Sphingolipid

Sphingolipids are a class of lipids containing a backbone of sphingoid bases, a set of aliphatic amino alcohols that includes sphingosine. They were discovered in brain extracts in the 1870s and were named after the mythological Sphinx because of their enigmatic nature.

These compounds play important roles in signal transmission and cell recognition. Sphingolipidoses, or disorders of sphingolipid metabolism, have particular impact on neural tissue. A sphingolipid with an R group consisting of a hydrogen atom only is a ceramide. Other common R groups include phosphocholine, yielding a sphingomyelin, and various sugar monomers or dimers, yielding cerebrosides and globosides, respectively. Cerebrosides and globosides are collectively known as glycosphingolipids.

Bioactive sphingolipids-ceramide, sphingosine, and their respective 1-phosphates (C1P and S1P)-are signaling molecules serving as intracellular second messengers. Moreover, S1P acts through G protein-coupled receptors in the plasma membrane. Accumulating evidence points to sphingolipids' engagement in brain aging and in neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's diseases and amyotrophic lateral sclerosis. Metabolic alterations observed in the course of neurodegeneration favor ceramide-dependent pro-apoptotic signaling, while the levels of the neuroprotective S1P are reduced. These trends are observed early in the diseases' development, suggesting causal relationship. Mechanistic evidence has shown links between altered ceramide/S1P rheostat and the production, secretion, and aggregation of amyloid β/α-synuclein as well as signaling pathways of critical importance for the pathomechanism of protein conformation diseases. Sphingolipids influence multiple aspects of Akt/protein kinase B signaling, a pathway that regulates metabolism, stress response, and Bcl-2 family proteins. The cross-talk between sphingolipids and transcription factors including NF-κB, FOXOs, and AP-1 may be also important for immune regulation and cell survival/death. Sphingolipids regulate exosomes and other secretion mechanisms that can contribute to either the spread of neurotoxic proteins between brain cells, or their clearance. Recent discoveries also suggest the importance of intracellular and exosomal pools of small regulatory RNAs in the creation of disturbed signaling environment in the diseased brain. The identified interactions of bioactive sphingolipids urge for their evaluation as potential therapeutic targets. Moreover, the early disturbances in sphingolipid metabolism may deliver easily accessible biomarkers of neurodegenerative disorders [1)].

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Czubowicz K, Jęśko H, Wencel P, Lukiw WJ, Strosznajder RP. The Role of Ceramide and Sphingosine-1-Phosphate in Alzheimer's Disease and Other Neurodegenerative Disorders. Mol Neurobiol. 2019 Jan 5. doi: 10.1007/s12035-018-1448-3. [Epub ahead of print] Review. PubMed PMID: 30612333.