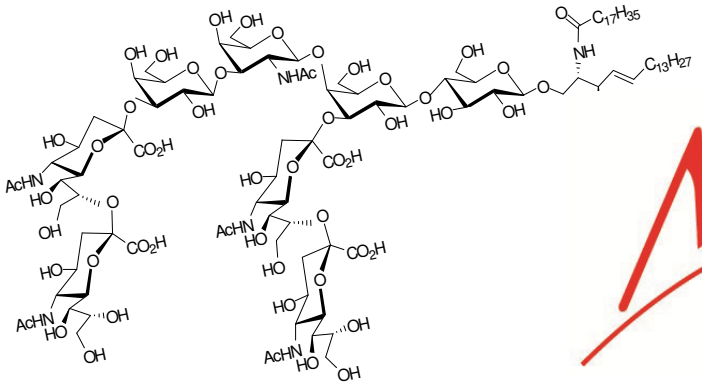

MATREYA LLC

Lipids and Biochemicals

NEWSLETTER FOR GLYCO/SPHINGOLIPID RESEARCH
APRIL 2017

Functions of the Neuronal Lipid Trisialoganglioside GT_{1b}

Gangliosides, consisting of a ceramide moiety, an oligosaccharide head group, and one or more sialic acids, are vitally important amphipathic lipids that have been found to be involved in a multitude of cellular tasks; gangliosides bind to lectins, serving as immunological and cell-adhesion receptors, participate in cell signaling, oncogenesis, and cell differentiation, affect placentation and nerve growth, participate in myelin stability and nerve regeneration, and function as viral and toxin entry points to cells. Although more than a dozen ganglioside species are known to exist GM_1, GD_{1a}, GD_{1b} and GT_{1b} compose 96% of brain gangliosides [(1)].

GT_{1b} is notable among gangliosides in that it exists almost exclusively in nerve cells, being expressed on the outer membrane. Both GM_1 and GT_{1b} promote neuronal differentiation and dendrite generation [(2)]. It has been found that both of these lipids promote the entry of neuronal progenitor cells into a post-mitotic stage, and thus neuronal maturation, by enhancing neural growth factor (NGF)-induced dimerization of TrkA and its phosphorylation[(2)]. Because of it's role in nerve cells, GT_{1b} produces nociceptive behavior and enhances hyperalgesia and allodynia [(3)]. GT_{1b} and GD_{1a} are known to complex with myelin-associated glycoprotein (MAG) which inhibits axonal growth [(4)].

GT_{1b} has also been associated with several neuronal cancers and is considered a brain metastasis-associated ganglioside. In particular, GM_1, GD_{1a}, and GT_{1b} have all been found to have inhibitory effects on epidermal growth factor receptor (EGFR) signaling and keratinocyte adhesion and migration [(2)]. Studies have found that GT_{1b} plays an important role in increasing the nuclear maturation rate and decreasing the intracellular ROS levels during IVM by maintaining intracellular Ca_2^+ in

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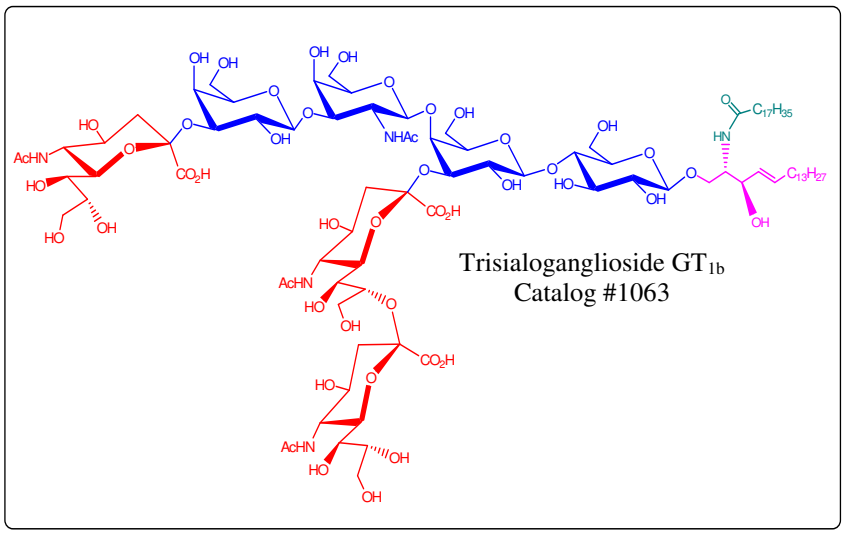
the process of oocyte maturation regardless of the cell cycle stage [5]. The presence of GT_{1b} could be a useful biomarker for estimating metastatic potentials in the brain [6]. GT_{1b} negatively regulates cell motility, spreading, and adhesion on fibronectin (FN) through direct molecular interactions with the α5 subunit of the α5β1 integrin, a finding that could be used to develop cancer therapies [7]. Botulinum neurotoxin type C, which enters nerve cells through GT_{1b} binding, has been studied for its possible neuroblastoma apoptosis effects [8].



