



Sphingolipids

Tinyee Hoang

March 28, 2002



Objectives

✦ History

✦ Sphingolipids

✦ Sphingolipids as chemopreventive agents

✦ Conclusions

History

J. L. W. Thudichum
(1884)

- ✦ Known as “Father of Neurochemistry”
- ✦ Discovered Sphingolipids while studying the chemical constituents of the brain



History

Hubert Carter (1930s)

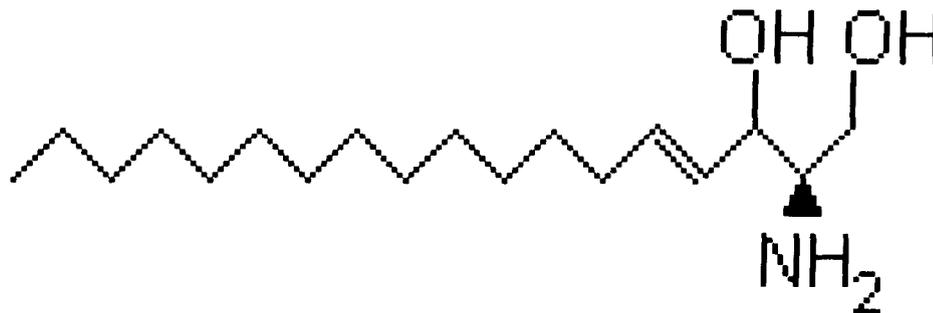
- ✱ Found full stereochemistry structure of sphingosine

In the 1950s

- ✱ More structures were found
- ✱ Sphingolipids found outside of brain

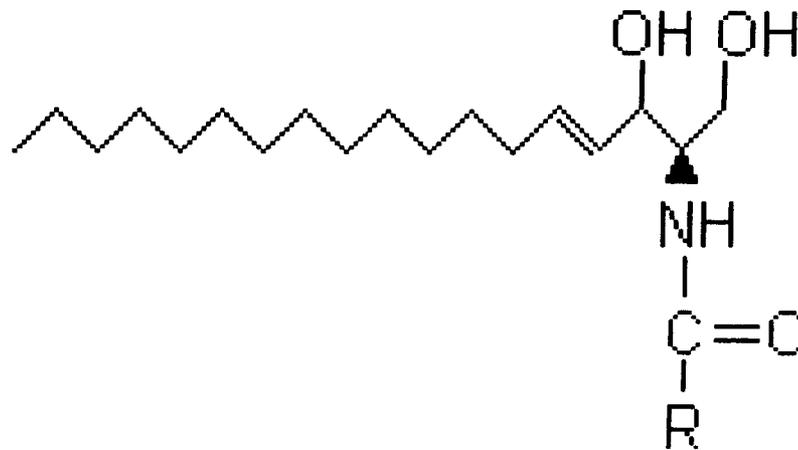
What's a Sphingolipid

- ✦ Lipids that contain amino alcohol sphingosine
- ✦ Sphingoid base: D-erythro-sphingosine
- ✦ Classified into: Ceramides, Sphingomyelins, and Glycosphingolipids



