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Review

Molecular properties of various structurally defined sphingomyelins – Correlation of structure with function

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ABSTRACT

Sphingomyelins are important phospholipids in plasma membranes of most cells. Because of their dominantly saturated nature, they affect the lateral structure of membranes, and contribute to the regulation of cholesterol distribution within membranes, and in cells. However, the abundance of molecular species present in cells also implies that sphingomyelins have other, more specific functions. Many of these functions are currently unknown, but are under extensive study. Mostly model membrane studies have shown that sphingomyelins (and other sphingolipids), in contrast to glycerophospholipids, have important hydrogen bonding properties which in several important ways confer specific functional properties to this abundant class of membrane phospholipids. The often very asymmetric nature of sphingomyelins, arising from mismatch in length between the long chain base and *N*-acyl chains, also impose specific properties (e.g., interdigitation) to sphingomyelins not seen with glycerophospholipids. In this review, the latest sphingomyelin literature will be scrutinized, and an effort will be made to correlate the molecular structure of sphingomyelin with functional properties. In particular, the effects of head group properties, interfacial hydrogen bonding, long chain base hydroxylation, *N*-acyl chain hydroxylation, and *N*-acyl chain methyl-branching will be discussed.

Contents

Abbreviations: CPE, ceramide-1-phosphoethanolamin; CPI, ceramide-1-phosphoinositol; CPS, ceramide-1-phosphoserine; DOPC, 1,2-dioleoyl-*sn*-glycero-3-phosphocholine; DPPC, 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine; DPPS, 1,2-dipalmitoyl-*sn*-glycero-3-phosphoserine; PS, phosphatidylcholine; PCer, *N*-palmitoyl-D-*erythro*-ceramide; POPC, 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine; PSM, *N*-palmitoyl-D-*erythro*-sphingomyelin; SL, sphingolipid; SM, sphingomyelin.

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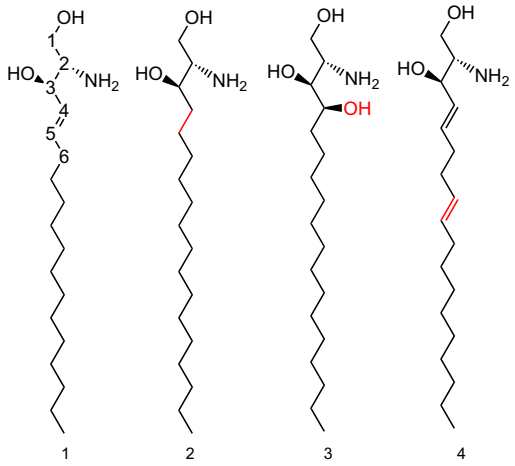
1. Introduction

Sphingomyelins (SMs) are among the most common sphingolipids (SLs) in many mammalian cells and tissues. The widespread scientific interest in SMs arises mainly from their central involvement in creating unique lateral structures (i.e., lipid rafts [1–3] and ordered domains [4–7]) in membranes, their specific binding to and functional regulation of membrane-spanning proteins [8], and because they are precursors for generating simpler sphingolipids which are directly involved in cell signaling events [9–11]. SMs are also important regulators of plasma membrane and cell cholesterol homeostasis [12–14].

The review presents observations from the recent literature regarding the biophysical and biological properties of various SM molecular species, and aims to correlate molecular structure with function. For older reviews on SM biology and biophysics, please refer to [15–19].

1.1. Molecular species of SMs found in mammalian cells and tissues

In the 1880s, Thudicum isolated SM from brain tissue, and made initial characterizations [20]. In 1927 it was revealed that the basic structure of SM was *N*-acylsphingosine-1-phosphocholine [21]. Much later the chirality of C2 and C3 in the long chain base of naturally occurring SMs was verified as D-*erythro* (Scheme 1) [22]. The most common long chain base in SM is 1,3-dihydroxy-2-amino-4-octadecene (i.e., sphingosine, or d18:1 [15], see Scheme 1 for long chain base structures) whereas SM from e.g., the eye lens has a fairly large proportion of 1,3-dihydroxy-2-amino-4-octadecane (i.e., sphinganine or d18:0, lacking the C4 *trans* double bond of sphingosine [23–25]). Palmitic acid (16:0) is the most common *N*-linked acyl chain of SM in mammalian peripheral cells, whereas stearic acid (18:0) is more common in SM of neural tissue [16,26]. Long chain fatty acids (e.g., 24:0 and 24:1) are also common constituents of SM from most tissues.



