Acceptance speech

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I want to express my deepest gratitude for the selection of glucagon-like peptide-1 as the subject for this year's Frontiers of Knowledge Award in Biology and Biomedicine. When we first pulled out this peptide from intestinal extracts and demonstrated its effect on insulin secretion, there was no way that we could predict the impact that this molecule has had on human health. We started by asking a simple question: I came from surgery and some patients developed hypoglycemia. This only occurred after meal intake, and we thought that it might be due to an insulin-stimulating hormone from the gut, a so-called incretin. But these hormones were hypothetical at the time. I found some gut cells that were producing a substance resembling glucagon. Glucagon is a hormone from the pancreas known to stimulate insulin secretion. Together with others, I managed to find out what it was: a peptide called glicentin, which has glucagon in the middle. We could also find the peptide in the pancreas, and we therefore proposed that it was the precursor of glucagon: proglucagon. Unfortunately, it did not stimulate insulin secretion. However, it seemed that glicentin might only represent a small part of the full proglucagon molecule, so the hunt for the full structure continued, and in 1983 the molecular biologist Graeme Bell managed to clone the nucleotide sequences encoding proglucagon from hamster pancreases. His results confirmed that glicentin made up half of the precursor, but also showed that it contained two additional glucagon-like stretches. This was exactly the information we needed. We had the potential hamster peptides synthesized and raised antibodies against them, enabling us to create radioimmunoassays for GLP-1 and GLP-2. We were able to show that, in the pancreas, proglucagon was not cleaved to produce the individual peptides, whereas in the gut they were formed separately and were actually secreted in response to glucose. Unfortunately, Bell's GLPs didn't do anything to insulin secretion from our favorite tool: an isolated, living pancreas from pigs. We therefore decided to search for the actual glucagon-like peptides in gut extracts using our radioimmunoassays. By biochemical isolation and purification, we could soon pull out the real GLP-1 from the extracts and determine its structure. It differed from the predicted structure and turned out to be a powerful stimulator of insulin secretion from our pancreases.

So, here was a new insulin-stimulating hormone from the gut. Was it also the peptide we were looking for? Several years later we were able to prove, using

an antagonist of the GLP-1 receptor, that GLP-1 was indeed responsible for the hypoglycemia of our patients. But what else could the peptide do? We could show that it also inhibited the secretion of glucagon from the pancreas, and this was interesting because people with diabetes have too much glucagon. Because it was a gut hormone, we also looked at its effects on gastric acid and pancreatic secretion as well as gastric emptying – it inhibited all of these and we could show that the actions involved the brain! And eventually we could also show that GLP-1 inhibited appetite and food intake in people. All of this would be of interest for people with type 2 diabetes, and in 1993 we could show, together with Michael Nauck from Göttingen, that blood glucose was completely normalized in patients with severe type 2 diabetes during a 4-hour intravenous infusion of GLP-1, and in 2002 we could show that a 6-week-long subcutaneous infusion of GLP-1 to people with long-standing type diabetes had tremendous effects on blood glucose, insulin secretion and even body weight.

But we could also show that the new peptide almost evaporated from the circulation after injection. Indeed, its half-life was only about 2 min. You cannot treat patients with a peptide like that. But we also found out why it disappeared so quickly: it was broken down by an enzyme called DPP4, and we could also demonstrate that breakdown could be prevented with inhibitors of the enzyme, and this would result in increased insulin secretion. Our discovery resulted in the development of the very successful DPP-4 inhibitors, like sitagliptin (Januvia), used all over the globe for diabetes therapy since 2006. But with the effect of the GLP-1 peptide in people with diabetes we eventually managed to attract the attention of NovoNordisk. They decided to go for it and developed a long-acting GLP-1 analog similar to their long-acting insulins. It was called liraglutide or Victoza and had a half-life of 12 hours. It was soon established as a superior antidiabetic agent. A second generation, weekly version, Semaglutide, was even more efficacious and caused weight losses of up to 18% in high doses. Sensationally, it also prevented complications and increased survival. Effective treatments for obesity and diabetes had finally been established.