GT_{1b} is a receptor for various toxins which recognize it's oligosaccharide structure. GT_{1b} (and possibly other polysialogangliosides) is the receptor by which botulinus neurotoxins from *Clostridium botulinum* bacteria enter nerve cells[9]. Tetanus toxin, a major threat to human and animal health which inhibits neurotransmitter release in the central nervous system to elicit spastic paralysis, gains entry to nerve cells by complexing with GT_{1b} and other nerve gangliosides [10, 11]. The merkel cell polyomavirus likely interacts with sialic acids on both branches of the GT_{1b} carbohydrate chain to gain access to cells [12]. Murine polyomavirus has been found to bind to gangliosides GD_{1a} and GT_{1b} and the BK virus to bind to gangliosides GD_{1b} and GT_{1b} to gain entry into cells [12].

GT_{1b} has also been found to affect the immune system. Ganglioside GT_{1b} has inhibitory effects towards human humoral immune responses and suppresses immunoglobulin production by human peripheral blood mononuclear cells [13]. Evidence suggests that GD_{1b}, GT_{1b}, and GQ_{1b} may enhance Th1 cytokine production while suppressing Th2 production by inhibiting adenylate cyclase activity [14].

Matreya produces all of the major gangliosides in very high purity. These products are useful for research exploring the cellular roles of these lipids and their association with various diseases and disorders. For over 25 years Matreya has specialized in extracting and purifying gangliosides in multi-gram quantities while maintaining the strictest quality assurance for purity. We are pleased to see how our products have been used over the years to further the understanding of these important lipids in healthy cells and in treating diseases.

Cat. #	Amount	Purity	Product Name
1063	5 mg	98+%	Trisialoganglioside GT_{1b} (NH_4^+ salt)

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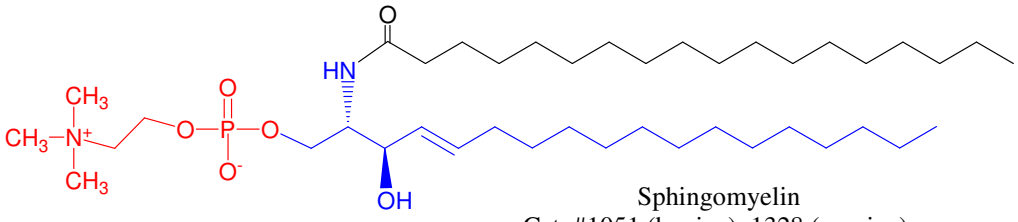
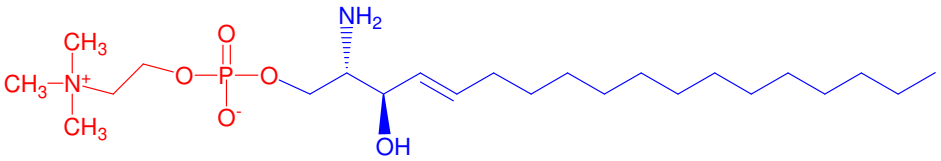
Sphingomyelin and Sphingosylphosphorylcholine: Vital Membrane Components



Sphingomyelin
Cat. #1051 (bovine), 1328 (porcine),
1329 (buttermilk), 1332 (egg)



D-*erythro*-Sphingosylphosphorylcholine
Cat. #1318

Sphingomyelin, sphingosylphosphorylcholine, and dihydrosphingomyelin are major and important phosphosphingolipids found in mammalian cell membranes, especially in the membranes of the myelin sheath. Sphingomyelin is the most abundant sphingolipid in mammals and is found mostly in the exoplasmic leaflet of the membrane. Sphingomyelin has numerous critical cellular functions including signal transduction, apoptosis, free sphingosine and ceramide metabolism, and myelin sheath formation [1]. Sphingomyelin also plays a significant role in Niemann-pick disease, types A and B, multiple sclerosis, neonatal respiratory distress syndrome, and abetalipoproteinemia.