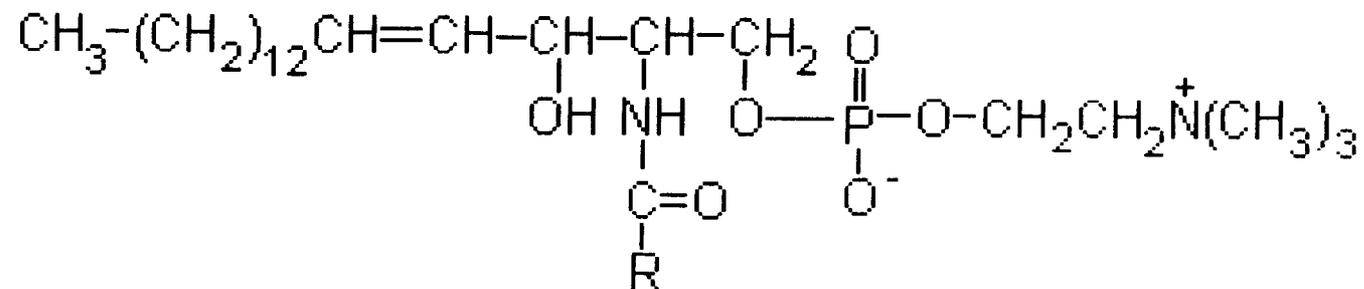
Ceramides

- ✦ Either a saturated or unsaturated long chain (C16, C18, C22, C24)
- ✦ Have a fatty acid linked to the amino group of sphingosine base.



Sphingomyelin

- ✦ Major component of plasma membranes, golgi, serum lipoproteins of animal tissue.
- ✦ Contains polar head group phosphoryl choline at primary alcohol of ceramide.
- ✦ Known also as phospholipid



Glycosphingolipid

- ✧ Has 1 or more carbohydrates linked to the primary alcohol of ceramide
 - ◆ Cerebrosides
 - Monosaccharide form: important constituents in the brain and nervous tissue.
 - Di-, tri-, and tetrasaccharide forms: Found in spleen, liver, plasma, and erythrocytes
 - ◆ Gangliosides
 - More complex sphingolipid
 - Abundant in gray matter of human brain
 - Unlike lipids, they are soluble in water and polar organic solvents

Function

- ✦ Critical for maintenance of membrane structure
- ✦ Modulate behavior of growth factor receptors and extracellular matrix proteins
- ✦ Serve as binding sites for m.o., microbial toxins, and viruses
- ✦ Function as “second messengers” for growth factors, cytokines, differentiation factors, $1\alpha,25$ -dihydroxycholecalciferol, and a list of agonists and toxins.

Function – Second Messengers

Growth factors and cytokines induce sphingomyelin (SM) hydrolysis to produce different metabolites by activating enzyme systems to alter cell behavior.

- ✦ Platelet-derived growth factor (PDGF) causes SM to undergo hydrolysis and further metabolic rxns to form sphingosine 1-phosphate, which is a potent mitogen and an inhibitor of apoptosis.

Second Messengers – Cont'd

- ✦ Tumor necrosis factor- α (TNF- α) induces SM to hydrolyze into ceramide, which inhibits growth and induces apoptosis

Sphingolipids in Food

Sphingolipids in selected foods and yearly consumption per capita

Product	Sphingolipid content mmol/kg	Consumption per capita mmol/year (g/year)
Dairy Products		38.5
Milk (3.5%)	0.16	5.76
Lowfat Milk (<2%)	0.09	5.49
Cheese (29%)	1.33	15.9
Frozen Dairy (11%)	0.5	7.04
Butter	0.46	0.92
Eggs	2.25	14
Total Meat Products		34.3
Beef and veal	0.39	11.3
Chicken and turkey	0.39 to 0.59	14
Fish	0.13	0.9
Vegetables	0.04 to 2.4	8.1 to 34
Potato	0.69	4.1
Tomato	0.42	1.7
Soybeans	2.4	n.a.
Fruits and nuts	0.07 to 0.8	3.2
Cereals	0.58	38
Total per year		153 to 181 116 to 139

//

Sphingolipids in Food

- ✠ Sphingolipids account for 0.01-0.02% of the diet.
- ✠ Vary with food type
 - ◆ Complex sphingolipids with different head groups and ceramide backbones – Animal tissue
 - ◆ Cerebrosides with glucose, galactose, mannose, and inositol – Plant tissue

Sphingolipids as Chemopreventive Agents

- ✦ Colon cancer is the second leading cause of cancer mortality
- ✦ Of the list of food constituents that have been shown to block colon carcinogenesis, Sphingolipids are most prominent
- ✦ Sphingosine inhibits protein kinase C, which has been associated with tumor promotion, and blocks induction of ornithine decarboxylase by phorbol esters, which is a biochemical marker of promotion of chemically-induced skin tumors in mice.
- ✦ Sphingosine and ceramides induce cell differentiation in some transformed cell lines.

