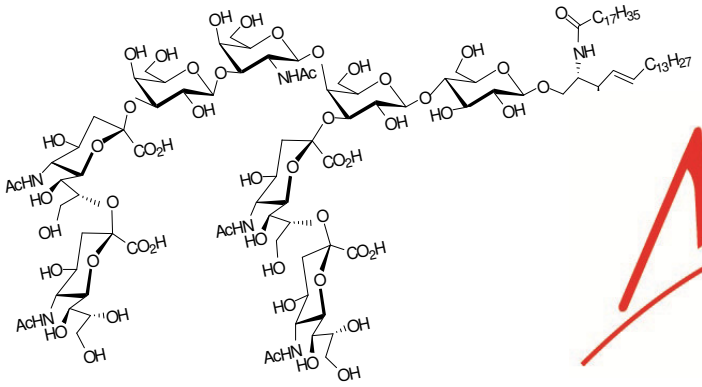


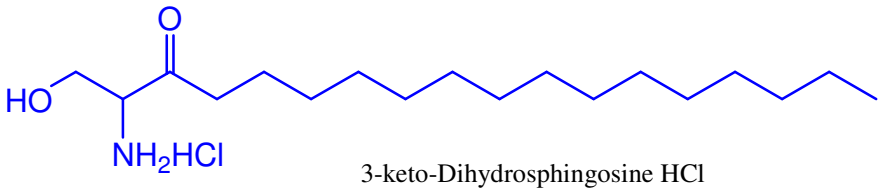
MATREYA LLC

Lipids and Biochemicals

NEWSLETTER FOR GLYCO/SPHINGOLIPID RESEARCH

NOVEMBER 2018

3-keto-Dihydrosphingosine is an Important Early Metabolite of Sphingolipid Biosynthesis



3-keto-Dihydrosphingosine HCl
Cat.# 1876

The sphingolipid anabolic *de novo* pathway begins with the condensation of serine and palmitoyl-CoA to form 3-keto-dihydrosphingosine, catalyzed by serine palmitoyltransferase. Then, 3-ketosphinganine reductase mediates the reduction of 3-keto-dihydrosphingosine to sphinganine, which is transformed into dihydroceramide through acylation by ceramide synthases. In the last step of the *de novo* pathway, ceramide is formed through the introduction of an (E)-4 double bond into dihydroceramide by dihydroceramide desaturase. Once formed, ceramide can be degraded through the catabolic route, which involves N-deacylation to sphingosine by ceramidases, further phosphorylation to sphingosine 1-phosphate (S1P) and final irreversible cleavage by S1P lyase.[1,2,3]

Experiments using 3-keto-dihydrosphingosine and its dideuterated analog demonstrated that high amounts are metabolized to dihydrosphingolipids in certain cancer cells while phosphorylation and N acylation do not seem to occur. The elevated levels of dihydrosphingolipids results in cells responding with induction of autophagy.[3] Vitamin K deficiency results in the inactivation of the serine palmitoyl transferase enzyme causing a resultant shortage of sphingolipids.[4]

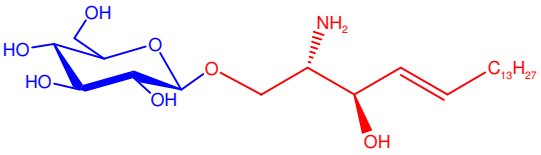
A recent HPLC-ESI-MS/MS method to directly quantify 3-keto-dihydrosphingosine generated by serine palmitoyl transferase is a powerful tool with significant resolution and quantitative power to study serine palmitoyltransferase activity.[5]

INSIDE THIS ISSUE

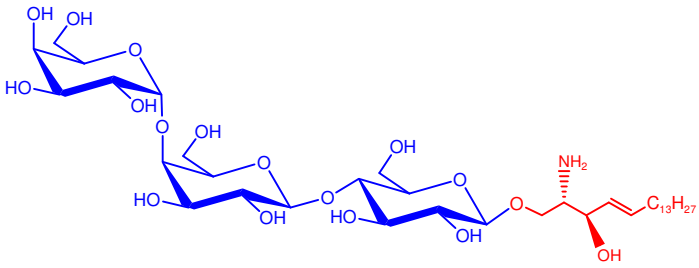
References:

