

What the Gila Monster Can Teach Us About Diabetes



Evan David Rosen, M.D., Ph.D.

Assistant Professor of Medicine, Harvard Medical School

A hot question in biology these days is "How many genes do we have?" Perhaps a more important question is "How many proteins are encoded by our genes?", because proteins actually do the work inside cells. The reason for the distinction is that some genes can give rise to many different proteins. Some hormone genes, for example, yield a single large protein that is then diced and sliced into several smaller proteins, each with its own specialized function.

One such "super-gene" encodes the hormone glucagon, which causes blood sugar levels to rise when they are too low. As it turns out, the gene for glucagon also contains the instructions for at least two other hormones, called glucagon-like peptides 1 and 2 (GLP-1, GLP-2). Not only do the GLPs come from the same gene as glucagon, but they actually have a very similar amino acid sequence as well. Despite these parallels, the GLPs have very different functions than glucagon, and there is a lot of excitement about using these hormones to treat problems ranging from diabetes and obesity to chemotherapy-induced intestinal damage.

From a diabetes perspective, the interesting GLP is GLP-1. GLP-1 is secreted from special cells in the gut in response to a meal, and helps to integrate many of the normal physiological responses that occur after eating. For one, GLP-1 induces insulin secretion from the pancreas, and simultaneously reduces glucagon release. This release of insulin actually seems to occur only when the ambient glucose concentration is high, thus reducing the chance that hypoglycemia will develop (an especially attractive feature in a diabetes therapy). Over a longer period, GLP-1 actually increases the number of insulin-producing beta cells. GLP-1 also acts directly on the GI tract, reducing the rate at which food spills out of the stomach and into the intestine, making the absorption and storage of energy more efficient. Finally, and perhaps most intriguingly, GLP-1 acts on the central nervous system to signal a sense of

fullness so that we don't overeat. It doesn't take a Ph.D in metabolism to figure out that these effects would all be beneficial in type 2 diabetes.

So why aren't we prescribing GLP-1 to everyone with type 2 diabetes already? Well, there are a few problems, but one of the most daunting has been that our bodies destroy GLP-1 within a few minutes. This means that it needs to be continuously infused (Because it is a protein, GLP-1 cannot be given orally), which is clearly not going to work for most people. The enzyme that destroys GLP-1 is called dipeptidyl-peptidase IV (DPP IV), and intense focus has been placed on figuring out ways to disable the enzyme so that GLP-1 can do its thing for longer periods of time.

One way to get around the problem of DPP IV is to administer a form of GLP-1 that is resistant to destruction. Such forms of GLP-1 have already been found, and the source is delightfully unexpected--the poisonous saliva of the Gila monster lizard. GLP-1 (called exendin-4) from these reptiles has a few key differences from the form found in humans, one consequence of which is immunity to DPP IV. There are pharmaceutical companies working on synthetic forms of exendin-4 (one imagines that it's easier to make the chemical from scratch than it is to harvest toxic lizard spit). Phase 2 clinical trials of exendin-4 in patients with type 2 diabetes show improvements in hemoglobin A1c levels comparable to those seen with currently available antidiabetic drugs. Other studies show reductions of caloric intake after exendin-4 administration.

Another strategy that is being pursued is the use of drugs that will inhibit DPP IV directly. A preliminary study showed that 24 hours after taking such a drug, patients with mild type 2 diabetes have reduced fasting, post-meal, and average blood sugar levels. The primary advantage of this approach (vs. exendin-4) is that DPP IV inhibitors can be given orally. On the other hand, DPP IV affects other hormones besides GLP-1, and there is concern that blocking the enzyme could cause other problems. One reassuring piece of data is that mice that are genetically engineered to lack DPP IV are viable and appear to do well, and this provides some reassurance that the strategy is sound. Still, longer term studies with both DPP IV inhibitors and exendin-4 need to be performed to assess possible toxicity. It is also unclear if the beneficial effects of GLP-1 will be sustained over time, and this too will have to be tested. Nonetheless, a drug that causes weight loss as well as improved insulin secretion in type 2 diabetes would be a potential blockbuster, so you can bet that those studies are going to get done.

References:

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