

Sweet Notes



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There are a lot of things going on in diabetes research that don't necessarily merit a full column. In this edition of *Diabetes In Control*, I'd like to highlight a few recent developments that I think are exciting and worth noting.

1. All roads lead to AMP kinase. One theory behind the development of type 2 diabetes is that fatty molecules build up in the wrong places, like liver, muscle, and pancreatic beta cells (as discussed in previous issues). One of the ways that cells can get rid of this unwanted lipid is to burn it as fuel, a process called "beta-oxidation." How do cells initiate this process? At least one important pathway relies on a molecule called AMP-activated protein kinase (AMPK). Recent data from a variety of labs has shown that AMPK is activated by exercise as well as by two different classes of antidiabetic drugs, metformin (Glucophage™) and thiazolidinediones (Avandia™ and Actos™). While we don't know for sure how these drugs improve diabetes, activation of AMPK is a good bet to play at least some part in the process. Now, new research shows that adiponectin (also called ACRP30) also activates AMPK and induces beta-oxidation of fats in liver¹. Why is this interesting? Well, we know that adiponectin is important in maintaining normal insulin sensitivity in rodents, and probably humans as well. This new finding raises speculation that activation of AMPK is the mechanism by which adiponectin achieves better glucose control, and it increases the already intense interest in AMPK as a direct drug target for diabetes therapy.

2. An exercise in futility. A classic principle of biochemistry is that cells do not like to do things both forwards and backwards. Such "futile cycles," as they are called, result in little or no metabolic gain, but a lot of wasted energy. To prevent this, many chemical reactions in cells are the equivalent of one-way streets. One example is found in fat cells. Fat cells store fatty acids by linking them to a molecule called "glycerol-3-phosphate," generating a storage form of fat called triglyceride. When triglycerides are needed as fuel, fat cells liberate the glycerol, but without the phosphate attached. This prevents the glycerol-3-phosphate from automatically reattaching to the fatty acid, and thus re-generating triglyceride. The reason the glycerol can't just add phosphates, and avoids the futile cycle, is because the key enzyme in the process (glycerol kinase) is not believed to be present in fat cells. Now, a group of researchers at the University of Pennsylvania have discovered that thiazolidinedione antidiabetic drugs induce glycerol kinase in fat cells². The end-result? Fatty acids are less likely to be released into the bloodstream by fat cells in the presence of TZD drugs—and other tissues are forced to burn glucose, thus lowering blood sugar levels. This

study may help explain how TZDs work and could provide the rationale for developing other drugs that target glycerol kinase.

3. Just say NO. One of the more painful and annoying complications of diabetes is peripheral neuropathy, which can manifest as tingling, burning, or searing pain, especially in the feet and legs. The ultimate cause of the neuropathy is not clear, but some studies have pointed to a deficiency in a molecule known as nitric oxide (abbreviated "NO") in affected areas. A new study tested whether spraying a drug called isosorbide dinitrate directly onto the feet of people with diabetic neuropathy would alleviate pain³. Isosorbide dinitrate, known as ISDN, is converted by the body to NO, and researchers hoped that restoring NO levels in the nerves of the feet would reduce pain. Participants sprayed ISDN for one month, or a placebo for one month, without knowing which was which; at the end of study, they chose which spray they wanted to keep using. 50% preferred ISDN, 18% chose the placebo, and 32% couldn't tell the difference. The bottom line is that more work should be done to investigate the role of NO in diabetic neuropathy, including the study of drugs that affect NO levels more effectively than ISDN.

References:

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