Chapter 17
Glycosphingolipid Disorders of the Brain

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Abstract  Glycosphingolipids, comprising a ceramide lipid backbone linked to one/more saccharides, are particularly abundant on the outer leaflet of the eukaryotic plasma membrane and play a role in a wide variety of essential cellular processes. Biosynthesis and subsequently degradation of these lipids is tightly regulated via the involvement of numerous enzymes, and failure of an enzyme to participate in the metabolism results in storage of the enzyme’s substrate, giving rise to a lysosomal storage disease. The characteristics, severity and onset of the disease are dependent on the enzyme deficient and the residual activity. Most lysosomal storage disorders found thus far are caused by a defect in the catabolic activity of a hydrolase, causing progressive accumulation of its substrate, predominantly in the lysosome. Storage of gangliosides, sialic acid containing glycosphingolipids, mostly found in the central nervous system, is a hallmark of neuronopathic forms of the disease, that include GM1 and GM2 gangliosidoses, Gaucher type II and III and Niemann-Pick C. Models for these diseases have provided valuable insight into the disease pathology and potential treatment methods.

Treatment of these rare but severe disorders proves challenging due to restricted access of therapeutics through the blood-brain barrier. However, recent advances in enzyme replacement, bone marrow transplantation, gene transfer, substrate reduction and chaperon-mediated therapy provide great potential in treating these devastating disorders.

Keywords  Glycosphingolipid · imino sugar · lysosomal storage disease · neurodegeneration · therapeutic strategies

Abbreviations  CBE: conduritol B-epoxide; CSF: cerebrospinal fluid; CMT: chaperon-mediated therapy; CNS: central nervous system; ER: endoplasmic reticulum; ERAD: endoplasmic reticulum associated degradation; ERT:
17.1 Introduction to Glycosphingolipid Metabolism and Disease

All eukaryotic cells contain a lipid outer membrane composed of glycerolipids, sphingolipids and sterols. All three lipids have been found to exhibit a wide range of combinatorial diversity and their biochemical and biophysical properties determine functionality.

The backbone of all sphingolipids from which the name is derived, is the sphingoid long-chain base. The most common of these lipids are sphinganine and sphingosine. Ceramide, the simplest sphingolipid and the common precursor for more complex lipids, consists of sphingosine to which a fatty acid is attached. Coupling of a glucose or galactose monosaccharide to ceramide is the first step in the formation of glycosphingolipids (GSLs). GSLs are the most structurally diverse sphingolipids and carry out an enormous range of essential cellular functions. In order to maintain the integrity of the cell, GSLs are continuously synthesised in the endoplasmic reticulum (ER) and the Golgi apparatus, and degraded in the lysosome. If there is a metabolic deficiency in the enzyme required for the degradation of a GSL, substrate accumulates to pathological levels, giving rise to a lysosomal storage disease (LSD). Therapy for treating these relatively rare but severe disorders proves challenging, especially when the nervous system is affected.

17.2 Metabolism

Glycosphingolipids are ubiquitous components of all eukaryotic plasma cell membranes and are particularly abundant at the cell surface. GSLs and their metabolites have been shown to act as intracellular signalling molecules that...