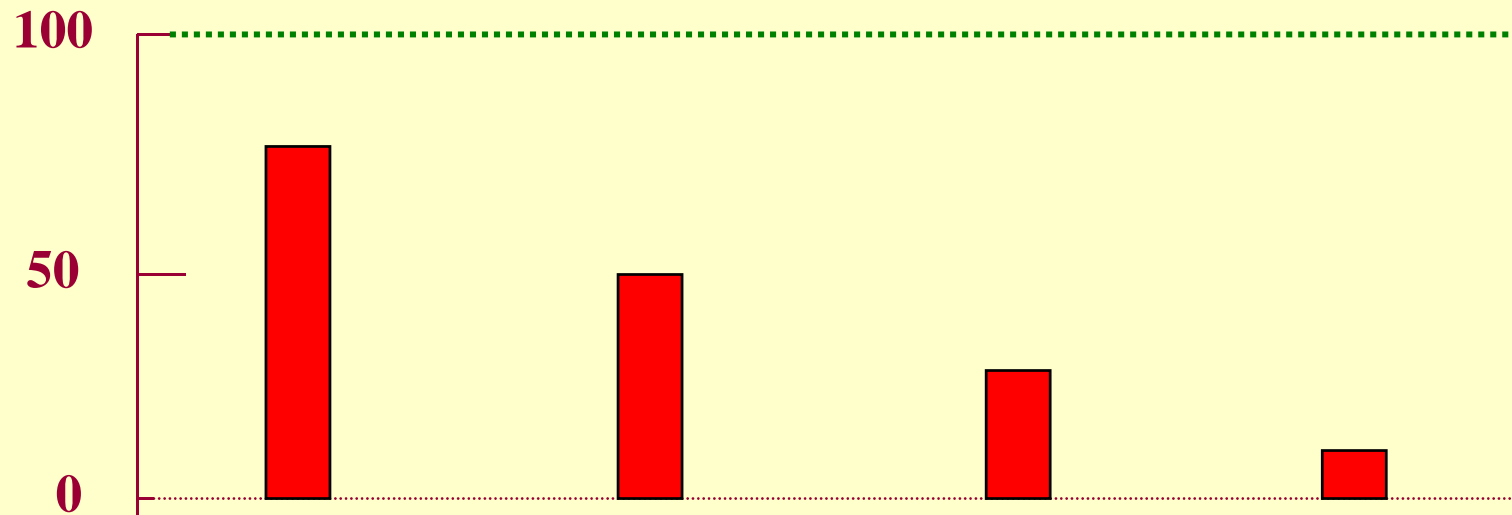
**FIGURE 2. Mean ( $\pm$ SD) plasma cholesterol and triacylglycerol concentrations in APOE\*3Leiden mice after food deprivation for 4 h**



# 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 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.

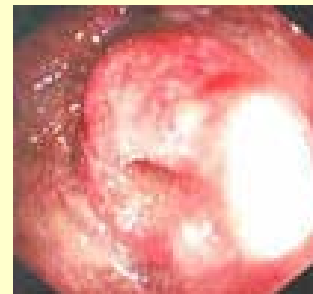
# Changes of Alkaline SMase in Human Biopsy Samples of Colonic Diseases (% of normal)



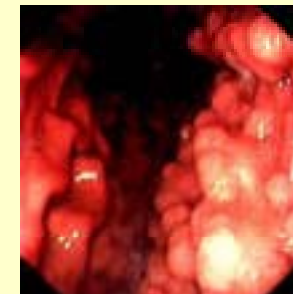
Ulcerative  
Colitis



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*

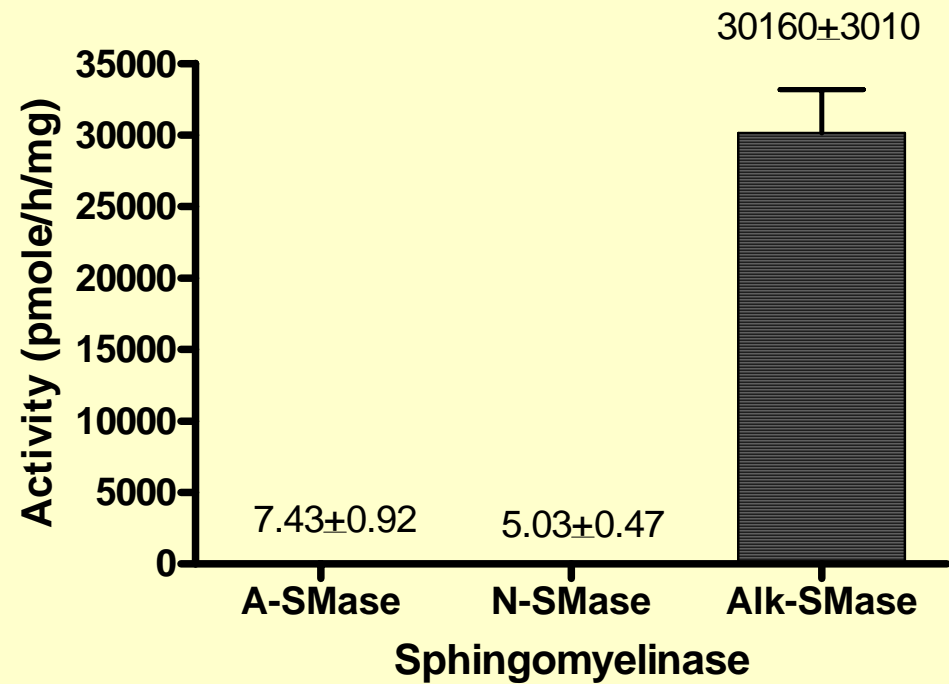
# Do sphingolipids have biological effects in the neonate?

- 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.

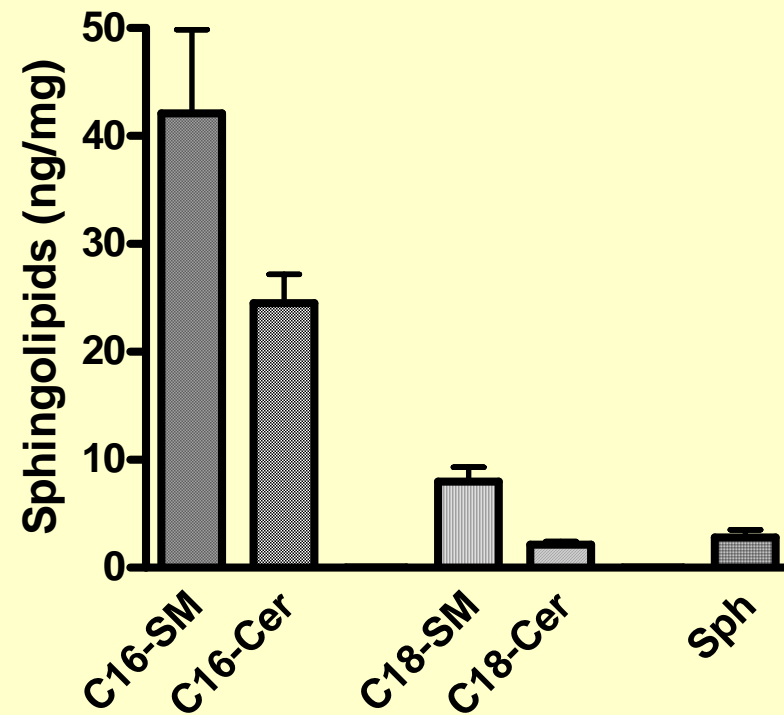
## Gut sphingomyelinases in fetus and newborns

- 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.

# Thanks to....

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