The Molecular Elements of Diabetes

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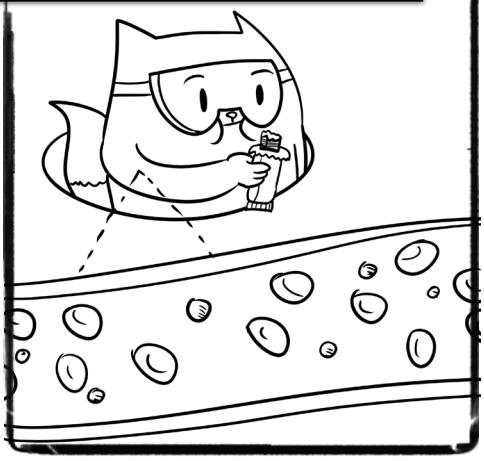
Your body uses chemical messengers, called hormones, to maintain healthy levels of sugar in your blood.



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Insulin stimulates the cells in your body to take up glucose, so that it can be used as fuel. Glucagon does the opposite: it helps the body move glucose out of cells, raising the level of sugar in the blood.

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But how does your body control insulin and glucagon to maintain healthy levels of sugar?

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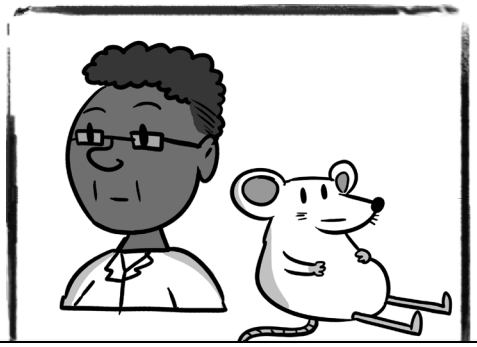

Using experiments in rodents and humans, the three scientists characterized two new gut hormones, called glucagon-like peptides (GLPs): GLP-1 and GLP-2.

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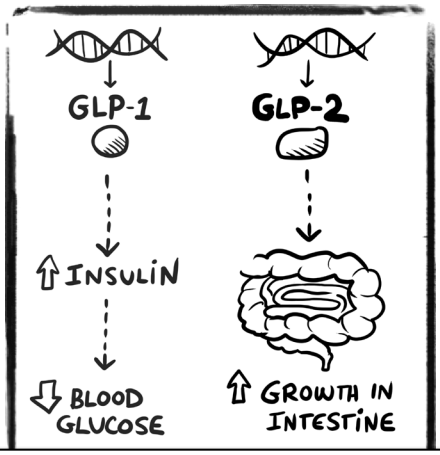

They found that GLP-1 stimulates the release of insulin, helping normalize high levels of glucose, while GLP-2 acts as a gut growth factor and stimulates growth in the intestine

This led to major advances in the treatment of Type 2 diabetes, obesity and intestinal disorders. In recognition of their work, Drucker, Habener and Holst were awarded a Canada Gairdner International Award in 2021.

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Art by Armin Mortazavi and text by Farah Qaiser. October 2021

The Molecular Elements of Diabetes

The characterization of glucagon-like peptides, has lead to major advances in the treatment of Type 2 diabetes, obesity and intestinal disorders.

Written by Farah Qaiser
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Every time you have a snack, your body's digestive system leaps into action.

Digestion begins in your mouth, where your teeth, and the enzymes present in your saliva, break food down into smaller pieces. Next, food enters the esophagus, and is pushed towards your stomach, small intestine, and large intestine to undergo additional digestion. For example, your stomach's enzymes and acidic environment will digest proteins, while the large intestine will reabsorb water and process any waste. Various organs, including your liver, pancreas and gallbladder, will help with food digestion by releasing different enzymes and secretions, such as bile (a digestive juice which breaks down fats).

This is simply a snapshot of the complex process of digestion! Your body coordinates all of the different players involved using chemical messengers, called **hormones**. Hormones travel to different parts of the body through the bloodstream, and tell cells what to do. They control many of the body's important processes, including growth, metabolism and development.

The human body makes around 50 different hormones, including **insulin** and **glucagon**. Both insulin and glucagon are produced by cells in the pancreas, and are critical for digestion. Insulin stimulates the cells in your body to take up **glucose** (a type of sugar) from the bloodstream, so that it can be used as fuel. This results in a lower amount of glucose in your blood. Glucagon does the opposite: it helps the body move glucose out of cells, raising the level of sugar in the bloodstream.