Recent Studies

- ✦ Colon tumor incidence in mice fed sphingomyelin was reduced to 20% compared to mice fed a control diet, which was 47%.
- ✦ Sphingomyelin resulted in a significantly lower number of aberrant crypts induced by DMH administration.
 - ◆ A feeding of GluCer, LacCer and G_{D3} (intermediate metabolites) at 0.025-0.1% of the diet inhibited aberrant crypt foci (ACF) by 50-60%

Recent Studies

- ✦ Substantial amounts of dietary sphingomyelin are digested and absorbed in the upper intestine, which reduces the amount of bioactive molecules reaching the colon.
 - ◆ Preparation of the conjugate (ceramide) with D-glucuronic acid will be poorly digested in the upper intestine, but sensitive to hydrolysis by bacterial β -glucuronidase in the colon.
 - ◆ Cer- β -glucuronide inhibited ACF formation by 30-37%
 - ◆ A longer colon, a longer exposure time to microbial enzymes, will give a stronger suppression of ACF

Factors that alter sphingolipid metabolism

-
- ✘ Fumonisin are mycotoxins produced by *Fusarium moniliforme* and other fungi.
 - ✘ Cause diseases in animals that were fed contaminated grain.
 - ✘ Results in hepatotoxicity and liver tumors in rats and affects the kidney.
 - ✘ Consumption of contaminated maize has been correlated with human esophageal cancer in areas of southern Africa and China

Fumonisin

- ✘ Structure similar to sphinganine.
- ✘ The cellular target is ceramide synthase, which catalyzes the addition of fatty acids to sphinganine in the de novo biosynthesis of sphingolipids
- ✘ Block the biosynthesis of complex sphingolipids and result in the accumulation of sphinganine.
- ✘ Sphinganine is a compound that is toxic to many cells and may account for many cellular effects of these mycotoxins.
- ✘ Sphinganine is a useful sphingolipid biomarker as an early clinical indicator of exposure to fumonisins and related mycotoxins.

Conclusions

- ✦ Hyperproliferation is a common property of tumors and can have several causes:
 - ◆ Increased rate of cell growth
 - ◆ Reduced rate of cell death (apoptosis)
 - ◆ Or a combination of both
- ✦ Sphingoid bases are highly cytotoxic, inhibit growth, and are potent inducers of apoptosis of transformed cells.
- ✦ Cer- β -glucuronide may be an effective chemopreventive agent for human colon cancer.
- ✦ Sphinganine is a good biomarker for mycotoxicity
- ✦ Bottom line: More studies need to be done on metabolism of Sphingolipids in humans

References

Dillehay, D. L., Webb, S. K., Schmelz, E.-M., and Merrill, A. H., Jr. Dietary Sphingomyelin Inhibits 1,2-Dimethylhydrazine-Induced Colon Cancer in CF1 Mice. *J. Nutr.* 1994; 124: 615-620

Merrill, A. H., Jr., Schmelz, E.-M., Wang, E., Schroeder, J. J., Dillehay, D. L., and Riley, R. T. Role of Dietary Sphingolipids and Inhibitors of Sphingolipid Metabolism in Cancer and Other Diseases. *J. Nutr.* 1995; 125: 1677S-1682S

Merril, A. J., Jr., Schmelz, E.-M., Wang, E., Dillehay, D. L., Rice, L. G., Meredith, F., and Riley, R. T. Importance of Sphingolipids and Inhibitors of Sphingolipid Metabolism as Components of Animal Diets. *J. Nutr.* 1997; 127: 830S-833S

Schmelz, E. M., Sullards, M. C., Dillehay, D. L., and Merrill, A. H., Jr. Colonic Cell Proliferation and Aberrant Crypt Foci Formation Are Inhibited by Dairy Glycosphingolipids in 1,2-Dimethylhydrazine-Treated CF1 Mice. *J. Nutr.* 2000; 130:522-527