The ratio of sphingomyelin to ceramide in different cell types plays a critical role in cellular function [2]. Sphingomyelin is an important amphiphilic component when plasma lipoprotein pools expand in response to large lipid loads or metabolic abnormalities [3]. In contrast to ceramides, N-hexanoyl-sphingomyelin does not initiate vesicle formation in cells [4] but has been used to enhance the uptake of anti-tumor drugs by cancer cells, thereby increasing their cytotoxicity [5]. Sphingosylphosphorylcholine, the deacylated form of sphingomyelin, has been shown to induce intracellular calcium release while its short chain analog, N-acetyl sphingosylphosphoylcholine, requires a significantly higher concentration to initiate the same level of response [6].

Sphingomyelin also has important implications in several severe diseases. Niemann-Pick disease is a rare lysosomal storage disorder with debilitating effects and is characterized by a deficiency of the enzyme acid sphingomyelinase. This results in the accumulation of sphingomyelin leading to hepatosplenomegaly, liver dysfunction, interstitial lung disease, thrombocytopenia, anemia, an atherogenic lipid profile, bone disease, and neurodegeneration [7,8]. Low levels of sphingomyelin is considered a blood biomarker for multiple sclerosis, although whether sphingomyelin is an active species in the disease remains unclear [9]. In neonatal respiratory distress syndrome the ratio of lecithin/sphingomyelin in amniotic fluid has been used to predict risk of the disease [10]. An excess of sphingomyelin in red blood cells leads to abetalipoproteinemia, causing decreased membrane fluidity [11].

Sphingosylphosphorylcholine (SPC) has been identified in normal blood plasma, ascites, and various

other tissues. SPC is similar in structure to sphingosine-1-phosphate and lysophosphatidylcholine and has at least low-binding affinity to some of the same receptors, such as the sphingosine-1-phosphate receptor. It is a bioactive lipid that acts as an intracellular and extracellular signaling molecule in numerous biological processes such as vasoconstriction, vasodilation, angiogenesis, stress fiber formation, cytoskeletal rearrangements, proliferation, differentiation, migration, wound healing, and stimulation of DNA synthesis. SPC can also inhibit the growth of various cell types, including tumor cells, causing much interest in its possible role as an anti-tumor therapy. It is a high-affinity ligand for the orphan receptor ovarian cancer G-protein-coupled receptor 1 (OGR1). The specific binding of SPC to OGR1 also activates p42/44 mitogen-activated protein kinases (MAP kinases) and inhibits cell proliferation [(12)]. SPC may be able to help treat inflammatory kidney diseases and has been found to trigger proteins known to reduce inflammation. SPC has also been shown to cause an increase in urine production in the kidneys with an abnormal accumulation of salt in the urine [(13)]. SPC acts as an inhibitor for calmodulin, a highly prevalent intracellular calcium sensor in eukaryotic cells [(14)].

The extracellular effects of SPC appear to be stereospecific while intracellular effects may not be. D-*erythro*-SPC, but not L-*threo*-SPC, stereoselectively stimulates the proliferation of human adipose tissue-derived mesenchymal stem cells and stimulates an increase in calcium concentration and cellular proliferation [(15)]. Both the L-*threo*-SPC isomer and the D-*erythro*-SPC isomer can act as second messengers by releasing calcium from internal stores.

Dihydrosphingomyelin, containing a saturated sphingosine chain, has been identified as a minor lipid component in many mammalian tissues but has recently been reported to be present in significant amounts in bovine brain and bovine milk [(16)]. It is also found in much greater amounts in human lens membranes (half of all the phospholipids) where it has a critical role in ocular function and perhaps in age-related nuclear cataracts [(17)]. However, dihydrosphingomyelin has been reported to occur only in small amounts in the lens membranes of other mammals. Dihydrosphingomyelin demonstrates good mixing properties with both sterols and sphingomyelin indicating that it could function as a membrane organizer and this may be the reason it is present in large amounts in human lens membranes where cholesterol is also enriched [(18)]. The enzyme *sphingomyelinase* is active towards dihydrosphingomyelin and readily converts it to dihydroceramide. Recent evidence has been presented that indicates that dihydrosphingomyelin impairs HIV-1 infection by rigidifying liquid-ordered membrane domains, a finding that could have great potential in providing a therapeutic treatment for this debilitating disease [(19)].

