

# GLUT1, glucose, fucose and glycosylation

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We all know that glucose is required for generating energy in the body. We also know, all too well, the consequences of insufficient glucose delivered to the brain: GLUT1 Deficiency Syndrome with all of its complications. While GLUT1 is the main delivery system for glucose and certainly needed for energy, there is another role that glucose plays in our cells and most organisms. Glucose is the raw material for generating many other sugars for a cellular process called glycosylation. That's the scientific term for the addition of a host of sugars to proteins and lipids. All of those 9 or 10 glycosylation sugars can be made from glucose after it is taken into the cell. But those sugars can also be imported directly from outside the cell. There is usually not very much of them in the diet.

One of these glycosylation sugars is called fucose—very rare in most diets, but we used that sugar to treat a patient with an inherited glycosylation disorder called LAD-II. This child was always getting infections because his white blood cells could not leave the circulation to attack the infection. His blood looked like tomato soup made with heavy cream. But within 5 days of fucose supplements, his white cell level returned to normal. That was very surprising. We eventually figured out the problem was poor delivery of an activated form of fucose to a compartment in the cells. But then we asked how did fucose enter cells from the blood? It turns out that our friend, GLUT1, is a major transporter of fucose.

Then Bobby Ng in my lab said, “what if GLUT1-DS is not only an energy deficiency, but also a glycosylation deficiency?”. Maybe we could provide dietary supplements to patients! Of course, before doing that, we need some experiments in a GLUT1-DS mouse model. Fortunately, Dr. Pasqual has such a model and Dr. Gentry has evidence that these mice are deficient in brain glycogen and glycosylation. So, both control and GLUT1-DS model mice were given modest amount of fucose for 10 days. Dr. Pascual's lab measured their gait by sophisticated motion analysis throughout the experiment and found that a few of the parameters improved after only 5 days. At 10 days, Dr. Gentry found that both glycosylation and glycogen content in the brains of Glut1-ds were nearly normal. These preliminary results are very encouraging, but they need to be repeated using more male and female mice. They also must be repeated using a different mouse model. Meanwhile, Dr. Caroline Pearson is looking into the effects of fucose on her human iPSC model. It's too early to tell if there is an effect, but stay tuned.

So you ask, “when can patients start taking fucose”? Well, not so fast, please. Fucose is likely quite safe (I've taken it), but until we have more results, it would be too early to start a “trial”, especially if individuals chart their own course on dosage, frequency and meaningful measures of improvement. It's important that we're all in agreement and well-coordinated before jumping into the big fucose pool. Be assured that we are looking into how such a trial might be done, but for now: Don't try this at home. Again: stay tuned!