1. N. Bartke and Y. Hannun. Bioactive sphingolipids: metabolism and function. *Journal of Lipid Research*. 2009;50:S91-S96
2. G. Jenkins and Y. Hannun. Role for de Novo Sphingoid Base Biosynthesis in the Heat-induced Transient Cell Cycle Arrest of Saccharomyces cerevisiae. *Journal of Biological Chemistry*. 2001;276:8574-8581
3. Y. Ordóñez et al. 3-ketosphinganine provokes the accumulation of dihydrosphingolipids and induces autophagy in cancer cell. *Mol Biosyst*. 2016;12(4):1166-73
4. A. Batheja et al. Characterization of Serine Palmitoyltransferase in Normal Human Tissues. *Journal of Histochemistry and Cytochemistry*. 2003;51:687-696
5. J. Ren et al. Quantification of 3-ketodihydrosphingosine using HPLC-ESI-MS/MS to study SPT activity in yeast *Saccharomyces cerevisiae*. *J Lipid Res*. 2018;59(1):162-170

Tale of Two Ceramides



Glucosylsphingosine
Cat. 2086



lyso-Ceramide trihexoside
Cat. 1520

The following is the abstract from:

Gaucher disease and Fabry disease: New markers and insights in the pathophysiology of two distinct glycosphingolipidoses. Maria J. Ferraz, Wouter W. Kallemeijn, Mina Mirzaian, Daniela Herrera Moro, André R.A. Marques, Rolf G. Boot, Lianne I. Willems, H.S. Overkleeft and Johannes M.F.G. Aerts, *Biochim Biophys Acta*. 1841(5), 811-825 (2014)

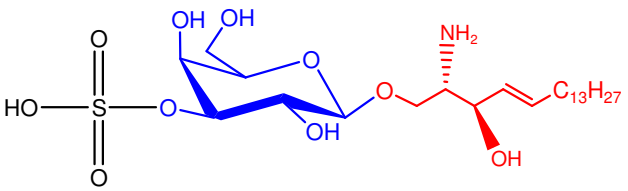
Abstract

Gaucher disease (GD) and Fabry disease (FD) are two relatively common inherited glycosphingolipidoses caused by deficiencies in the lysosomal glycosidases glucocerebrosidase and alpha-galactosidase A, respectively. For both diseases enzyme supplementation is presently used as therapy. Cells and tissues of GD and FD patients are uniformly deficient in enzyme activity, but the two diseases markedly differ in cell types showing lysosomal accumulation of the glycosphingolipid substrates glucosylceramide and globotriaosylceramide, respectively. The clinical manifestation of Gaucher disease and Fabry disease is consequently entirely different and the response to enzyme therapy is only impressive in the case of GD patients. This review compares both glycosphingolipid storage disorders with respect to similarities and differences. Presented is an update on insights regarding pathophysiological mechanisms as well as recently available biochemical markers and diagnostic tools for both disorders. Special attention is paid to sphingoid bases of the primary storage lipids in both diseases. The value of elevated glucosylsphingosine in Gaucher disease and globotriaosylsphingosine in Fabry disease for diagnosis and monitoring of disease is discussed as well as the possible contribution of the sphingoid bases to (patho)physiology. This article is part of a Special Issue entitled New Frontiers in Sphingolipid Biology.

