Gangliosides: structure, occurrence, biosynthesis and analysis.

GANGLIOSIDES
STRUCTURE, OCCURRENCE, BIOLOGY AND ANALYSIS

The name ganglioside was first applied by the German scientist Ernst Klenk in 1942 to lipids newly isolated from ganglion cells of brain. They were shown to be oligoglycosylceramides containing N-acetylneuraminic acid (sialic acid or ‘NANA’ or ‘SA’ or Neu5Ac) residues (or less commonly N-glycoloylneuraminic acid, Neu5Gc), joined via glycosidic linkages to one or more of the monosaccharide units, i.e. via the hydroxyl group on position 2, or to another sialic acid residue. As a result, the polar head groups of the lipids carry a net-negative charge at pH 7.0 and they are acidic. These lipids can amount to 6% of the weight of lipids from brain, but they are found at low levels in all animal tissues where like the neutral oligoglycosphingolipids they are concentrated in ‘rafts’ in the plasma membrane. They are not found outwith the animal kingdom. One of the common monosialo-gangliosides (ganglioside G\textsubscript{M1}) is illustrated –

![Ganglioside GM1 Diagram](image)

It can also be depicted as –

![Ganglioside GM1 Diagram](image)

Most of the common range of gangliosides are derived from the ganglio- and neolacto-series of oligoglycosphingolipids (see the web page), and they should be named systematically in the same way with the position of the sialic acid residue(s) indicated as for branched structures. However, they are more conveniently defined by a short-hand nomenclature system proposed by Svennerholm in which M, D and T refer to mono-, di- and trisialogangliosides, respectively, and the numbers 1, 2, 3, etc refer to the order of migration of the gangliosides on thin-layer chromatography. For example, the order of migration of monosialogangliosides is G\textsubscript{M3} > G\textsubscript{M2} > G\textsubscript{M1}.

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To indicate variations within the basic structures, further subscripts are added, e.g. \( G_{M1a} \), \( G_{D1b} \), etc. Although alternatives have been proposed that are more systematic in structural terms, the Svennerholm nomenclature is that encountered most often in the literature.

In general, the ceramide structures of gangliosides tend to be relatively simple. Sphingosine tends to be the main sphingoid base, accompanied by the C\( _{20} \) analogue in gangliosides of the central nervous system mainly. Stearic acid (18:0) can be 80 to 90\% of the fatty acid constituents, accompanied by small amounts of 16:0, 20:0 and 22:0, but with little or no 2-hydroxy acids other than in some exceptional circumstances (e.g. some carcinomas).

Although the nature of the ceramide component is relevant to the biological function of gangliosides, it is the carbohydrate moiety that has the primary importance for most of their functions. However, detailed discussion of these structures would take us into realms of chemistry best left to carbohydrate experts (see the reading list below). As with the neutral oligosaccharides, an enormous range of structural forms varying in the nature of the carbohydrate moiety exist, from a sialo-cerebroside upward, although lactosylceramide is the primary precursor for most gangliosides. In any given cell type, the number of different gangliosides may be relatively small, but their nature and compositions may be characteristic and in some way related to the function of the cell.

In brief, the pathways for the biosynthesis of the common series of gangliosides of the ganglio-series, for example, involve sequential activities of sialyltransferases and glycosyltransferases as illustrated.

The required enzymes are bound to the membranes of the Golgi apparatus, in a sequence that corresponds to the order of addition of the various carbohydrate components. The sialyltransferase
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that catalyses the synthesis of the relatively simple ganglioside \( \text{G}_{\text{M}3} \) is located in the \( \text{cis} \)-region of the Golgi, while those that catalyse the terminal steps of ganglioside synthesis are located in the distal or \( \text{trans} \)-Golgi region. At least five distinct sialyltransferases are known to operate, each using CMP-SA to transfer the sialic acid residue to the oligosaccharide chain. Finally, the gangliosides are transferred to the plasma membrane by a transport system involving vesicle formation.

As the brain develops, there is an increase in the content of gangliosides and in their degree of sialylation. There are large differences between species and tissues. The main gangliosides of human brain are \( \text{G}_{\text{M}1} \), \( \text{G}_{\text{D}1\text{a}} \), \( \text{G}_{\text{D}1\text{b}} \) and \( \text{G}_{\text{T}1} \), while \( \text{G}_{\text{M}3} \) is found mainly in the extraneural tissues. Compositional changes can be induced by nerve stimulation, environmental factors or drug treatments.

In experimental systems, gangliosides have been shown to control growth and differentiation of cells, and they have an important role in the interactions between cells. In particular, they have key functions in the immune defense systems, and they are involved in pathological states such as cancer. They act as receptors of interferon, epidermal growth factor, nerve growth factor and insulin and in this way may regulate cell signalling. Intact gangliosides inhibit growth by rendering cells less sensitive to stimulation by epidermal growth factor, but removal of the N-acetyl group of sialic acid enhances this reaction and stimulates growth. Gangliosides bind specifically to various bacterial toxins, such as those from botulinum, tetanus and cholera. The techniques of molecular biology, which enable specific enzymes to be eliminated from experimental animals, are now leading to a better understanding of the function of specific gangliosides.

As with the neutral oligoglycosylceramides, a number of unpleasant lipidoses have been identified involving storage of excessive amounts of gangliosides in tissues. The most important of these is Tay-Sachs disease, a fatal genetic disorder (mainly in Jewish populations) in which harmful quantities of ganglioside \( \text{G}_{\text{M}2} \) accumulate in the nerve cells in the brain and other tissues. As infants with the most common form of the disease develop, the nerve cells become distended and a relentless deterioration of mental and physical abilities occurs. The condition is caused by insufficient activity of a specific enzyme, \( \beta \)-N-acetylhexosaminidase, which catalyses the biodegradation of gangliosides.

In addition, a generalized gangliosidosis has been characterized in which ganglioside \( \text{G}_{\text{M}1} \) accumulates in the nervous system leading to mental retardation and enlargement of the liver.

Analysis

Gangliosides are not the easiest of lipids to analyse, as they are most ‘un-lipid-like’ in many of their properties. For example, in the conventional Folch method for extraction of lipids from tissues, the gangliosides partition into the aqueous layer rather than with the conventional lipids in the chloroform layer. Nonetheless, methods have been devised for quantitative extraction, and they can then be sub-divided into the various molecular forms by high-performance thin-layer chromatography (or less commonly by high-performance liquid chromatography). Nowadays, mass spectrometry is the probably main method for structural analysis and especially for identifying and sequencing the carbohydrate chains, with invaluable assistance from nuclear magnetic resonance spectroscopy.

Recommended Reading

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- Lingwood, C.A. A holistic approach to glycolipid function; is the lipid moiety important? Trends Glycosci. Glycotechnol., 12, 7-16 (2000).

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