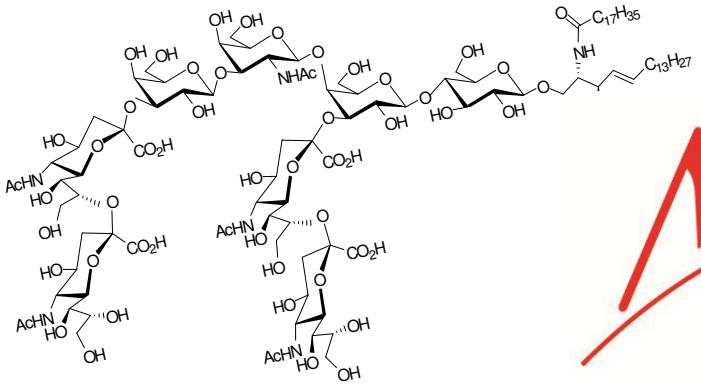

MATREYA LLC

Lipids and Biochemicals

NEWSLETTER FOR GLYCO/SPHINGOLIPID RESEARCH
OCTOBER 2016

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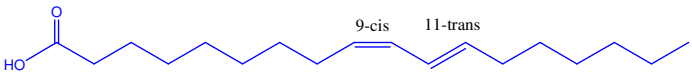
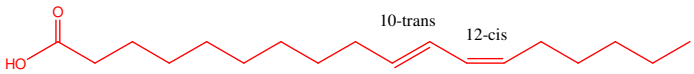
cis-9,*trans*-11-Conjugated Linoleic Acid Reduces Clinical Arthritis



9(Z),11(E)-Octadecadienoic acid
Catalog #1245



10(E),12(Z)-Octadecadienoic acid
Catalog #1249

Conjugated linoleic acids (CLAs) have been implicated in numerous physiological activities including anti-carcinogenic, anti-atherogenic, and anti-inflammatory.[1] In addition they have been demonstrated to decrease low-density lipoprotein cholesterol and increase lean body mass. CLAs comprise a number of linoleic acid isomers with varying double bond positions and *cis/trans* configurations. The major natural CLA is *cis*-9,*trans*-11-octadecadienoic acid (c9t11-CLA) which comprises over 90% of the CLAs in ruminant fats. The other major natural CLA isomer, *trans*-10,*cis*-12-octadecadienoic acid, has been implicated in anticarcinogenic activity; suppressing *in vitro* growth of human melanoma, colorectal, and breast cancer cells; and exhibiting anti-atherogenic activity.[2] When assimilated through the diet of animals CLA is found in the intestinal mucosa, liver, and adipose tissue. Recently the role of CLA in chronic inflammation has undergone renewed investigation.

Chronic inflammation is a debilitating disorder affecting a large percentage of the population. There is now increasing evidence that various lipids can affect the progression of inflammation positively or negatively. The anti-inflammatory effect of c9t11-CLA has been shown in dendritic cells,[3] peripheral blood mononuclear cells,[4] and splenic macrophages.[5] Recently, S. Huebner and colleagues[6] have demonstrated that as little as 0.125% (w/w) c9t11-CLA maximized anti-inflammatory effects in clinical arthritis of a collagen-induced mouse model. Although the anti-inflammatory mechanism is not fully understood, CLA appears to reduce TNFα, IL-1β, and IL-6. Additionally, when fed a butter containing as little as 0.02% total dietary c9t11-CLA, arthritic measurements were

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found to be as low as when fed 0.125% CLA supplements. These results offer exciting insights into the effectiveness of dairy products and CLA supplements in reducing inflammation. Ongoing research offers great promise in finding effective treatments for those suffering from chronic inflammation.