Cat. #	Amount	Purity	Product Name
1051	25 mg	98^{+}%	Sphingomyelin (bovine)
1328	25 mg	98^{+}%	Sphingomyelin (porcine)
1329	25 mg	98^{+}%	Sphingomyelin (buttermilk)
1332	25 mg	98^{+}%	Sphingomyelin (egg)
1907	5 mg	98^{+}%	N-C2:0-Sphingosylphosphorylcholine
1890	5 mg	98^{+}%	N-C17:0-Sphingosylphosphorylcholine
1911	5 mg	98^{+}%	N-C18:0-Sphingosylphosphorylcholine
1917	500 µg	98^{+}%	N-C20:0-Sphingosylphosphorylcholine
1918	500 µg	98^{+}%	N-C22:0-Sphingosylphosphorylcholine
2200	1 mg	98^{+}%	N-1-^{13}C-C16:0-Sphingosylphosphorylcholine
1912	100 µg	98^{+}%	NBD-C6:0-Sphingosylphosphorylcholine
1619	100 µg	98^{+}%	NBD-C12:0-Sphingosylphosphorylcholine
1318	5 mg	98^{+}%	D-*erythro*-Sphingosylphosphorylcholine
1319	5 mg	98^{+}%	L-*threo*-Sphingosylphosphorylcholine
1321	10 mg	98^{+}%	D-*erythro*/L-*threo*-Sphingosylphosphorylcholine
1913	1 mg	98^{+}%	D-*erythro*/L-*threo*-Dihydrosphingosylphosphorylcholine
1327	5 mg	98^{+}%	N-Acyl-Sphingosylphosphorylethanolamine

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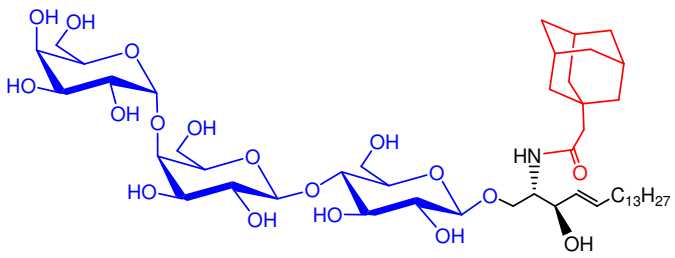
Novel Adamantane Labeled Sphingolipids



Catalog# 1947

Unlike the water-soluble ceramide-free globotriaosylceramide (Gb_3) oligosaccharide, N-(1-adamantaneacetyl)-ceramide trihexoside ($adaGb_3$) retains high affinity for verotoxin binding in aqueous solutions and also shares some properties of Gb_3-cholesterol complexes in solution which may relate to its several bioactivities [1,2]. $AdaGb_3$ has also been shown to functionally mimic Gb_3 microdomains, providing a new class of molecular tools for studying the role of glycolipids and lipid rafts in such areas as HIV-1 fusion and other biological processes. $AdaGb_3$ may be able to disrupt HIV gp120-glycolipid interactions, thereby obviating the problem of resistance mutants selected by current antiretroviral treatments and opening a new route for controlling HIV-1 replication in infected individuals [3]. $AdaGb_3$ has recently been proposed as a regulator for multidrug resistance in cancer cells by taking advantage of the interaction between Gb_3 and the glycoprotein MDR1, thus modulating the function of MDR1 across the intestinal endothelium [4].

N-(1-Adamantaneacetyl)-glucosylceramide (adaGlcCer), at low doses and at pH 7, has been found to inhibit glucocerebrosidase, thereby increasing cellular glycosphingolipids and making it a useful tool in the study of Gaucher disease. However, at 40µM adaGlcCer (which was converted to adaLacCer) inhibited lactosylceramide synthase, decreasing lactosylceramide levels as well as more complex glycosphingolipid levels, and making it the first cellular lactosylceramide synthase inhibitor [1].

N-(1-Adamantaneacetyl)-galactosylceramide (adaGalCer) stimulates glucocerebrosidase at pH 5 (but not at pH 7), reducing glucosylceramide levels in cells. At 40 µM adaGalCer reduces globotriaosylceramide (Gb_3) and globoside (Gb_4) synthesis in Fabry's disease cells by acting as a substrate for Gb_3 synthase. Gb_3 synthase converts adaGalCer to a novel $adaGb_2$ which is readily lost from cells, making it a "safety valve" to offset Gb_3 accumulation in Fabry's disease. AdaGalCer has also been found to inhibit cell sulfatide synthesis [1].

Cat. #	Amount	Purity	Product Name
1945	5 mg	98^{+}%	N-(1-Adamantaneacetyl)-glucosylceramide
1946	5 mg	98^{+}%	N-(1-Adamantaneacetyl)-galactosylceramide
1947	5 mg	98^{+}%	N-(1-Adamantaneacetyl)-ceramide trihexoside

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