Trends in Medical Research

ISSN 1819-3587

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Agents That Keep Insulin Working Longer Developed

More than half a century after researchers identified a promising way to treat diabetes based on blocking the breakdown of insulin in the body, a research team led by a scientist at the Mayo Clinic campus in Florida has developed potent molecules that can do just that.

The researchers say their findings, published in the May issue of PLoS ONE, could lay the foundation for a new class of drugs for treating diabetes. The tiny molecules they developed work by inhibiting a powerful molecular machine known as Insulin-Degrading Enzyme (IDE) from chewing up the insulin hormone. That keeps insulin in the body longer to help remove glucose (simple food sugar) from the blood.

The discovery may lead to drugs that diabetics can use to help insulin work better and longer, says the study's Lead Researcher, Malcolm Leissring, Ph.D., from Mayo Clinic's Department of Neuroscience. Diabetes affects over 200 million people worldwide, and the incidence is growing at an alarming rate, so new treatments are greatly needed, he says.

IDE is a protease, an enzyme that chops proteins or peptides into smaller pieces. According to Dr. Leissring, inhibitors have been developed for practically all biomedically important proteases in the body. "It was very surprising that IDE inhibitors had not been developed before, particularly given IDE's special relationship with insulin, a very important hormone," he says.

This was especially puzzling because IDE was discovered more than 60 years ago. In fact, finding an IDE inhibitor was a major goal of diabetes research in the 1950s. In a landmark study, one group of early researchers managed to purify a naturally occurring IDE inhibitor, and showed that it made insulin more effective at lowering blood glucose in animals, precisely the desired effect for treating diabetes. However, the composition of the agent was never determined.

The research team initially tried to find IDE inhibitors using sophisticated technologies. They used robots to test hundreds of thousands of compounds at the Laboratory for Drug Discovery in Neurodegeneration (LDDN), a part of Brigham and Women's Hospital and Harvard Medical School. Surprisingly, these modern methods did not identify any good inhibitors, Dr. Leissring says.

"Our robots wound up being powerless for tackling this particular problem," he says. "Ironically, it was an old-fashioned method that made this breakthrough possible."

The old-fashioned approach involved using a technology invented in 1950 to figure which peptide sequence -- among trillions of possible combinations -- IDE chops up most efficiently. Benjamin Turk, Ph.D., of Yale University School of Medicine, conducted this critical step. Then, a team of chemists led by Gregory Cuny, Ph.D., director of Medicinal Chemistry at the LDDN, generated a compound that contained the preferred peptide sequence, together with a special chemical group that binds to zinc. The resulting compound is called "li1" (IDE inhibitor 1).

"li1" is about a million times more potent than any previous IDE inhibitors, but additional work will be needed to turn it into a drug suitable for therapeutic use, Dr. Leissring says. In a key step towards this goal, Dr. Leissring, together with Wei-Jen Tang, Ph.D., and other colleagues from the University of Chicago, solved the 3-dimensional crystal structure of li1 bound to IDE. This crystal structure will facilitate the development of inhibitors that are more stable in the body than li1 is predicted to be.

The structure of IDE is unlike other proteases, the researchers say. It is shaped like a hinged clamshell that opens and shuts, like the well-known video game protagonist, Pac-Man.

The researchers found from their crystal structure that the li1 peptide acts like a magnetic latch that holds the clamshell shut. "Think of a coin purse that uses a magnet at the top to keep the purse from opening up," Dr. Leissring says. "li1 is analogous to the magnetic latch, holding the two halves of IDE closed."

If IDE is inhibited, insulin remains in the body longer. Normally, about half of the insulin produced by the pancreas is immediately destroyed by the liver; no one knows why this occurs but it may be a way to regulate how much insulin enters the bloodstream?" he says.

IDE inhibitors would slow the rate of this initial destruction. However, according to a surprising finding from the study, they would also help prevent degradation of insulin at the "destination" cells that are responsible for removing sugar from the bloodstream. "When insulin reaches cells, it is normally destroyed very rapidly by IDE. We show that when you stop that process with an IDE inhibitor, insulin stays around longer inside the cell, allowing the hormone to function more efficiently," Dr. Leissring says.

IDE inhibitors may also be beneficial for other diseases besides diabetes, the researchers suggest. "Insulin is involved in a surprisingly wide range of important processes, including memory and cognition, so IDE inhibitors may turn out to have multiple uses. They also will be very valuable as tools for basic research," says Dr. Leissring.

The study was funded by grants from the National Institutes for Health, the Ellison Medical Foundation, and by a gift from The Unforgettable Fund, a charitable foundation based in Palm Beach County, Fla.

Source: PLoS ONE, 2010; DOI: 10.1371/journal.Pone.0010504