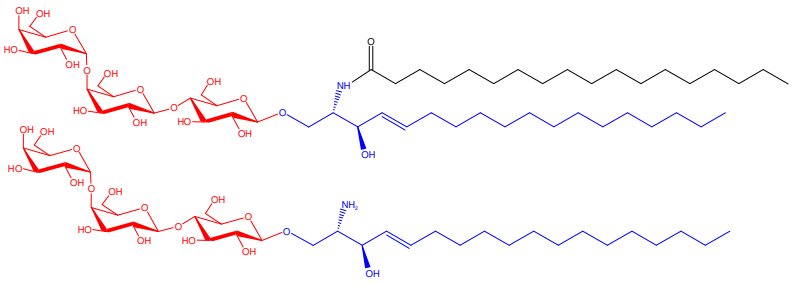
Many past studies have utilized mixtures of c9t11-CLA and t10c12-CLA making it hard to demonstrate which isomer was responsible for specific effects and what competing mechanisms there were between them. By using pure isomers a more defined role of each CLA specie can be measured. Matreya is proud to offer four highly purified CLA isomers for research and comparison studies.

References:
1. C. Liew et al., Carcinogenisis 16 (1995) 3037-3043
2. H. MacDonald, Journal of the American College of Nutrition 19:90002 (2000) 111S-118S
3. C. Loscher et al., The Journal of Immunology 175:8 (2005) 4990-4998
4. L. Zhao et al., Arch Anim Nutr. 59:6 (2005) 429-438
5. M. Yang and M. Cook, Exp Biol Med 228:1 (2003) 51-58
6. S. Huebner et al., Lipids 51:7 (2016) 807-819

Product Name	Catalog #	Amount	Purity
9(Z),11(E)-Octadecadienoic acid	1245	25 mg	98+%
Methyl 9(Z),11(E)-octadecadienoate	1255	25 mg	98+%
9(Z),11(E)-Octadecadienoic acid, Na^+ salt	1278	25 mg	98+%
9(E),11(E)-Octadecadienoic acid	1181	25 mg	98+%
Methyl 9(E),11(E)-octadecadienoate	1257	25 mg	98+%
9(Z),11(Z)-Octadecadienoic acid	1248	25 mg	96+%
Methyl 9(Z),11(Z)-octadecadienoate	1256	25 mg	98+%
10(E),12(Z)-Octadecadienoic acid	1249	25 mg	98+%
Methyl 10(E),12(Z)-octadecadienoate	1254	25 mg	98+%
10(E),12(Z)-Octadecadienoic acid, Na^+ salt	1279	25 mg	98+%

Please visit www.matreya.com for a full list of fatty acids and fatty acid methyl esters

Advances in Fabry Disease Diagnosis and Monitoring



Globotriaosylceramide
(Gb_3, CTH) catalog #1067

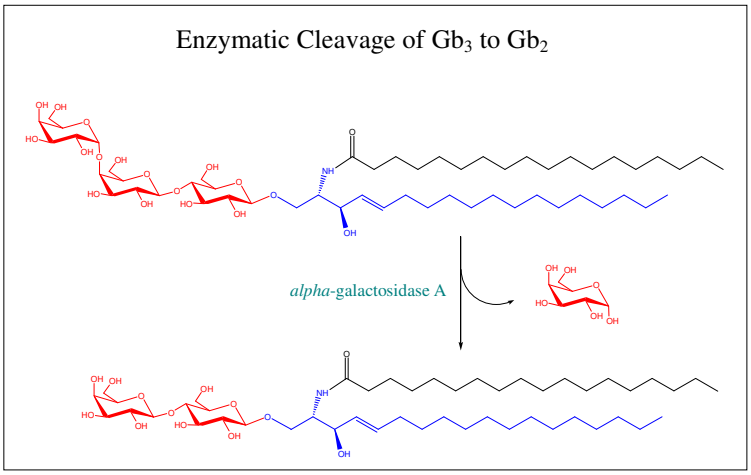
Globotriaosylsphingosine
(*lyso*-Gb_3, *lyso*-CTH) catalog #1520

Lysosomal storage disorders are a set of more than 70 inherited conditions that result in the accumulation of various lipids in cells due to an inability to enzymatically degrade them. Fabry disease (FD) is one such disorder that is characterized by a deficiency of the enzyme α-galactosidase A, resulting in an accumulation of globotriaosylceramide (Gb_3), globotriaosylsphingosine (*lyso*-Gb_3), galabiaosylceramide (Ga_2), and blood group B glycolipids. FD is an X-linked chromosomal disorder and early diagnosis of this disease is critical as progression will lead to multiorgan dysfunction and early death. To aid in early diagnosis several disease biomarkers have been identified including Gb_3 and *lyso*-Gb_3.

