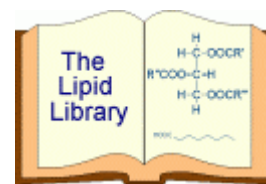
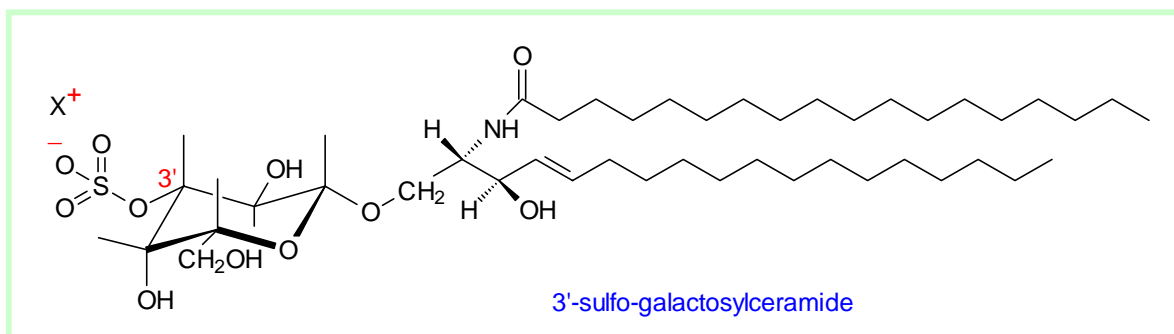


GLYCOSPHINGOLIPID SULFATES

STRUCTURE, OCCURRENCE, BIOLOGY AND ANALYSIS



Glycosphingolipid sulfates (sometimes termed “sulfatides” or “sulfoglycosphingolipids”) are glycosphingolipids carrying a sulfate ester group attached to the carbohydrate moiety. They were first identified in brain tissue by the pioneering lipid chemist Thudichum in 1884, although it was much later before they were properly characterized. Although sulfoglycosphingolipids tend to be minor components of tissues, 3'-sulfo-galactosylceramide (or galactosylceramide-1³-sulfate or 'cerebroside sulfate') illustrated is one of the more abundant glycolipid constituents of brain myelin, and it is also present in many other organs, especially the kidney.



Many other sulfoglycosphingolipids have now been characterized but from animal tissues only (sea urchins to invertebrates). For example, sulfo-lactosylceramide or lactosylceramide-1³-sulfate and other sulfate esters derived from oligoglycosylceramides of the globo- and ganglio-series have been isolated from human kidney, where they show some structural kinship with the “brain-type” gangliosides. Such lipids with one to four hexose units, and usually one but occasionally two sulfate groups have been isolated from the kidneys of rats and mice. As of 2009, 24 such lipids with variations in the carbohydrate chain had been characterized in vertebrates alone.

Two oligoglycosphingolipids with terminal glucuronic acid residues having sulfate ester moieties in the 3' position occur in the peripheral nervous system. Further oligoglycosphingolipids, including gangliosides, with sulfate groups have been isolated from human, mouse and monkey kidney cells. For example, with kidney cells from the African green monkey, nine distinct sulfated glycolipids were characterized. In most if not all of these, the sulfate ester moiety is attached to the C3 hydroxyl group and has an equatorial conformation.

Many parallels can be drawn between the biosynthesis, metabolism and function of the sulfoglycosphingolipid, **seminolipid**, and sphingolipid sulfates, as described elsewhere on this website. Also, there are separate web pages dealing with the plant sulfonolipid, **sulfoquinovosyldiacylglycerol**, and the microbial **sulfonolipids**.

The fatty acid components of sulfo-lipids in animals vary with the nature of the lipid and the tissue. In myelin from the central nervous system, 24:0 and 2-hydroxy saturated fatty acids predominate in the sulfo-galactosylceramide. The corresponding lipid from peripheral tissues often contains a high proportion of 16:0 and 18:0 fatty acids, and this can also be the case in some of the sulfo-oligoglycolipids of brain. On the other hand, 22:0 together with 23:0 and 24:0 are the main fatty acids of kidney sulfo-lipids.

