Sphingolipids

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March 28, 2002
Objectives

- History
- Sphingolipids
- Sphingolipids as chemopreventive agents
- Conclusions
History

J. L. W. Thudichum (1884)

- Known as “Father or 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

\[
\begin{align*}
\text{CH}_3-(\text{CH}_2)_{12}\text{CH}=\text{CH}-\text{CH}-\text{CH}-\text{CH}_2\text{O} \\
\text{OH NH O-P-O-CH}_2\text{CH}_2\text{N(CH}_3)_3 \\
\text{C=O O-} \\
\text{R}
\end{align*}
\]
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, 1α,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

<table>
<thead>
<tr>
<th>Product</th>
<th>Sphingolipid Content</th>
<th>Consumption per capita</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmol/kg</td>
<td>mmol/year (g/year)</td>
</tr>
<tr>
<td><strong>Dairy Products</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milk (3.5%)</td>
<td>0.16</td>
<td>38.5</td>
</tr>
<tr>
<td>Lowfat Milk (&lt;2%)</td>
<td>0.09</td>
<td>5.76</td>
</tr>
<tr>
<td>Cheese (29%)</td>
<td>1.33</td>
<td>15.0</td>
</tr>
<tr>
<td>Frozen Dairy (11%)</td>
<td>0.5</td>
<td>7.04</td>
</tr>
<tr>
<td>Butter</td>
<td>0.46</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>Eggs</strong></td>
<td>2.25</td>
<td>14</td>
</tr>
<tr>
<td><strong>Total Meat Products</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beef and veal</td>
<td>0.39</td>
<td>11.3</td>
</tr>
<tr>
<td>Chicken and turkey</td>
<td>0.39 to 0.59</td>
<td>14</td>
</tr>
<tr>
<td>Fish</td>
<td>0.13</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Vegetables</strong></td>
<td>0.04 to 2.4</td>
<td>8.1 to 34</td>
</tr>
<tr>
<td>Potato</td>
<td>0.69</td>
<td>4.1</td>
</tr>
<tr>
<td>Tomato</td>
<td>0.42</td>
<td>1.7</td>
</tr>
<tr>
<td>Soybeans</td>
<td>2.4</td>
<td>na</td>
</tr>
<tr>
<td>Fruits and nuts</td>
<td>0.07 to 0.8</td>
<td>3.2</td>
</tr>
<tr>
<td>Cereals</td>
<td>0.58</td>
<td>38</td>
</tr>
<tr>
<td><strong>Total per year</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>153 to 181</td>
<td>116 to 139</td>
</tr>
</tbody>
</table>
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

- Fumonisins are mycotoxins produced by *Fusarium moniliforme* and other fungi.

- Cause diseases in animals that were fed contaminated grain.

- Results in hepatoxicity 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.
Fumonisins

- 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


References