The use of *lyso*-Gb_3 for the determination of Fabry disease has now been well established, resulting in the development

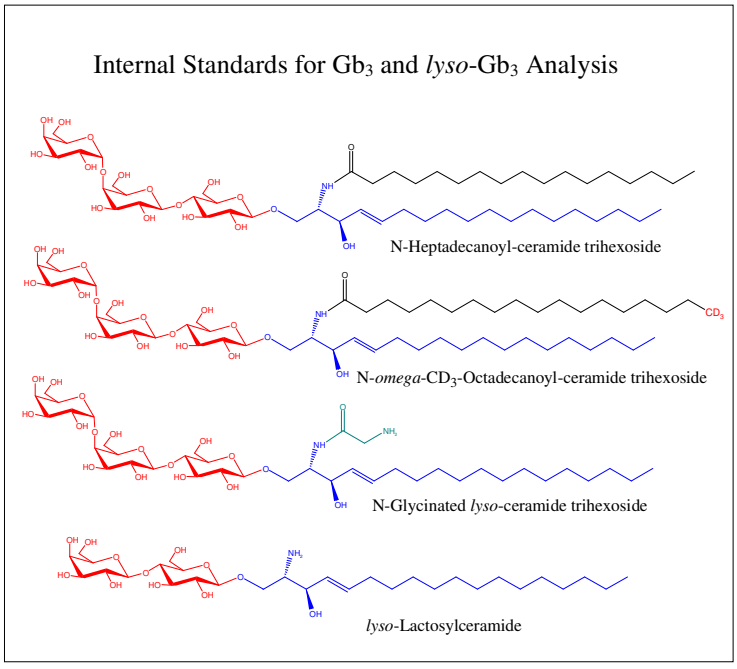
of reproducible and highly sensitive methods that require extremely small plasma, dried blood spot, or urine samples.[4,7] *lyso*-Gb_3 has been demonstrated to be an effective biomarker for FD in symptomatic patients, showing higher diagnostic sensitivity than Gb_3.[4] However, this lipid has not always been found to be a good candidate biomarker for asymptomatic females.[1] Heterozygous females can also manifest symptoms of FD making early detection of critical importance in these cases as well. Urinary Gb_3 (but not plasma Gb_3) has been reported to be elevated in both symptomatic and asymptomatic males and females even though it's sensitivity is lower than *lyso*-Gb_3. Although levels of Gb_3 do not necessarily correlate with disease severity, and though false positives do occur using this biomarker, nevertheless Gb_3 has been recognized as a useful diagnostic marker and may also indicate the formation of antibodies during enzyme replacement therapy.[1] Other possible biomarkers for FD include galabiaosylceramide (Ga_2)[3] and blood group B glycolipids.

Currently FD is most often treated by enzyme replacement therapy (ERT) and the levels of Gb_3 and *lyso*-Gb_3 have also been found to be useful in monitoring the levels of replacement enzymes needed as well as disease progression. ERT has shown a reduction not only in plasma Gb_3 but also in plasma *lyso*-Gb_3. Because FD is a result of a deficient enzyme activity, ERT is able to successfully halt the disease progress in many patients. This is especially evident in patients that begin treatment early in the disease progression as untreated patients can quickly develop irreversible organ damage.[6]



