Leapin' Lizards: Amylin Targets Diabetes and Obesity via Incretins

Wendy Wolfson
DOI 10.1016/j.chembiol.2007.03.005

Diabetes mellitus is a progressive disorder that prevents the body from effectively regulating blood glucose levels. Patients with Type II diabetes either do not make enough insulin or become resistant to it. In contrast, Type I diabetes, otherwise known as juvenile diabetes, is an autoimmune disease in which an individual loses the ability to produce insulin.

The symptoms associated with diabetes were recognized in ancient times. However, only in the late 19th century was the relationship between diabetes and the pancreas discovered. About 40 years later, Nicolae Paulescu reported the first isolation of insulin, the active hormone that is secreted by the pancreas. Frederick Banting and Charles Best followed a few months later and subsequently shared a Nobel Prize with John Macleod. The distinction between Type I and Type II diabetes was only made in 1936.

"Most people with type II diabetes will need pharmacological agents," said Dr. Christopher Saudek, professor of Endocrinology and Metabolism at Johns Hopkins Medical School.

Normally, body glucose is regulated by secretions of hormones from both α and β cells in the pancreas. The α cells secrete a hormone, glucagon, which promotes breakdown of glycogen in the liver. β cells secrete insulin, which induces uptake of glucose into cells, primarily muscle, fat, and liver. Incretin hormones GLP-1 (glucogen-like peptide) and GIP (glucose-dependent insulinotropic polypeptide) secreted in the gut modify the activity of both cell types. GLP-1 and GIP enhance the release of insulin by β cells when glucose levels go up. GLP-1 signals α cells to suppress glucagon release.

In many diabetic patients, the normal response to glucose and production of insulin is disrupted. Insulin-resistant diabetics typically have high levels of both glucose and insulin. α cells lose glucose sensitivity, releasing too much glucagon when glucose is normal or high. As the disease progresses, the β cells become exhausted from overproduction of insulin and eventually die. It is estimated that by the time diabetes is diagnosed, 50% of the β cells have already died. The individual becomes dependent on outside insulin to regulate blood sugar. The physiological toll of poorly managed blood sugar is drastic over time; individuals can experience retinal damage, circulatory problems, nerve damage leading to amputations; and kidney disease.

Genes Load the Gun. Lifestyle Pulls the Trigger

As global obesity rates rise, the number of people developing Type II diabetes is skyrocketing. The World Health Organization estimates that 180 million people worldwide have diabetes, and that the number will double by 2030. The American Diabetes Association asserts that approximately 7% of the U.S. population has diabetes. While diabetes usually strikes adults over 40, the number of children developing Type II diabetes seems to be rising rapidly as well. However, opportunity emerges from crisis, and diabetes research programs both in academic institutions and drug companies are flourishing.

Type II diabetes runs in families; it has a genetic component. As only 15%–20% of the people who become obese become diabetic, the implication is that a genetic predisposition is triggered by obesity and inactivity, which are lifestyle choices. (Another explanation is defective β cells.) "Most people with type II diabetes will need pharmacological agents," said Dr. Christopher Saudek, professor of endocrinology and metabolism at Johns Hopkins Medical School. "In the early stages of type II diabetes, you may be able to control the diabetes with diet and activity.… Most people won't be able to go a lifetime taking just one kind of pill, because the ability of the pancreas to make insulin is progressively deteriorating in Type II diabetes."

Existing Treatments Leave Room for Improvement

The tried and true drugs targeting diabetes all have drawbacks. For example, sulfonylureas and the newer glitinides induce the pancreas to secrete insulin but can lead to hypoglycemia and weight gain. α-Glucosidase inhibitors prevent absorption of carbohydrates, but cause unpleasant gastrointestinal symptoms. Thiazolidinediones (TZDs) increase peripheral sensitivity to insulin but are unsuitable for cardiac patients and can cause fluid retention and weight gain.

While these drugs ameliorate symptoms, they do not arrest progression of the disease and they also stop working after a certain point. "The ideal dream drug would both reverse the disease and prevent its progression," said Dr. Joel Habener, chief of the Laboratory of Molecular Endocrinology at Massachusetts General Hospital, "by stimulating the β cells and at the same time increase their lifespan."

Discovery of Incretin Mimetics

A major breakthrough in diabetes research occurred in the 1970s with the discovery by Habener of the GLP-1 system that regulates release of insulin, which occured in the course of researching how the pancreas worked through the examination of marble-sized pancreases of angler fish. Dr. Jens Holst, of the department of medical physiology at the University

of Copenhagen, working with Prof. Dr. Michael Nauck of Ruhr-University in Germany, showed how GLP-1 functioned in humans.

GLP-1 is a hormone derived from the proglucagon gene and is secreted from the intestine after meals. It stimulates β cell insulin secretion in response to glucose, but it doesn't increase insulin blood levels at low glucose concentrations. GLP-1 also functions as an appetite suppressant, causing patients to lose weight. Unfortunately, GLP-1 was unsuitable as a drug due to its fleeting half-life; it is rapidly degraded by the enzyme dipeptidyl peptidase-IV.