Maintaining optimal levels of insulin and glucagon is critical for your health. For example, **diabetes** is the disease which occurs if your body can't make enough insulin (**Type I Diabetes**) or isn't able to use insulin well (**Type II Diabetes**). Without enough insulin, there will be too much sugar in

your blood. This can cause damage to nerves, organs and blood vessels, leading to complications, such as kidney and eye disease.

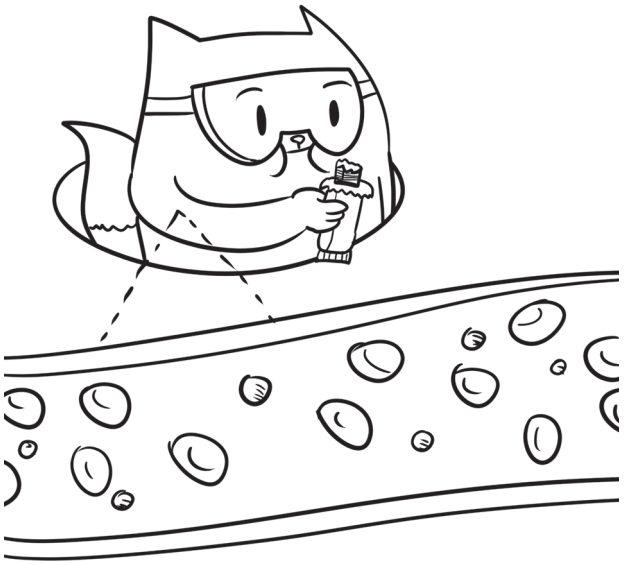
But how does your body control insulin and glucagon to maintain healthy levels of sugar?

This is the question that Drs Daniel Drucker, Joel Habener and Jens Holst have been investigating for over 30 years.

Exploring mysteries in the gut

In the 1970s, Holst was a surgical resident in Denmark. He curiously observed that after meals, many of his intestinal surgery patients were experiencing spikes in insulin, resulting in a drop in blood sugar. This was a clue: perhaps there was another molecule involved in regulating the levels of blood sugar, in addition to glucagon and insulin.

"That was interesting to me," says Holst. "It seemed to involve the gut."



At the same time, researchers in Habener's laboratory used pancreatic cells from anglerfish to show that glucagon – the hormone which helps the body move glucose out of cells – is produced from a larger precursor hormone, called **proglucagon**. Habener's laboratory found that proglucagon contained the sequences to produce glucagon, as well as two previously unknown hormones related to glucagon, called **glucagon-like peptides** (GLPs): **GLP-1** and **GLP-2**. In essence, proglucagon is broken down to three separate hormones: glucagon, GLP-1 and GLP-2.

But what did these mystery glucagon-like molecules do?

In the summer of 1984, Drucker joined as a research fellow in Habener's laboratory in Boston, Massachusetts. Drucker had completed medical school and hoped to pursue research related to the thyroid gland, but was instead assigned to work on the proglucagon gene, where he investigated how proglucagon was processed, and how GLP-1 acted on insulin-producing cells.

"I was pretty unhappy and feeling sorry for myself – that my dream of thyroid research had been sort of stopped in its tracks, but we know how this story ends. It was serendipitously an amazing stroke of luck for me," says Drucker, recalling the early days of his research.

A snapshot of GLP-1's many functions

Through different experiments in rats, pigs and human cells, Holst, Drucker and Habener showed that when food is ingested, GLP-1 is released into the bloodstream, stimulating the release of insulin, and suppressing glucagon. Additional studies showed that GLP-1 injections could help normalize high levels of glucose in patients with Type II diabetes, offering enormous potential for therapeutics.

