Targeting Glucosylceramide Synthesis in the Treatment of Rare and Common Renal Disease

James A. Shayman, MD

Summary: Sphingolipids, including ceramides, glycosphingolipids, sphingomyelin, and sphingosine-1-phosphate, have been recognized as important molecules that regulate critical cellular functions. Although originally studied in the context of lysosomal storage diseases, the roles of these compounds in more common disorders involving metabolism, vascular disease, and aberrant growth has been the focus of recent studies, including in disorders that affect the kidneys. These efforts have led to new insights into Fabry disease, a classic disorder of lysosomal function that results in renal failure as well as in more common renal diseases including diabetic nephropathy and polycystic kidney disease. Pathways for glycosphingolipid synthesis can be targeted with orally available small-molecule inhibitors, creating new opportunities for the treatment of both rare and common kidney diseases.
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Johann Ludwig Wilhelm Thudicum, a physician and chemist, is credited with the discovery of sphingolipids.[1] It is believed that Thudicum was impressed by the enigmatic properties of these novel compounds and he referred to them as *sphingolipids* as an allusion to the riddle of the sphinx. Although much has been elucidated about this class of lipids following Thudicum's characterization almost 130 years ago, the roles of sphingolipids in health and disease remains an active area of exploration.

An important milestone in sphingolipid biology was the discovery by Christian de Duve of the lysosome as a distinct cellular organelle.[2] The work of de Duve and Wattiaux[2] work was followed rapidly by the observation that the loss of activity of lysosomal hydrolases involved in sphingolipid metabolism was the causal basis of a variety of disorders that were phenotypically unique and robust. His seminal work was an important catalyst in efforts to understand the roles of these lipids in health and disease.[3] In particular, the recognition that lysosomal storage disorders result in the pathologic accumulation of phospholipids including sphingomyelin, ceramides, and glycolipids led to the identification of a myriad of additional complex structures that fall within the category of sphingolipids, the distinct pathways responsible for their synthesis and catabolism, and the genes and transcription factors that regulate their metabolism.

The functions of sphingolipids are remarkably varied and include recognized roles as structural elements that define the physical properties of membranes, as membrane receptors, as receptor ligands, as intracellular second messengers, and as transcriptional regulators. Much of the work on the biochemistry and functional biology of sphingolipids has focused on the kidney owing to the diversity of sphingolipids found there and renal diseases that are sphingolipid-based. This brief review highlights historically important work and more recent efforts to understand the role and importance of sphingolipid metabolism in both rare disorders and more common clinical syndromes involving the kidney. The primary goals of this review are to introduce the reader to the basics of sphingolipid biology and to argue that insights into the functional roles of sphingolipids are providing opportunities for the development of therapeutics that target both rare and common renal disorders. Although several excellent reviews are available that detail the biochemistry and cellular biology of these compounds, the reader is referred to a particular scholarly and comprehensive treatise in this area by Merrill.[4]

STRUCTURES AND METABOLIC PATHWAYS OF SPHINGOLIPIDS

A sphingolipid is defined as a compound containing a long-chain base or sphingoid amine. Ceramides, a type

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Address reprint requests to James A. Shayman, MD, Department of Internal Medicine, University of Michigan, Room 1560 MSRBII, 1150 West Medical Center Dr, Ann Arbor, MI 48109-0676. E-mail: jshayman@umich.edu,

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of sphingolipid, are defined by the presence of an acyl group in amide linkage. Glycosphingolipids are defined by the presence of one or more sugar groups at carbon 1 of the long-chain base. If this base is unmodified by acylation or glycosylation, then one of three common sphingoid amines are commonly present, namely sphingosine, dihydrosphingosine, or phytosphingosine. These bases vary in terms of saturation, typically with a 4,5-double bond, and in terms of the presence of hydroxyl groups. Sphingoid base synthesis begins with the condensation of serine and palmitoyl-CoA to form dihydrosphingosine. Sphingosine is not formed directly from dihydrosphingosine, rather dihydrosphingosine is first acylated to form dihydroceramide. Dihydroceramide subsequently is desaturated, forming ceramide. Sphingosine can be formed via the action of a ceramidase, a deacylase, and further metabolized. However, ceramide is also a central intermediate in the formation of a variety of other sphingolipids. The most abundant of these products is sphingomyelin, formed by the exchange of phosphorylcholine from phosphatidylcholine to ceramide.[5] Sphingomyelin comprises 10% to 15% of the total phospholipid in the plasma membrane. Other products of ceramide include ceramide 1-phosphate, 1-*O*-acylceramide, and glycosphingolipids.