Scheme 1. Molecular structures of (1) 1,3-dihydroxy-2-amino-4-octadecene (sphingosine, (2) 1,3-dihydroxy-2-amino-4-octadecane (sphinganine), (3) 4-hydroxysphinganine (phytosphinganine), (4) 4,8-sphingadiene. The interfacial carbon numbering is shown for structure 1.

The increased availability of mass spectrometric techniques has furthered our knowledge about the cell-specific distribution and occurrence of molecular species of SMs. Lipidomic studies of human fibroblasts revealed that their SM fraction contained at least 18 different molecular species, with d18:1/16:0 SM being the dominant species, followed by markedly lower amounts of d18:1/24:1 and d18:1/24:0 [27]. The other molecular species were present only in trace amounts and included additionally 14:0, 17:0, 18:0, and 22:0 *N*-linked acyl chains. The d18:1 long chain base was most prominent, but d18:0 and d18:2 long chain bases are also present. Some additional long chain bases are present in trace amounts only [27]. When rat cerebellar granule cells were analyzed for SM species, d18:1/18:0 was the dominant SM, followed by d18:1/16:0. Surprisingly, these two fatty acids were the only ones present among SMs, whereas the long chain base variations was larger (5 different reported), but d18:1 was still the most dominant (>90%) [27].

Sheep erythrocytes are known to have a high proportion of SM in their membranes. The most common molecular species is d18:1/24:1 (about 50%) whereas d18:1/16:0 had a much lower abundance (18.5%). In total, the sheep red blood cells contained at least 18 different molecular species of SM, mostly present in trace amounts [28].

Analysis of meat SM species (e.g., from pork, beef, wild boar and roe deer) revealed that while d18:1 was the most common long chain base; all four meat types also had 4-hydroxysphinganine (phytosphinganine) and 4-hydroxy-8-sphingenine in significant amounts [29]. Palmitic and stearic acids were most commonly present in the SM species.

Analysis of SM molecular species in human atherosclerotic plaques revealed that shorter chain SM (d18:1/14:0, d18:1/15:0 and d18:0/15:0) were selectively retained in the plaque tissue. Since these species were not typical of the plasma SM composition, it was speculated that the shorter chain SM species were either selectively retained or *de novo* produced *in situ* [30].

Human breast milk was recently analyzed for SM molecular species, and while sphingosine (d18:1) was the predominant long chain base (about 84%), 4,8-sphingadiene (d18:2) and 4-hydroxysphinganine (t18:0) were also present (about 7% and 6%, respectively [31]). Most of the SM species in human breast milk had saturated acyl chains (73%).

The hydroxylation of fatty acids (in the C2 position) in sphingolipids is fairly common (for a review, see [32]). Still, the presence of 2-hydroxylated acyl chains in SM species is low. Such species have, however, been detected in testes and spermatozoa [33], in kidney and intestinal mucosa [34], and in neural tissues [35]. Guinea pig Harderian glands have also been reported to contain 2-hydroxylated SM species [36]. In cells from patients with mutated fatty acid 2-hydroxylase enzyme, blood lymphocytes had normal levels of SMs with 2-hydroxylated acyl chains, whereas fibroblasts and erythrocytes displayed reduced levels of 2-hydroxylated SM species [37]. This discrepancy is not clearly understood.

A peculiar SM species with a C3 *O*-acyl was reported to be present in human umbilical cord and in newborn pig plasma [38]. This particular SM was no longer observed in samples from adults, or after 4 weeks of piglet age, or in samples from adults. The C3 *O*-acyl chain was predominantly 16:0.