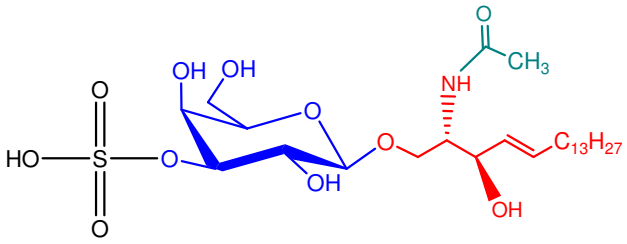
Product Name	Catalog #	Purity
Glucosylsphingosine, synthetic	2086	98+%
Glucosylsphingosine, buttermilk	1306	98+%
Glucosylsphingosine, plant	1310	98+%
N-Glycinated glucosylsphingosine (MS standard)	2089	98+%
lyso-Ceramide trihexoside	1520	98+%
N-Glycinated *lyso*-ceramide trihexoside (MS standard)	1530	98+%

Please visit www.matreya.com for a full list of sphingolipid standards

lyso-Sulfatides Demonstrate Strong Anticoagulant Activity



lyso-Sulfatide
Cat. 1904



N-Acetyl-sulfatide
Cat. 2076

Sulfatide is a sulfated galactosylceramide that is found primarily in the central nervous system and is a myelin-specific sphingolipid. A deficiency of sulfatide in white and gray matter has been associated with Alzheimer's disease and other types of dementia. Apolipoprotein E plays an important regulating role in the metabolism of sulfatides. The production of anti-sulfatide antibodies in the cerebrospinal fluid, leading to a deficiency in sulfatides, may be a cause of degeneration of the myelin sheath, leading to multiple sclerosis.

lyso-Sulfatide demonstrates strong anticoagulant activity, inhibiting more than 90% of prothrombin (II) activation. N-acetyl-sulfatide was not an anticoagulant, implying that the free amine group was essential for the anticoagulant effects of *lyso*-sulfatide. *lyso*-sulfatide is an anticoagulant lipid that inhibits the protein factor Xa when this enzyme is bound to either phospholipids or to the protein factor Va.[1]

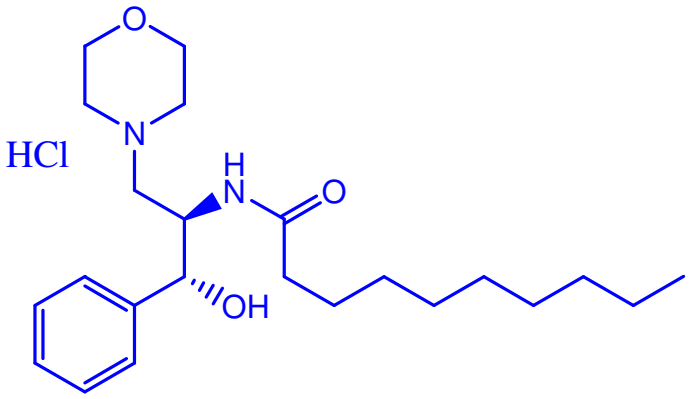
Reference:

1. S. Yegneswaran et al. Lyso-Sulfatide Binds Factor Xa and Inhibits Thrombin Generation by the Prothrombinase Complex. PLoS One. 2015;10(8): e0135025. doi:10.1371/journal.pone.0135025

Product Name	Catalog #	Purity
Sulfatide	1049	98+%
lyso-Sulfatide	1904	98+%
N-Glycinated *lyso*-sulfatide (MS standard)	2092	98+%
N-Hexanoyl-biotin-sulfatide	2207	98+%
N-Acetyl-sulfatide	2076	98+%
N-Heptadecanoyl-sulfatide	1934	98+%
N-Octadecanoyl-sulfatide	1932	98+%

Please visit www.matreya.com for a full list of sulfatide standards

D-PDMP Demonstrates Important Implications of Glucosylceramides and Lactosylceramides



D-*threo*-PDMP
Cat. 1756

D-*threo*-1-phenyl-2-decanoylamino-3-morpholino-1-propanol (D-PDMP) is a glucosylceramide synthase inhibitor that closely resembles the natural sphingolipid substrate ceramide and is an analog of glucosylceramide. It has been used to inhibit glucosylceramide synthesis in patients with Gaucher's disease, which is characterized by an accumulation of glucosylceramide and glucosylsphingosine. However, this compound can directly inhibit the activity of purified lactosylceramide synthase as well. D-PDMP is a small molecular weight compound and is well tolerated by experimental animals, such as mice, rats, and rabbits, up to 10 times the effective dose. In mice, the effective dose of D-PDMP is 10 mg per kg (mpk) body weight when given orally compared to the use of 100 mpk of various adamantane derived inhibitors. Since D-PDMP turnover time is short, approximately 52 minutes in mice, it is rapidly detoxified and excreted with little or no side effects. Delivery of D-PDMP by oral gavage or intraperitoneal injection has no effect on appetite and overall well-being of the experimental animals.[1]

