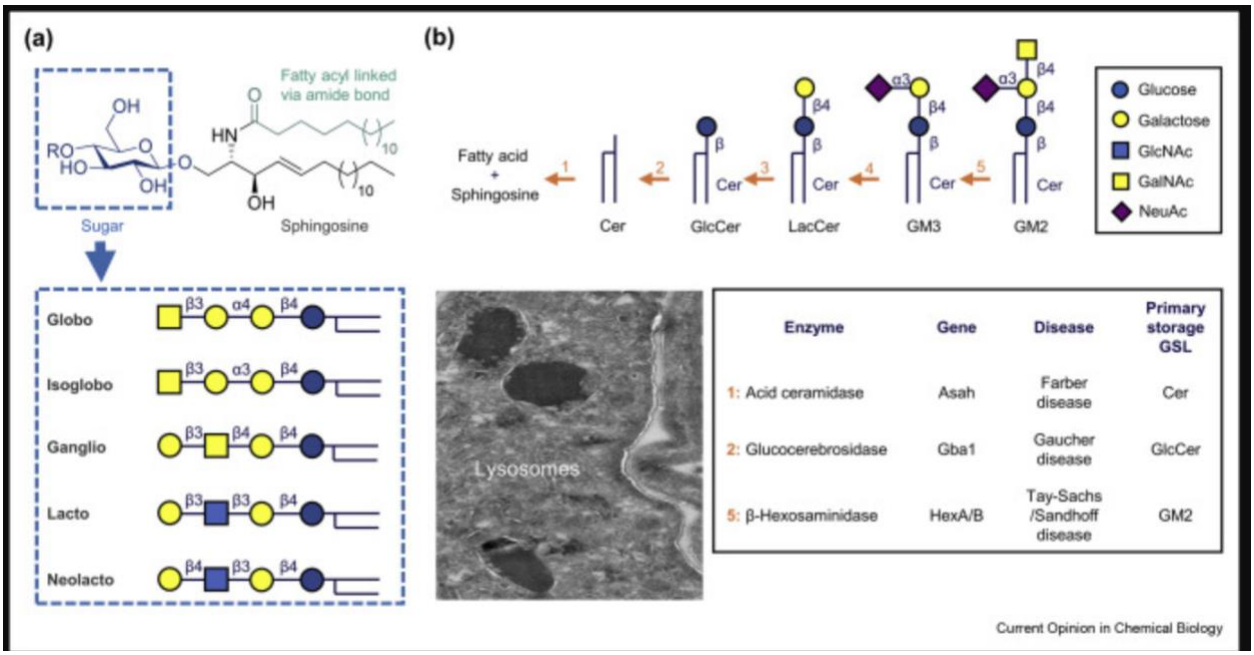
Enzyme Replacement Therapy

Since we are learning about protein metabolism this week, I decided to do some additional investigation into the use of enzyme replacement therapy for Lysosome Storage Disorders (LSDs). In short, the evolution of these therapeutics has gone through multiple generations of research – evolving from the use of "additive" replacement enzymes now to more sophisticated treatments that add "inhibitor" enzymes.

Within the category of LSDs, there are sub families of diseases such as Pompe disease, mucopolysaccharidoses (MPS) and Gaucher disease. The common underlying problem in these diseases are missing enzymes that cause the build-up of certain metabolites: different forms of carbohydrates (glucose, saccharides) or lipids; resulting in dramatic, systemic physiological impacts. The figure below shows some of the relationships of LSDs, the structure of glycosphingolipids (GSLs), and the associated missing enzyme and expressed gene (4).



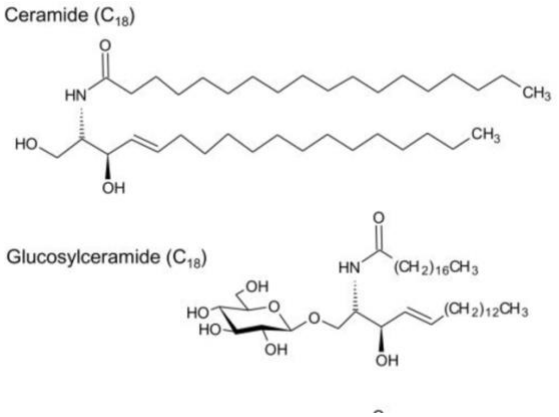
The idea for enzyme replacement therapy was first researched in 1964 – with the simple theory that "any substrate taken up intracellularly is likely to end up in the lysosome". At that time, though there were two barriers to treatment. First the specific signaling activity were not yet fully understood; and second the pharmaceutical processes to purify and produce a stable supply chain of the enzyme had to be invented (1).

The first successful enzyme replacement treatment for LSD involved the use of a synthetic version of glucocerebrosidase (GCase) for Gaucher's (pronounced go-SHAY) disease (2). Those first-generation enzyme replacement therapies were approved in the early 2000's under the names velaglucerase and taligluceras.

One of the tricky things about researching this topic is terminology - ***glucocerebroside*** is also known as ***glucosylceramide*** (GlucCer). Additionally, the replacement enzyme, glucocerebrosid*ase* (GCase) is also known as B-glucosidase. After unthreading all of the naming convention, and cross referencing the technical research, the bottom line on the biochemistry and enzyme treatment is as follows:

GCase is a lysosome that cleaves glycolipid glucosylceramide (GlcCer) into glucose and ceramide (3). A simplified way to represent this reaction is as follows:

Glucocerebrosidase (GCase) + glycolipid glucosylceramide (GlcCer) -> Glucose + Ceramide



There is another twist in this story GCase, reenables the metabolic pathway by inhibiting another enzyme - glucosylceramide synthase.

The earlier research in enzyme replacement therapy used drugs that were "additive" enzymes that replaced GCase (the missing enzyme). A more recent treatment, Miglustat operates in a different paradigm – it does not replace a missing enzyme, instead it actively inhibits a competing enzyme, preventing the build-up of the toxic lipids.

The step shown above is a critical reaction of ceramide glycosylation – which is part of sphingolipid metabolism, effectively the metabolism of "brain lipids". From there – it is pretty straight forward to understand how the missing enzyme, could have neurological impacts, even though we have not yet studied the details of lipid metabolism.

Other possible discussion topics

- What are other enzyme replacement therapies for LSDs, beyond Gaucher's disease?
- Are there any risks in enzyme replacement therapy – in other words does adding an enzyme have unintended consequences on homeostasis and metabolism in other ways?
- Should the names of enzymes be standardized and governed in a way to reduce confusion and create consistency in medical literature? (that is rhetorical and meant to be funny, I guess we have to ask the organic chemists the same question!)

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2. Ashmus, Roger A., David L. Shen, and David J. Vocadlo. “Chapter Seven - Fluorescence-Quenched Substrates for Quantitative Live Cell Imaging of Glucocerebrosidase Activity.” In *Methods in Enzymology*, edited by Barbara Imperiali, 598:199–215. Chemical Glycobiology Part B. Monitoring Glycans and Their Interactions. Academic Press, 2018. https://doi.org/10.1016/bs.mie.2017.06.014.

3. Liu, Yong-Yu, and Yu-Teh Li. “Ceramide Glycosylation Catalyzed by Glucosylceramide Synthase and Cancer Drug Resistance.” *Advances in Cancer Research* 117 (2013): 59–89. https://doi.org/10.1016/B978-0-12-394274-6.00003-0.

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