Biosynthesis of galactosylceramide-1³-sulfate involves sulfation of galactosylceramide catalysed by the enzyme galactosylceramide sulfotransferase in the lumen of the Golgi apparatus, with 3'-phosphoadenosine-5'-phosphosulfate as the activated sulfate donor. Oligoglycosphingolipids are presumably sulfated by similar mechanisms.

Like the gangliosides, sulfoglycosphingolipids are acidic and relatively soluble in aqueous systems, properties that must have a bearing on their functions in tissues, especially in ion transport. Indeed stable layers of water up to 44 Angstroms thick can form around the polar head group. The free hydroxyl groups in the fatty acid and sphingoid base constituents greatly strengthen hydrogen-bonding effects in surface membrane, where sulfoglycosphingolipids may be essential components as amphiphilic donors of negative charges. For example, sulfatides have been shown to be important in the transport of sodium and potassium ions in salt glands of ducks and in organs associated with osmoregulation in fish. There are strong indications that they may have a similar role in kidney. A high content of sulfatides in the gastric and duodenal mucosa, where membranes can be attacked by acid, pepsin and bile salts, may be closely related to a function in mucosal protection. Membrane sulfatide may also have a role in platelet function.

The most active period for galactosylceramide-1³-sulfate synthesis in brain coincides with myelin formation during fetal development in animal models, and there is considerable evidence pointing to a specific role in this process. During development, there is a rapid increase in the relative concentration of molecular species with C₂₄ as opposed to C₁₈ fatty acids. Experiments with genetically modified animals have confirmed that sphingolipid sulfates are essential for myelin development, maintenance and function. It is believed that sulfatide is a key regulator of the differentiation of oligodendrocytes.

Catabolism: The principles of lysosomal degradation of sphingolipids are outlined in our webpage dealing with **glycosylceramides**. Catabolism of cerebroside sulfate within lysosomes is aided by a non-enzymic protein, known as 'saposin B' (or as the 'cerebroside sulfate activator' or CS-Act), which is one of a group of four cysteine-rich proteins with a common ability to interact with membranes, amongst other functions. It is believed that saposin B acts by binding to the lipid, presenting it to the hydrolase in a form that facilitates reaction. Structural studies have revealed that the molecule is a dimer with a large hydrophobic cavity into which the lipid fits and is presumably orientated in an appropriate manner to enable attack by the hydrolase.

Aberrant sulfoglycosphingolipid metabolism has been associated with various pathogenic conditions, including cancer, autoimmune diseases and sphingolipid storage disorders. For example, sulfoglycosphingolipids accumulate as a consequence of elevated galactosylceramide sulfotransferase activity in a number of human cancers. In contrast, reduced levels of brain sulfatides have been found at the earliest stages of Alzheimer's disease, possibly as a consequence of an impaired sulfatide transport mechanism mediated by apolipoprotein E.

Lysosulfatide (sulfogalactosylsphingosine), i.e. without the fatty acid constituent, in addition to the acylated form accumulates in tissues from patients with the metabolic disorder - metachromatic leukodystrophy. The enzyme arylsulfatase A is lacking, leading to fatal de-myelination of both central and peripheral nervous systems. Lysosulfatide also appears to have signalling functions akin to those of sphingosine 1-phosphate and sphingosine phosphorylcholine. All three lysolipids are transported in plasma in the high-density lipoprotein fraction (see the appropriate web pages).

Sponges have been found to contain many novel lipid compounds, and the freshwater sponge *Ephydatia syriaca* contains a strange sulfated ceramide glycoside, termed '**syriacin**', in which a fucose residue is linked to ceramide via a sulfate bridge. The fatty acid linked to the ceramide is also novel, i.e. (all *Z*)-34*S*-methylhexatriaconta-5,9,12,15,18,21-hexaenoic acid.

Analysis

Sulfoglycolipids tend not to be quite as water-soluble as the **gangliosides**, but they resemble them in some of their physical properties, and comparable methods are used for analysis. One advantageous strategy is to remove the sulfate ester moiety to reduce the polarity, so that the methodology devised for neutral glycosphingolipids can be employed. Modern mass spectrometric methods are now being used increasingly for characterization purposes.

Recommended Reading

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