

Viewpoint on Diabetes



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Resistance is Futile

Two months ago I wrote a *Viewpoint* (will be reprinted in 2 weeks) about lipid accumulation in places where it ought not to be, such as liver and muscle, and how this can contribute to the development of insulin resistance and type 2 diabetes. That article also discussed how the hormone leptin can eliminate that extra lipid by causing it to be burned as fuel. Leptin has long been known to reduce appetite and weight gain, so it has been a hotly pursued target of drug development as an anti-obesity agent. The new studies indicated that leptin could have an important role in reducing type 2 diabetes above and beyond its beneficial effects on body weight.

Unfortunately, in medicine things don't always turn out as hoped. Trials of leptin administration to obese adults showed no significant benefit, and a collective sigh of disappointment could be heard coming from researchers, patients and physicians, not to mention investors. In retrospect, those disappointing results were not totally unexpected. Most obese people actually have very high levels of leptin in their blood. This suggests that the problem in obesity isn't "not enough leptin," but rather "leptin isn't working correctly." This has in fact proven to be the case, and we spend a lot of time nowadays talking about so-called "leptin resistance." What we need to give people is not more leptin, but something that will make them listen better to the leptin they already have. This is philosophically identical to the use of metformin and thiazolidinedione drugs in type 2 diabetes; these agents do not increase insulin levels, but they make our tissues respond better to the insulin that's already there.

Amazingly, the search for other drugs that act as insulin sensitizers may have provided an important clue for dealing with leptin resistance as well, in a classic case of "ain't life funny?" Here's how the story unfolded:

Researchers had identified a crucial question -- how does a cell turn off the signal given by insulin once the message has been delivered? This is a critical issue; cells have to respond to rising and falling levels of insulin in the blood on a minute-to-minute basis. If they don't turn off an insulin signal shortly after receiving it, they will be responding inappropriately when insulin levels drop between meals, and they will not be ready to receive the next insulin signal after an upcoming meal. Still, if one could tamp down the inactivating factors, one could get a lot more bang for the buck from any given amount of insulin.

It turns out that insulin receptors activate signaling by causing inorganic phosphate to stick to specific tyrosine amino acids in the receptor and in downstream molecules, a process called tyrosine phosphorylation. These phosphates are removed by proteins in the cell called protein tyrosine phosphatases (PTPs). Reducing the activity of the PTPs that target the insulin receptor seemed like a good way to get more insulin signaling. As it turns out, there are probably a few different PTPs that work on the insulin receptor, but one in particular, called PTP1B, seemed to be most important. To prove this, researchers made genetically altered mice that lack the gene for making PTP1B. And, as expected, these mice have a stronger response to insulin than other mice do.

The interesting thing was that most insulin sensitive animals tend to be a little fatter than usual, because insulin promotes adipose deposition. The mice without PTP1B were surprisingly lean, however, which raised suspicions that something else could be going on in addition to the effects on the insulin receptor. That something else appears to be effects on leptin receptor signaling. The leptin receptor sends its message by phosphorylating a protein called Jak2, and Jak2, it turns out, is also a target of PTP1B. By preventing the inactivation of Jak2, leptin resistance is overcome, and the mice eat less and gain less weight.

As yet, there are no good, safe PTP inhibitors for human use, but these results will push the hunt to fever pitch. A few wrinkles still need to be ironed out, however. For example, PTP1B looks a lot like other PTPs, and it may be hard to inhibit just one specific PTP. One tactic being explored is the use of bidentate inhibitors, which attach to both the common, active site of the enzyme in addition to a more unique, PTP1B-specific area as well. Another potential problem is that PTP1B may have effects on other organ systems, which would be affected by even a very specific PTP1B inhibitor. Nonetheless, a single drug that can improve insulin sensitivity *and* reduce body weight is something of a Holy Grail in type 2 diabetes, and the company that gets there first may well have a blockbuster on its hands.

[For a complete CV on Dr. Rosen click here](#)

References:

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