Habener's research opened the door to what became incretin mimetics (and to later research on developing DPP-4 inhibitors that stimulate internal incretin hormones), a new class of glucoregulatory hormones that may not be the "dream" drugs but which are incrementally closer. Later research developed classes of DPP-IV enzyme inhibitors to prolong the action of endogenous incretin hormones.

Drooling over Gila Monsters

In the 1980s, John Eng, a researcher at the Bronx Veterans Administration Medical Center, was studying peptides produced in the saliva of the gila monster (Heloderma suspectum), a lizard that eats only three or four times a year. He realized that a peptide isolated from the lizard saliva, exendin-4, was similar to human GLP-1 but was longer lived and lowered blood glucose in a mouse model. As the story goes, scientists at San Diego-based Amylin (http://www.amylin.com) licensed it from Eng and developed Exenatide, a long-lasting, 39 amino acid synthetic analog of GLP-1. Now marketed with Eli Lilly and Company as Byetta, this GLP-1 agonist stimulates the pancreas to produce insulin in response to rising blood sugar levels and inhibits the liver from breaking down glycogen to release glucose after meals. Byetta was approved by the FDA in 2005 for patients who fail treatments with oral drugs, and Lilly plans to launch it in Europe in 2007. It has similar efficacy to bedtime insulin (without the weight gain), but it is more expensive.

Another welcome effect of Byetta is weight loss, according to Dr. Michael Hanley, vice president of discovery research at Amylin. However, Byetta must be injected twice daily and its side effects include nausea and mild hypoglycemia. Amylin and Alkermes (http://www.alkermes.com) are codeveloping Exenatide LAR, a therapeutic peptide encapsulated in microspheres for weekly injection. According to Hanley, Byetta shows promising results in restoring β cell mass and function in laboratory animals, but this effect has not so far been tested in humans. "This is a pretty generally agreed robust result obtained by multiple labs, particularly in laboratory animals, and anecdotally I've heard evidence that also in large animals—that in various types of induction of damage… Byetta can restore β cell mass as needed," said Hanley.

SIMLYN, Amylin's other lead compound, approved by the FDA in 2002, is a synthetic amylin analog (pramlintide). Amylin, a hormone ordinarily cosecreted with insulin by the β cells, lowers blood sugar, suppresses glucagon secretion, and slows gastric emptying after meals, causing weight loss. Pramlintide is linked to insulin-induced hypoglycemia when used in conjunction with insulin, as absorption of carbohydrates is slowed, so the insulin dosage must be calibrated.

Along with diabetes drugs, Amylin is developing a portfolio of antiobesity therapeutics. Positioned as an alternative to bariatric surgery, the platform features compounds based on Exenatide and SYMLIN used in conjunction with the fat-derived hormone leptin. While reducing body weight by around 5% is a welcome side effect of Byetta, any ensuing antiobesity formulation would have to sustain a more substantial weight loss without serious side effects.

Amylin was founded in 1987. The company now counts 1600 employees including its sales force and is publicly traded. Most of Amylin's current financial support comes from a collaboration agreement with Lilly to develop and market Byetta. Amylin reported total revenue of $510.9 million for 2006, including net product sales of $474 million. However, like many biotechs, it still operates at a loss ($218.9 million in 2006).

DPP-IV Inhibitors Come to Market

DPP-IV inhibitors, a new class of oral antidiabetic medicines working by incretin enhancement, are starting to be approved by the FDA. Dozens of companies are now engaged in their development. DDP-IV inhibitors block the enzyme dipeptidyl peptidase-IV that breaks down GLP-1 and GIP, effectively increasing the circulating levels of the incretin hormones and stimulating the pancreas to produce insulin. The hope is that DPP-IV inhibitors will produce fewer side effects than existing medications. Merck's Januvia (sitagliptin, a piperazine derivative) is a synthetic small molecule in a once-a-day tablet that was approved by the FDA in October 2006 for solo use or in combination therapy.

Merck's competitor Novartis just hit a pothole on the road to approval as the FDA demanded new data on its investigational drug Galvus (vildagliptin, a cyanopyrrolidine derivative) after monkeys developed skin lesions during testing, delaying approval for at least a year. The FDA wants additional tests in patients with impaired kidneys who would be slower to process the drug from their system. Galvus is currently being evaluated by European regulators.

Other entrants to the DPP-IV sweepstakes include saxagliptin (1-*cis*-4,5-methanoprolinenitrile) that is now in late-stage clinical trials conducted jointly by Bristol Myers Squibb and AstraZeneca. This lead has also caused skin lesions in monkeys at high doses. Takeda's SYR-322 (a pyrimidine derivative) is in Phase III trials, and Novo Nordisk's Liraglutide, based on Habener's work, is in stage III trials.

There are glimmers that these drugs can reverse β cell destruction, but just glimmers. There is still no cure for Type II diabetes. Lifestyle changes remain the best strategy to stave off its onset for those with susceptibility. Although they still need to be field tested in general use, these new classes of drugs are promising—and any potential weight loss derivatives could be an utter bonanza.

Wendy Wolfson (wendywolfson@nasw.org) is a California-based science and technology writer.

