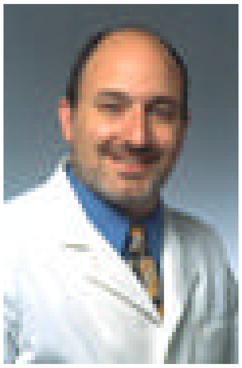

Glucokinase: Teaching An Old Dog New Tricks

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Glucose from the blood gets into different cell types by a variety of means, ranging from tightly regulated transport by special proteins (as in muscle and fat), or by passive diffusion (as in the cells that line blood vessels). Either way, once glucose gets into the cell, it has to be trapped there so that it doesn t leave.

Cells accomplish this trapping function through the actions of a family of enzymes called *hexokinases*. Hexokinases come in several different forms, but they all share the ability to stick a chemical known as a phosphate group onto glucose, thus changing both the size and electrical charge of the sugar molecule and preventing its escape from the cell. Perhaps the best known of the hexokinase proteins is one found in the liver and in the insulin-producing pancreatic beta cells, known as *glucokinase*.

Glucokinase in liver and beta cells traps sugar and allows it to be metabolized—broken down into energy. Glucokinase serves as a signal to both the beta cells and the liver that sugar levels in the blood are high, leading to insulin secretion and reduced glucose production by the liver. There are rare patients who carry a mutation in the glucokinase gene that renders them deficient in the activity of the enzyme. The result is a form of diabetes called MODY (Maturity Onset Diabetes of the Young). On the flip side, there are also patients with mutations that cause too much glucokinase activity, and these folks have dangerously low blood sugar levels associated with uncontrolled insulin secretion.

All this information about glucokinase has been known for years, and there has long been speculation that a drug that could juice up glucokinase activity a little bit might be beneficial in treating type 2 diabetes. The problem has been that while one can fairly readily find drugs that inhibit enzymes, it is very difficult to find drugs that make enzymes work better. One of my old professors used to give the example of a finely tuned Swiss watch—if you hit it with a rock, you can make it run less well quite easily. It would be pretty unlikely, on the other hand, to deliver a blow that would make the watch run better than it already does.

Amazingly, researchers at Hoffmann-LaRoche have done just that to glucokinase. By screening 120,000 drugs of different types, they were able to identify a single one that actually made glucokinase work better than it already does. This drug, which so far has been given the unsexy name of RO-28-1675, seems to have no effect on other forms of hexokinase, an important test of its specificity.

When the drug was given to obese, insulin-resistant rats and mice, blood sugar levels dropped in a predictable manner. By carefully controlling blood sugar and insulin levels in the mice using special techniques, the researchers were able to show that RO-28-1675 has effects in both the liver and in beta cells. The beta cells, however, seem to be the dominant site of action, as mice that lack insulin no longer respond to the drug. (If the effect in liver were dominant, one would expect to see the drug reduce blood sugar at least a bit in the absence of insulin.) This is important because it makes it unlikely that this drug will be useful for patients with type 1 diabetes, or with type 2 diabetes of an advanced stage where the beta cells have pooped out.

Given the close similarities in the structure of rodent and human glucokinase, this drug will probably have similar effects in people. Care will have to be taken, however, because we already know that too much glucokinase activity is a bad thing. I don t see this as a major obstacle: we already have several drugs on the shelf that increase insulin secretion (e.g., sulfonylureas and metiglinide drugs such as Prandin™ and Starlix™). We have learned how to dose these properly without causing significant hypoglycemia. I think we ll figure this one out as well. On the contrary, I wonder if the drug represents a big enough therapeutic leap over what we already have to make it compelling enough to bring to market.

Regardless of the answer to that question, there is likely to be one very positive effect of this new finding: it may spur the search for other "activator" drugs for other targets. An activator of the Glut4 glucose transporter, for example, would be useful, and activators of the pathways that regulate appetite might also come in handy.

There are a lot of old dogs like glucokinase out there; perhaps we can look forward to seeing some of them perform some new tricks.

Reference:

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