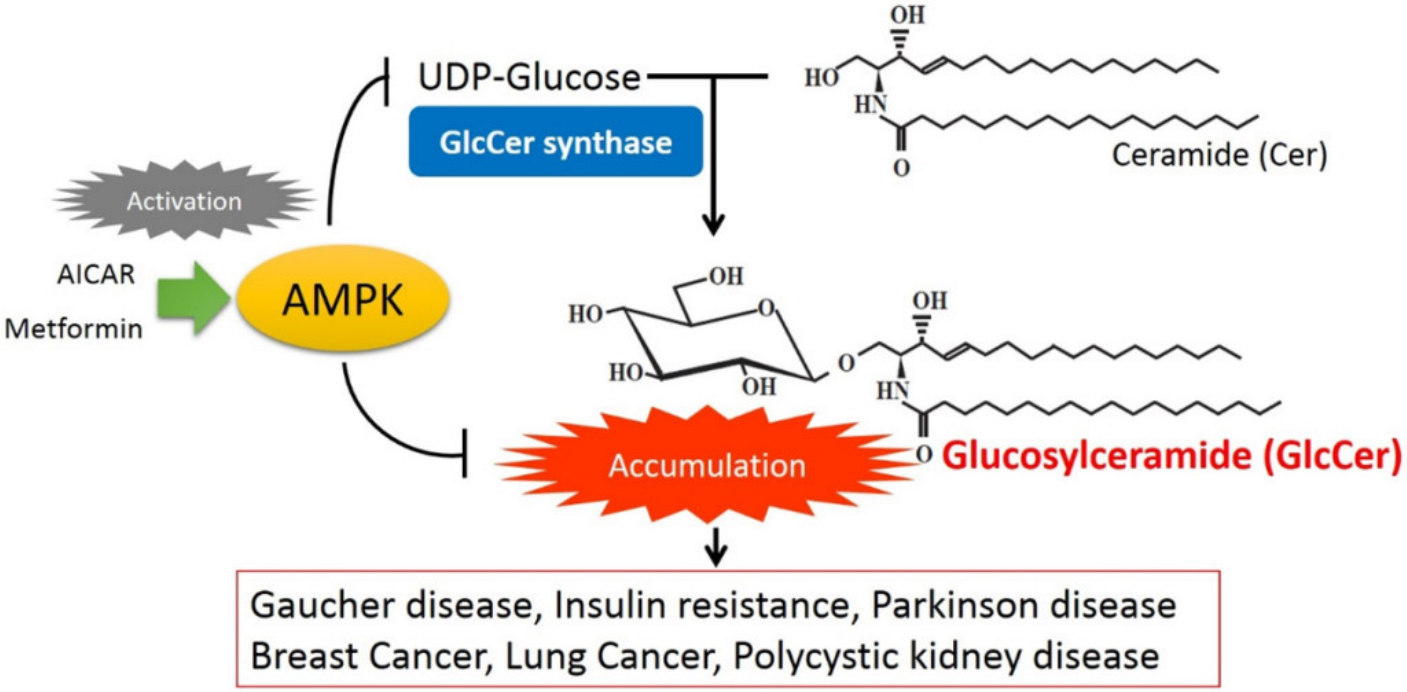
Metformin is a potential remedy for the treatment of Gaucher disease

Glycosphingolipids (GSLs) are amphipathic compounds consisting of oligosaccharides and hydrophobic chain of ceramide. They are ubiquitously distributed in the outer leaflet of the plasma membrane and believed to be involved in a large number of cellular processes, including signal transduction, membrane trafficking, cytoskeletal organization, and pathogen entry. Most mammalian GSLs are generated from glucosylceramide (GlcCer), which is synthesized by GlcCer synthase (UDP-glucose:ceremide glucosyltransferase; UGCG) from ceramide and uridine diphosphate-glucose (UDP-Glc) at the cytosolic surface of the Golgi apparatus. In vivo studies demonstrate that UGCG plays critical roles in development, differentiation, and energy homeostasis. On the other hand, abnormal accumulation of GlcCer and GSLs is shown to be closely related to several diseases or disorders. A deficiency of the GlcCer-degrading enzyme GBA1 leads to the abnormal accumulation of GlcCer in lysosomes and eventually is manifested as Gaucher disease. Enzyme replacement therapy, i.e., supplementation of GBA1 to lysosomes, and substrate reduction therapy using UGCG inhibitors have been utilized to decrease the cellular GlcCer levels of Gaucher disease patients.



In this study, we found that AMP-activated protein kinase (AMPK) affects the GlcCer biosynthesis pathway. The hydrolysis of ATP drives all energy-requiring processes in living cells. To maintain ATP at a sufficient level, eukaryotic cells have an important nutrient and energy sensor, AMPK that regulates glucose and lipid metabolism to maintain energy homeostasis. Intracellular GlcCer levels

and UGCG activity were reduced by AMPK-activating drugs, such as 5-aminoimidazole-4-carboxamide 1-?-D-ribofuranoside (AICAR) and the anti-diabetic drug metformin. On the other hand, an AMPK inhibitor and AMPK siRNA overrode the reduced GlcCer synthase activity or cellular GlcCer levels under AMPK-activating conditions, indicating that AMPK is a negative regulator of GlcCer synthesis. The expression or phosphorylation levels of UGCG were unchanged under AMPK-activating and AMPK-inhibiting conditions. Instead, we found that cellular sugar nucleotides including UDP-Glc, a precursor of GlcCer synthesis, were decreased by AMPK-activating compounds. Importantly, AMPK activators were capable of reducing cellular GlcCer levels of cells derived from patients with Gaucher disease. Our findings suggest that reducing GlcCer through AMPK activation may lead to a new strategy for treating diseases caused by abnormal accumulation of GlcCer. Since both AICAR and metformin do not directly inhibit UGCG activity, we hypothesize that GlcCer reduction may be synergistically induced by combining them with direct inhibitors of UGCG that are used for substrate reduction therapy. Due to its safety and efficacy, metformin is now used as a first choice oral anti-diabetic drug to suppress blood glucose levels, and it is prescribed to more than one hundred million people worldwide. Although the in vivo effects of metformin on GlcCer metabolism was not examined in this study, its safety profile would make it possible to use metformin as a therapy for Gaucher disease or other diseases caused by GlcCer accumulation.

Yoshio Hirabayashi, Ph.D
RIKEN Brain Science Institute
Laboratory for Molecular Membrane Neuroscience

Publication

AMP-activated Protein Kinase Suppresses Biosynthesis of Glucosylceramide by Reducing Intracellular Sugar Nucleotides.
Ishibashi Y, Hirabayashi Y.
J Biol Chem. 2015 Jul 17