Targeting a Double Bond in Ceramides to Treat Metabolic Disease

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Abstract

Overnutrition and physical inactivity promote the accumulation of fat-derived molecules in tissues not suited for lipid storage, leading to tissue dysfunction that underlies diabetes and cardiovascular disease. Of the myriad of lipids that accumulate, sphingolipids such as ceramides may be amongst the most deleterious, as they antagonize insulin-stimulated glucose disposal and mitochondrial lipid oxidation. Inhibition of ceramide biosynthesis in rodents ameliorates insulin resistance, hypertriglyceridemia, type 2 diabetes, cardiomyopathy, atherosclerosis, and steatohepatitis. Owing to a strong association of certain serum ceramides with insulin resistance and major adverse cardiovascular events, the Mayo Clinic is now marketing tests to measure circulating ceramides as markers of cardiovascular mortality resulting from metabolic disease. The author will discuss the development of a new therapeutic strategy to lower ceramides and combat these metabolic disorders.