Chatterjee et al.[1] found that inhibition of glycosphingolipid synthesis with D-PDMP in mice and rabbits fed a western diet ameliorates atherosclerosis and arterial stiffness in apolipoprotein E–/– mice and rabbits. Feeding of this diet resulted in elevated levels of several biomolecules, including lactosylceramides, and increased the activity of glucosylceramide and lactosylceramide synthases. These were dose-dependently decreased by D-PDMP which also prevented atherosclerosis. Thus, inhibition of glycosphingolipid synthesis may be a novel approach to improve atherosclerosis and arterial stiffness.

In another paper, Chatterjee et al.[2] demonstrated that a mouse renal cancer model was ameliorated by administration of D-PDMP. The mouse model revealed a significant increase in lactosylceramide, demonstrating a strong correlation between tumor progression and glycosphingolipid biosynthesis. Administration of D-PDMP resulted in a decrease in lactosylceramide and an increase in glucosylceramide and decrease in tumor volume. Thus inhibiting glycosphingolipid synthesis can be a bonafide target to

prevent the progression of other types of cancer.

Chatterjee et al.[3] used D-PDMP to prevent cardiac hypertrophy in apolipoprotein E–/– mice fed a high fat and high cholesterol diet. These mice revealed an age-dependent increase in indicators of maladaptive pathological cardiac hypertrophy and dysfunction. There was an accompanying increase in glycosphingolipids which were dose-dependently decreased by the administration of D-PDMP. Studies showed that D-PDMP inhibited cardiac hypertrophy by inhibiting the phosphorylation of mitogen–activated protein kinase.

Bedja et al.[4] observed a decrease in ceramide and glucosylceramide levels with an associated increase in lactosylceramide in apolipoprotein E–/– mice fed a diet rich in cholesterol and fat. This diet caused skin inflammation, hair discoloration and loss in the mouse model. Inhibition of glycosphingolipid synthesis by D-PDMP, unbound or encapsulated in a biodegradable polymer, reversed these phenotypes. Thus, inhibition of glycosphingolipid synthesis represents a unique therapeutic approach relevant to human skin and hair biology.

References:

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2. Chatterjee S, Alsaeedi N, Hou J, et al. Use of a Glycolipid Inhibitor to Ameliorate Renal Cancer in a Mouse Model. Samant R, ed. *PLoS ONE*. 2013;8(5):e63726. doi:10.1371/journal.pone.0063726.
3. Mishra S, Bedja D, Amuzie C, Avolio A, Chatterjee S. Prevention of Cardiac Hypertrophy by the Use of a Glycosphingolipid Synthesis Inhibitor in ApoE–/– Mice. *Biochemical and biophysical research communications*. 2015;465(1):159-164. doi:10.1016/j.bbrc.2015.07.159.
4. Bedja D, Yan W, Lad V, et al. Inhibition of glycosphingolipid synthesis reverses skin inflammation and hair loss in ApoE–/– mice fed western diet. *Scientific Reports.* 2018;8(11463):1-11. doi: https://doi.org/10.1038/s41598-018-28663-9

Product Name	Catalog #	Amount	Purity
D-*threo*-PDMP	1756	5 mg	98+%
D,L-*threo*-PDMP	1719	100 mg	98+%
L-*threo*-PDMP	1749	10 mg	98+%
D,L-*erythro*-PDMP	1755	100 mg	98+%
D-*threo*-PPMP	1865	10 mg	98+%
D,L-*threo*-PPMP	1720	100 mg	98+%
L-*threo*-PPMP	1868	10 mg	98+%
D,L-*erythro*-PPMP	1753	100 mg	98+%

Please visit www.matreya.com for a full list of sphingolipid enzyme inhibitors