STORY OF DISCOVERY

Studies of Underlying Biology of Insulin Secretion Pave the Way to New Treatment for Neonatal Diabetes

In the 1950s, little did scientists know that new drugs being used to treat type 2 diabetes in adults would be used half a century later to treat a rare form of diabetes in babies.

The drugs are called "sulfonylureas." The initial obser vation about these drugs came in the early 1940s, when French scientists used them to treat typhoid patients. After treatment, the patients had symptoms of dangerously low blood sugar levels (hypoglycemia). Tests of the same drugs in dogs showed that they stimulate insulin secretion, leading to hypoglycemia. Insulin is a hormone released by the beta cells of the pancreas in response to elevated blood sugar levels. Its release then promotes the uptake of sugar by cells in the body. These novel findings paved the way to clinical trials to test this class of drugs in people with the form of diabetes now known as type 2. People with type 2 diabetes produce insufficient amounts of insulin to compensate for diminished responsiveness of cells to the hormone. In the mid-1950s, sulfonyl-ureas were found to be effective for treating human type 2 diabetes. Sulfonylureas were the first diabetes pills used as an alternative to insulin injections for people with type 2 diabetes.

This result was great news, but it remained unknown exactly *how* sulfonylureas stimulated insulin secretion. Teasing out this mystery has been the subject of research for several decades. A clue came in 1985, when NIDDK-supported scientists demonstrated that sulfonylureas inhibit a potassium ion channel. This type of channel allows movement of potassium ions between the inside and outside of the beta cell, a common method the cell uses to control its processes. Although this observation shed some light on how the drugs may work, it also led to several new questions: what protein (or proteins) comprised the potassium ion channel? Were sulfonylureas binding directly to the channel or were they binding to an intermediate protein to stimulate insulin release?

A breakthrough came in 1995, when NIDDK-supported scientists cloned a gene encoding the sulfonylurea receptor, or SUR. This protein was the target to which the drugs were binding in beta cells. Interestingly, mutations in the gene encoding SUR were found to be linked to a rare genetic disease, called persistent hyperinsulinemic hypoglycemia of infancy (PHHI). People with this disease have high levels of insulin and correspondingly low blood sugar levels. These findings suggested that SUR was a critical component of cellular pathways regulating insulin secretion. Was SUR the potassium ion channel that was inhibited by sulfonylureas? Research showed that SUR alone could not function as an ion channel. However, a few months later, the same group of NIDDK-supported scientists identified SUR's partner—a protein called Kir6.2. The combination of SUR and Kir6.2 worked together as a potassium ion channel. This research demonstrated that the previously unidentified potassium ion channel was composed of SUR and Kir6.2; sulfonylureas bound directly to the SUR subunit of the channel to inhibit it.

These pioneering NIDDK-supported discoveries contributed to a model of the regulation of insulin secretion by sugar. The SUR/Kir6.2 ion channel regulates the balance of potassium and calcium ions inside and outside the beta cell, which in turn helps to regulate insulin secretion. In healthy people, when blood sugar levels are low, the channel is "open" and insulin is not secreted. When blood sugar levels are high (e.g., after a meal), sugar metabolism in the beta cell closes the ion channel, and insulin is secreted. Sulfonylureas cause the same biological effect as high

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sugar levels—they close the channel and stimulate insulin release from the beta cell. Mutations causing PHHI also result in a similar biological effect—they prevent the channel from opening and promote insulin release.

Building on this research foundation, researchers in Europe hypothesized that SUR/Kir6.2 may be involved in monogenic diabetes. These forms of diabetes result from mutations in a single gene; in contrast, type 1 and type 2 diabetes involve variations in multiple genes. The two main forms of monogenic diabetes are neonatal diabetes mellitus and maturity-onset diabetes of the young (MODY). Neonatal diabetes is a rare condition, usually occurring within the first 6 months of life, and may either be permanent, or transient—with the possibility of relapse later in life. While a number of genes had been found that each could cause MODY—the monogenic form of diabetes that is usually diagnosed later in childhood or young adults—the genetic cause of permanent neonatal diabetes was unknown.

In 2004, the European researchers examined the gene encoding Kir6.2 in patients with permanent neonatal diabetes. Several people with the disease had mutations in this gene. Upon examination of the underlying biology of the mutant channels, researchers found that the mutations caused the channels to be "open" all the time, even in the presence of high levels of sugar. Thus, these mutations appeared to prevent insulin release. These findings helped to explain why children with these mutations produce insufficient amounts of insulin and require insulin administration. They also suggested that, if there were another way to close down the channels—such as through treatment with sulfonylureas—perhaps insulin secretion could be restored.

These observations laid the foundation for a recent clinical trial by the same group of scientists to test the effect of switching neonatal diabetes patients from insulin to oral sulfonylurea treatment. People in the trial had mutations in their gene encoding Kir6.2. Strikingly, 90 percent of patients successfully discontinued insulin after receiving the oral drugs. Average blood sugar control improved in all patients who switched treatment strategies. These results are extremely exciting because oral therapy is a much less burdensome treatment strategy than insulin administration, which requires daily injections or use of a pump. It is of particular benefit for babies and young children to be able to take oral medication for their neonatal diabetes, rather than experience an arduous regimen of daily insulin administration.

NIDDK-supported scientists have also recently shown that some people with permanent and transient neonatal diabetes have mutations in their gene encoding SUR. People with these mutations who were switched from insulin to sulfonylurea therapy appeared to respond favorably. Together, these studies demonstrate that mutations in the gene encoding Kir6.2 are the most common cause of permanent neonatal diabetes; mutations in the gene encoding SUR account for fewer cases of permanent and some cases of transient neonatal diabetes.

How do people with PHHI and neonatal diabetes have mutations in the same ion channel, but PHHI patients have too much insulin and patients with neonatal diabetes have insufficient amounts? It turns out that mutations causing PHHI have the opposite effect on the function of the ion channel than mutations causing neonatal diabetes. The mutations causing PHHI prevent the channel from opening, which causes beta cells to secrete insulin continually. The mutations causing neonatal diabetes cause the channels to always remain open, which prevents insulin release. Thus, even though the same ion channel is involved in both diseases, the effects of the different mutations lead to completely opposite biological responses.

These studies identify a novel mechanism for the development of a significant fraction of permanent and transient neonatal diabetes mellitus and identify

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a less burdensome treatment strategy for some patients. They also pave the way for genetic testing to inform personalized treatments for people with the disease. Importantly, this research elegantly demonstrates how long-term studies of underlying biological mechanisms directly led to an improved treatment option for patients. Incremental studies of how sulfonylureas worked in the beta cell culminated with the NIDDK-supported discovery of the SUR/Kir6.2 potassium ion channel. This discovery not only informed key genetic studies, but also provided a much greater understanding of the basic biology of insulin secretion. Recently, using a whole genome association study, NIH-supported investigators have confirmed that the gene for Kir6.2 can contribute to type 2 diabetes. These studies now serve as the foundation for additional research on the role of this ion channel in diabetes, with the potential to improve and personalize therapies by targeting specific treatments to patients with specific genetic changes underlying their diabetes.

Genetic testing could be helpful in selecting the most appropriate treatment for people with monogenic diabetes. If you think that you or a family member has a monogenic form of diabetes, you should seek help from a healthcare provider. For more information on monogenic forms of diabetes, please see an NIDDK fact sheet available at: *http://diabetes.niddk.nih.gov/dm/pubs/mody/mody.pdf*