Glycosphingolipids are the result of the addition of between 1 and 20 sugars to ceramide. When a single sugar is present, the glycosphingolipid is termed a *cerebroside*. Glucosylceramide and galactosylceramide formed by glucosylceramide synthase (*Ugcg*)[6] and galactosylceramide synthase (*Ugt8a*),[7] respectively, are the most abundant cerebrosides. Glycosphingolipids may be neutral or negatively charged. Negatively charged carbohydrate head groups are associated with sulfate or sialic acids, resulting in the formation of sulfatides or gangliosides. Both of these anionic species are abundant in the kidney.[8] Approximately 85% of mammalian glycolipids have glucose as their first sugar. Most glycosphingolipids with more than one sugar are built upon the addition of galactose, resulting in the formation of lactosylceramide through the action of lactosylceramide synthase (*B4galt1*). Glycosphingolipids, comprising one of four series, are formed based on the next sugar to be added to the lactosylceramide. These series and the responsible enzymes include the globo series (Gb3 synthase, *A4galt*); the isoGlobo series (iGb3 synthase, *A3galt3*); the lacto-/neoLacto series (Lc synthase, *B3gnt5*); and ganglio series (β1,4-N-acetylgalactosamine (GalNAc) transferase, *B4Galnt1*) (Fig. 1).[9]

Glycosphingolipids are both organ- and cell-type–specific. Although glycosphingolipids circulate in the plasma and are re-incorporated into cells, the cell specificity is owing primarily to differences in the expression and activity of specific enzymes and glycosidases that favor the synthesis and accumulation of individual species. Within cells, glycosphingolipids tend to localize to the outer leaflet of the plasma membrane. They cycle within the cell through endocytic pathways that involve the lysosome, but are extralysosomal as well.

Sphingolipids, most notably sphingomyelin and glycosphingolipids, form aggregates with cholesterol in distinct domains, commonly termed *lipid rafts*.[10] These rafts are hypothesized to be sites for many signaling complexes that include receptors, phospholipases, tyrosine kinases, and structural proteins such as caveolins. Changes in the molar ratios and composition of these raft lipids have been reported to result in aberrant changes in ligand signaling and may provide a potential mechanism linking abnormal sphingolipid metabolism and disease.

There are more than 30 distinct glycosphingolipids (GSLs) present in mammalian kidney as defined only by their carbohydrate composition and linkages.[8] However, based on the diversity of the associated sphingoid bases and fatty acyl groups that can comprise the ceramide portion of these glycosphingolipids, there are hundreds of distinct species found in the kidney. One GSL in particular has been established as the basis for renal disease, namely globotriaosylceramide (Gb3). Gb3, present on renal endothelial cells, is the receptor for shiga toxin and mediates injury associated with infectious forms of hemolytic uremic syndrome.[11] Gb3 is also the primary substrate for the lysosomal enzyme α-galactosidase A (GLA). Loss of GLA activity is the basis for Fabry disease, which is discussed in greater detail later.[12]

SPHINGOLIPIDS AS CELLULAR MEDIATORS OF SIGNALING AND METABOLISM

Although sphingolipids comprise in aggregate a relatively small mass of total cell lipids, they play a disproportionately significant role in the regulation of cell metabolism and differentiation. Cell growth and death appear regulated by sphingolipids. Sphingolipids also are modulators of growth factors, are ligands in and of themselves, and also may be cellular second messengers. The potential second messenger functions of sphingolipids have been the focus of considerable effort over the past 25 years, with most attention directed toward ceramide and sphingosine-1-phosphate (S1P). Ceramide, liberated by the hydrolysis of sphingomyelin or formed via de novo synthesis, has been implicated in growth arrest and apoptosis.[13] An early model for the mechanism of action of ceramide was akin to that of diacylglycerol and protein kinase C. A number of ceramide-specific targets have been identified over the years, including protein kinase C ζ

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