Edible Compound Mimics Insulin

An obscure compound plucked from a central African fungus works like insulin to boost glucose metabolism, tests on mice show. Unlike insulin, however, the compound can stand up to the onslaught of digestive juices present in the mouth and stomach, and might therefore serve as an edible drug.

Several oral diabetes drugs are on the market already, but they all risk side effects. If the new chemical fares as well in human tests as it has in mice, it holds the potential for replacing these drugs or even insulin injections in some uses.

That's a big "if," of course. The substance is still untested in primates.

Nonetheless, the U.S. and European researchers who discovered it have high hopes for the chemical, which for now is simply named L-783,281. The scientists report their findings in the May 7 SCIENCE.

The compound stood out among more than 50,000 substances tested because it reacted to a molecule on the surface of cells called an insulin receptor. The receptor in this case, called tyrosine kinase, acts as a metabolic switch. When insulin attaches to it, the molecule ignites a chain reaction within a cell that starts the processing of glucose that is circulating in the blood.

However, some obese people and many diabetes patients have insulin resistance, in which insulin and its receptors become estranged and fail to bind, thwarting glucose processing. This produces high blood sugar.

Additional insulin can help, but some diabetes patients need more and more as their cells become increasingly resistant. To find a replacement signaler that would start the chain reaction, the researchers engineered Chinese hamster ovary cells to have human insulin receptors. The scientists noted that L-783,281 mimicked insulin by stirring these cells to process glucose in laboratory dishes. It was 50 to 100 percent as effective as insulin, depending on the concentration of L-783,281 used.

Next, they fed the compound to 32 insulin-resistant mice. "We achieved glucose lowering comparable to that elicited by insulin injection," says study coauthor Bei Zhang, a biologist at Merck Research Laboratories in Rahway, N.J. In a series of tests ranging from a few hours to several days, mice getting L-783,281 experienced falling blood-glucose concentrations, whereas mice fed an inert substitute had little decline. Cells in the treated mice apparently took up the glucose to use as fuel, she says.

Because the new compound isn't a protein like insulin, it survives the mammalian digestive tract, Zhang says. Moreover, to increase glucose metabolism, L-783,281 uses a mechanism distinct from those of the four classes of oral diabetes drugs already on the market. Therefore, the researchers might be able to combine it with them, she says.

The oral drugs have side effects, such as weight gain or low blood sugar. Whether the new compound will avoid such problems is still unknown, she says.

The fungus harboring L-783,281 came from the leaf of a plant in the Democratic Republic of Congo, formerly Zaire. Researchers have grown more of the fungus in Merck's laboratory in Spain. While the plant remains unidentified, the scientists have the fungus, which is what matters, says Zhang.

Drug development is highly competitive; Merck isn't divulging its next step. Zhang says only that the company is pursuing "various different approaches."

In fact, companies are screening thousands of compounds these days, looking for potential diabetes treatments in molecules that are impervious to digestive juices, says endocrinologist Derek LeRoith of the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, Md. LeRoith, who called the study "an excellent paper," suspects Merck might try to modify this chemical. "This is not the compound that may finally be used in [a human] trial," he surmises. "They may get their chemists to alter it slightly, improve on it." —*N. Seppa*

Altered buckyballs go straight to bone

Scientists are one step closer to using fullerenes—spherical carbon molecules—to deliver powerful drugs straight to diseased tissues. Direct delivery can increase drugs' potency while reducing their harmful side effects.

Unlike other molecules that are used to encapsulate drugs, fullerenes resist breakdown by the body. This stability is especially important for holding compounds that would cause harm if released in healthy cells. For example, some cancer therapies attack tumors with compounds containing radioactive metal atoms. If the metals escape from their molecular capsules before they arrive at their targets, the stray radiation can damage normal tissue.

Kelly A. Gonzalez and Lon J. Wilson of Rice University in Houston have modified 60-carbon fullerenes, called buckyballs, to home in on bone when injected into the body. Wilson presented the findings this week at a meeting of the Electrochemical Society in Seattle.

"The traditional way to target tissues is with antibodies," complex molecules that seek out specific proteins on cell surfaces, says Stephen R. Wilson of New York University, who also studies the medical applications of fullerenes. The Rice scientists' design of a simple molecule that chemically attaches to a particular tissue is "the kind of thing that a lot of people are trying to do."

Gonzalez and Wilson designed their compound to stick to a bone mineral called hydroxyapatite. They attached a chemical group called an amide bisphosphonate to a buckyball and then added 16 hydroxyls to make the molecule water-soluble. The bisphosphonate binds to hydroxyapatite, and the fullerene compound interferes with the mineral's crystal growth.

While this effect might be undesirable in a therapeutic treatment, it offers a way to determine whether the molecule sticks to bone. Hydroxyapatite-crystal formation releases tiny amounts of hydrochloric acid. Wenju Wu and George H. Nancollas of the State University of New York at Buffalo earlier developed a technique to measure how well compounds adhere to bone by detecting this acid.

Together, the SUNY and Rice scientists found that in a test tube, the new compound reduces the rate of hydroxyapatite formation, indicating that the modified buckyballs bind well to bone.

They also got a surprise when characterizing the compound: The molecule has one unpaired electron, making it magnetic. "This is a very curious beast," says Lon Wilson. This property makes the compound a potential contrast agent for magnetic resonance imaging (MRI). A contrast agent injected into a patient can sharpen an MRI picture, revealing otherwise invisible features.

In the April 27 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, Lon Wilson and his coworkers also report on rat studies showing that water-soluble buckyballs containing a radioactive atom build up in bone but are slowly cleared out of other tissues. Such excretion has "never been seen for a fullerene material before," he says. It's crucial to demonstrate that fullerenes can be flushed out of the body before they're developed into drugs, he adds. —*C. Wu*