Glycogen 101

An overview of glycogen: how it's detected, its functions, and potential therapeutic routes for Lafora disease.

RESEARCH SIMPLIFIED BY

Tomás Quintero, Chelsea's Hope Science Communications Intern

QUESTIONS?

Please feel free to contact Kit, at katherine@chelseashope.org

The multifaceted roles of the brain glycogen: https://pubmed.ncbi.nlm.nih.gov/37554056/

WHAT IS GLYCOGEN?

Glycogen is a molecule known to store energy across the body, one that which the brain depends to access sugar. To store energy, glycogen is assembled using glycogen synthase (GYS1) and glycogen branching (GBE1) enzymes, and is broken down into sugar as glucose with glycogen phosphorylase (PYG) and debranching (AGL) enzymes. glycogen typically dissolves in water; but due to mutations or illness, it undergoes changes in length, branching, and chemical properties. As a result glycogen becomes insoluble, clumping into 'polyglucosans' seen in many diseases.

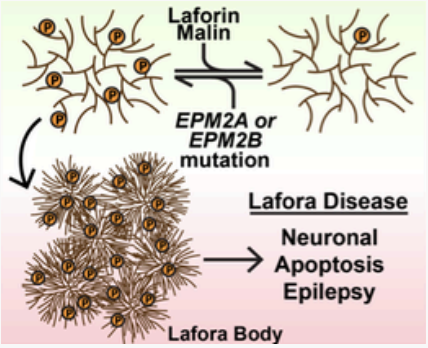

Image adapted from Dr. MK Brewer

HOW DO WE DETECT GLYCOGEN?

Many methods have been developed to identify glycogen in tissue collected from samples:

- **Periodic acid-Schiff (PAS) Staining:** a rapid technique to identify glycogen in tissue extracted from the body, considered the ideal method in clinical pathology labs today
- **α-glycogen antibodies:** monoclonal mouse antibodies IV58B6 and ESG1A9 can specifically detect glycogen in tissue extracted from the body, allowing for more advanced experimentation

However the biggest challenge to researching brain glycogen is its rapid degradation, with up to 95% of glycogen degrading before being analyzed. As a result, there is push to track glycogen levels in the body

- **GCMS, MALDI-MSI, MRS, and MRI** accurately detect glycogen presence and its spatial distribution.
- **MRI (glycoNOE)** is the most promising glycogen detection method. As the least invasive approach, it offers live glycogen imaging in the brain, allowing researchers to study glycogen in current patients.

THE MANY ROLES OF GLYCOGEN IN THE BODY

- **Glycogen as backup energy source:** glycogen provides temporary energy to the body, explaining why it is found across the body. While the liver and skeletal muscle tissue store the majority of glycogen, the brain has its own emergency storage too.
- **Thermoregulation and Viscosity:** glycogen helps maintain a cell's viscosity and the rate at which particles cross the membrane, allowing the neuron to continue transmitting signals at high temperatures.
- **Gene Expression:** glycogen is recognized to affect histone acetylation, the "on" switch for cell growth genes. Accumulated glycogen is a hallmark for some cancers.

GLYCOGEN IN THE BRAIN

Thanks to technology overcoming challenges to detecting brain glycogen, researchers found glycogen across the brain and in many brain cell types including astrocytes (having the most glycogen), as well as neurons and microglia (which have the largest glycogen stores). They proposed brain glycogen has two roles: providing the brain with energy in low oxygen conditions and allowing for memory formation. In neurons, glycogen is mainly found around the synapses, the primary message relay site to other neurons.

- **Neurotransmitter synthesis:** glycogen is used to create glutamate, a neurotransmitter that activates other neurons.
- **Memory formation:** glycogen is linked to memory, researchers determined impaired memory and learning in chickens and mice with impaired glycogen storage
- **Glycosylation:** In the brain, glycogen stores multiple types of sugars to modify proteins. This can influence cell-cell interactions, the synapse, and inflammatory pathways. Errors to glycosylation are linked to 100+ diseases, including some cancers, as well as Alzheimer's, Pompe, and Lafora disease.

GLYCOGEN AND DISEASE - THE GSD

Starting in 1929, diseases related to glycogen formation and breakdown were first discovered, since then over 16 types of Glycogen Storage Diseases (**GSD**) have been identified, including Pompe, APBD, Cori, and RBCK1. GSDs are inherited, with mutated genes affecting the enzymes involved in glycogen metabolism. The majority of GSDs accumulate glycogen across the body, resulting in various symptoms; among them is the **n-GSD** which affects the brain.

In Lafora Disease The n-GSD produces neurological symptoms, with the severity ranging from mild cognitive delay to severe seizures and death. In the brain, glycogen accumulation affects cells differently. In astrocytes, glycogen accumulation results in increased brain inflammation, while in neurons it results in seizures. Given its disease pathology, Lafora disease is considered an n-GSD, with many patients being adolescents and young adults. While there are currently no effective therapies, the genetic basis of GSDs allows for therapeutically actionable research avenues.

TARGETING GLYCOGEN

There are many GSD treatment therapies being explored, some of which have offered optimistic data in pre-clinical trials including Antisense Oligonucleotide (ASO) Therapy and Substrate Reducing Therapy (SRT). Ionis Pharmaceuticals created ION283, an ASO that interferes with the GYS1 production to reduce glycogen assembly. In addition, MAZE Therapeutics developed MZE001, an SRT that prevents GYS1 from taking up glucose to stop glycogen aggregate formation. Both MZE001 and ION283 have received FDA orphan drug designations. Parasail LLC provides another treatment option with VAL-0417, an Antibody Enzyme Fusions (AEFs) that degrades glycogen aggregates and restores proper glycogen metabolism. VAL-0417 is an interesting therapeutic candidate because it enters cells with equilibrative nucleoside transporter 2 (ENT2), which allows for the treatment of other n-GSDs.

This variety of treatment strategies allows for exciting overlap in n-GSD research and result in accelerated therapy development for the GSD community.