Internal standards for Gb_3 and *lyso*-Gb_3 are critical for the effective quantitation of these FD biomarkers. Glycinated *lyso*-Gb_3 (cat. #1530) was explored as an internal standard and the physical and chemical properties were found to be almost identical to that of natural *lyso*-Gb_3 in terms of extraction, stability, and sensitivity, making it an excellent internal standard for clinical work.[2] This internal standard contains a glycine molecule attached to the amine of *lyso*-Gb_3, preserving the key primary amine functionality. Another commonly used internal standard for *lyso*-Gb_3 analysis is *lyso*-lactosylsphingosine (*lyso*-Gb_2, cat. #1517) which lacks the terminal galactose of *lyso*-Gb3 but does contain a primary amine.[2,7] For Gb_3 analysis the most useful internal standard is a stable isotope labeled standard (such as deuterated octadecanoyl-Gb_3, cat. #1537) or a well-defined Gb_3 containing an unusual fatty acid (such as heptadecanoyl-Gb_3, cat. #1523). Armed with these internal standards, diagnosis and monitoring of FD can go forward steadily.

An example of the ongoing development of sensitive and efficient analyses of *lyso*-Gb_3 in FD is seen in the work by J. Lukas and coworkers[7]: three 3.2 mm dried blood spot samples were extracted with DMSO:water 1:1 in the presence of *lyso*-Gb_2 (as an internal standard) in ethanol with agitation and sonication. After particle filtration by centrifugation the sample was ready for analysis. Similarly, 25 µL of plasma was extracted in ethanol in the presence of *lyso*-Gb_2 (again as an internal standard). After protein precipitation the supernatant was filtrated by centrifugation and analyzed. Analysis was performed by UPLC/triple quadrupole mass spectrometer in MRM mode, monitoring the mass transitions of both *lyso*-Gb_3 and *lyso*-Gb_2.



Another method has been evaluated for the analysis of *lyso*-Gb_3 from dried blood spots by B. Johnson and colleagues.[5] This HPLC-MS/MS method yielded reproducible results in patients with Fabry disease, although the method was found to be unsuitable for newborn screening and late onset females.

A method that takes advantage of detectable *lyso*-Gb_3 in urine is reported by H. Gold and coworkers and includes the use of a stable isotope labeled *lyso*-Gb_3 (not yet commercially available).[4] Urine was extracted in methanol/chloroform along with the internal standard. The sample was

centrifuged and the supernatant diluted with chloroform/water to make an upper and lower layer. The upper methanol/water phase was collected, evaporated, and partitioned with butanol/water. The upper butanol phase was collected, evaporated, and re-dissolved in methanol for analysis by UPLC-ESI-MS/MS.

It will be interesting to see what the future holds for enhanced early diagnosis, treatment, and monitoring of FD. As methods become more refined we hope to see such techniques as solid phase microextraction being developed for even more efficient analysis. Equipped with an expanding array of standards, researchers can continue to delve deeper into the role of accumulated lipids in this disease's devastating pathogenesis. The recent and ongoing push to make newborn screening for α-galactosidase A more prevalent will undoubtedly have tremendous benefits for the generations ahead.

References:

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6. R. Hopkin et al. Molecular Genetics and Metabolism (2016) http://dx.doi.org/10.1016/j.ymgme.2016.06.007
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Product Name	Catalog #	Amount	Purity
Ceramide trihexoside (Globotriaosylceramide, Gb_3)	1067	1 mg	98$^+$%
lyso-Ceramide trihexoside (Globotriaosylsphingosine, *lyso*-Gb_3)	1520	1 mg	98$^+$%
N-Glycinated *lyso*-ceramide trihexoside	1530	1 mg	98$^+$%
N-Heptadecanoyl-ceramide trihexoside	1523	1 mg	98$^+$%
N-*omega*-CD_3-Octadecanoyl-ceramide trihexoside	1537	500 µg	98$^+$%
lyso-Lactosylceramide, synthetic	2088	1 mg	98$^+$%
lyso-Lactosylceramide, bovine buttermilk	1517	1 mg	98$^+$%

Please visit www.matreya.com for a full list of ceramide trihexosides and other lipid standards

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