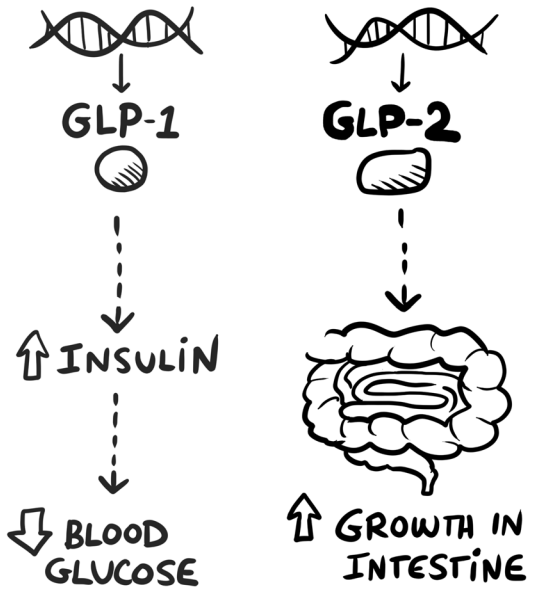
But despite this exciting breakthrough, there was an issue: it only took 1.5 to 2 minutes for GLP-1 levels to be halved in patients with diabetes. This meant that GLP-1 injections were disappointingly ineffective, due to the human body's fast metabolism. Why was GLP-1 being digested so quickly?

Using experiments in pigs, Holst and Dr. Carolyn Deacon found that GLP-1 was broken down by the enzyme dipeptidyl-peptidase-4 (**DPP-4**), and that blocking (**inhibiting**) DPP-4 could completely protect GLP-1. As a result, researchers have developed clinically useful oral DPP-4 inhibitors,

offering new treatments for diabetes. The first DPP4 inhibitor (sitagliptin) was approved to treat Type II diabetes in 2006.

"The amazing thing about these pills is that they basically had no side effects. They didn't even cause low blood sugar. You didn't need to prick your finger to check your blood sugar. That was a huge advance for people," says Drucker.

By better understanding GLP-1, Habener, Drucker and Holst's research also spurred the development of GLP-1 receptor **agonists**, basically molecules which could mimic the action of GLP-1, without having to worry about DPP-4 breaking it down quickly. In 2005, the first GLP-1 receptor agonist, to be used twice daily, was approved for diabetes treatment, and helped prevent the level of blood sugar from rising too high. Today, there are GLP-1 receptor agonists that only need to be used once a week.



Unravelling GLP2's role in digestion

But what about GLP-2 – what does this gut hormone do?

This was what Drucker continued to investigate when he returned to Toronto in 1987. Using experiments in rodents, members of Drucker's laboratory found that GLP-2 acts as a gut growth factor, stimulating intestinal growth and enhancing intestinal function.

These GLP-2 findings in animals were extended to humans with short bowel syndrome, a disorder where fluids are poorly absorbed in the small intestine (usually due to surgical removal of parts of the intestine). In the early 2000s, Holst, Jeppesen and a group of researchers found that when humans with short bowel syndrome received GLP-2 injections twice a day, the patients experienced increased nutrient absorption and weight gain over 35 days.

This critical breakthrough led to the launch of another drug development program, where clinical studies tested the effectiveness of *teduglutide*, a GLP-2 **analogue** (that is, a molecule with a similar structure as GLP-2), as a therapeutic. In 2012, teduglutide was approved for clinical use in the treatment of short bowel syndrome.

Understanding GLPs have led to many medical breakthroughs

This is simply a snapshot: Drucker, Habener and Holst's characterization of GLPs have led to many major advances in the treatment of Type 2 diabetes, obesity and intestinal disorders. In recognition of their work, Drucker, Habener and Holst were awarded a Canada Gairdner International Award in 2021 – the same year which also happens to mark the 100th anniversary of the discovery of insulin. So, what are Drucker, Habener and Holst doing today?

"Actually, I'm still working on exactly the same thing I was working on 30 years ago, because it's been a really cool story and I'm trying to figure out how it works and how to make it better," says Drucker.

He points out that to "make a drug, you don't really have to know how it works. You have to know if it works, and you have to know that it's safe. We know the GLP-1 works really well, and [that] GLP-2 works really well [too]. We know their safety profile thankfully, it looks all good, but the real detail scientifically of how all of these actions

happen, is largely still a mystery."

Similarly, Holst continues to research gut hormones today, especially their role in obesity and intestinal disorders. He has a simple message for budding young scientists.

"Have open eyes, and be curious," says Holst. "Once you get somewhere, find something, stay on it, and continue to work hard. It will pay off."