Peptides come to the rescue of pancreatic β cells

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Insulin and glucagon are well-known peptide hormones that keep glucose levels within a healthy range in the body. But they are only part of a complex network that controls concentrations of this ubiquitous sugar in blood and tissues. Other molecules regulate glucose by controlling insulin secretion from the pancreas or protecting pancreatic β cells against stresses that lead to cellular dysfunction or cell death (1).

One of these protective regulators is glucagon-like peptide 1 (GLP-1), a 30-amino-acid-long peptide produced in specialized epithelial cells of the intestine, called L cells, and also in the brain and other organs and tissues (2).

GLP-1 belongs to a group of peptides that mediate the “incretin effect,” an endocrine response to glucose arising from food digestion in the intestines (2, 3). This response helps regulate food intake and the fate of dietary glucose. Specifically, GLP-1 is released from the intestinal cells when food is ingested and then binds to and activates the GLP-1 receptor (GLP-1R), a G protein–coupled receptor on many cell types, including β cells in which GLP-1R signaling stimulates insulin synthesis and secretion (3). Notably, the incretin effect stimulates insulin secretion from pancreatic β cells more strongly than exposure to glucose alone.

An article published in the Journal of Biological Chemistry (4), recognized as a Classic here, added to our understanding of the incretin effect by showing that GLP-1R signaling protects β cells from cell death (Fig. 1). This finding was significant for preventing or managing type 2 diabetes, in which β-cell apoptosis occurs (5) and may contribute to insufficient pancreatic insulin production (6).

Yazhou Li and Daniel Drucker at Toronto General Hospital in Ontario, Canada, along with colleagues exposed WT and GLP-1R–knockout mice to the compound streptozotocin, which induces β-cell death, in the presence and absence of the specific GLP-1R agonist exendin-4. The authors then assessed the effect of the GLP-1R stimulation on glucose tolerance, blood and pancreatic insulin levels, and pancreatic cell viability and proliferation.

To find out what spurred this seminal paper and to learn more about its findings, JBC reached out to Drucker, now at the Lunenfeld Tanenbaum Research Institute, Mt. Sinai Hospital, in Toronto.

What prompted your investigation? In particular, what was unknown about GLP-1 and GLP-1R and their effects on β-cell viability, and what motivated you to study these questions?

GLP-1 had previously been shown to expand β-cell mass by stimulating β-cell proliferation. We wondered whether GLP-1 might also contribute to the control of β-cell mass by reducing cell death. We were also aware that cell-survival pathways were activated by cAMP, an important downstream messenger that is increased by GLP-1R activation.

What were your main findings?

We made several interesting discoveries. First, pharmacological activation of the GLP-1R with exendin-4 reduced β-cell death we had produced by experimental pancreatic injury with streptozotocin in mice. We noted that this reduction in β-cell apoptosis is associated with preservation of β-cell function and glucose homeostasis in the mice.

Second, we found that basal GLP-1R signaling is physiologically essential for β-cell survival, as the GLP-1R–knockout mice exhibited enhanced β-cell injury when challenged with streptozotocin.

Third, we saw that GLP-1’s anti-apoptotic activities are direct, and we, that is, our collaborator Philippe Halban, could also demonstrate them ex vivo in purified rat β cells exposed to cytotoxic cytokines, a model of tissue inflammation. We also discovered that GLP-1’s anti-apoptotic properties are not unique to β cells and can be conferred to heterologous cells transfected with the gene encoding GLP-1R.

Why did you use exendin-4, rather than GLP-1, to stimulate GLP-1R?

We used exendin-4 because it is a highly stable, degradation-resistant GLP-1R agonist that is more biologically potent in animals and humans than is GLP-1. It was also the lead GLP-1R agonist in clinical trials and became the first GLP-1 drug approved for the management of diabetes.

Does repeated exendin-4 stimulation down-regulate the receptor, as is sometimes the case with repeated receptor stimulation?

In most tissues, there is little evidence that continuous GLP-1R activation by agonists down-regulates this receptor. This fortuitous finding enables the development of long-acting GLP-1R agonists for managing diabetes and obesity.

As your JBC paper has shown, the GLP-1R stimulation prevents β-cell apoptosis and increases pancreatic islet mass. Could this increase heighten the risk for uncontrolled cell growth or cancer?

This has always been a theoretical concern, but there’s no evidence that would support it. The first GLP-1R agonist (exenatide, the common drug name for exendin-4, used in diabetes management) was approved for clinical use as an anti-diabetic medication in April, 2005. After 14 years of clinical use, with multiple drugs and millions of patients taking the medication, we have not seen an increase in cancer rates due to exenatide or GLP-1R agonist use.
Is GLP-1 the major incretin hormone or does it have some overlapping functions with other incretins, and do other incretin hormones also promote β-cell mass?

Both GLP-1 and another peptide, gastric inhibitory polypeptide (GIP), are important naturally occurring incretin hormones. GIP is likely the more important incretin under physiological conditions. And, yes, most peptide ligands that, like GLP-1, increase cAMP levels in β cells—such as pituitary adenylate cyclase–activating polypeptide (PACAP), GIP, and fatty acids—also reduce β-cell apoptosis.

Were your findings expected, and how has your own work and the field progressed since your paper’s publication?

Before our study, I do not think anyone had clearly addressed the question of whether GLP-1R signaling can inhibit β-cell death. Since our JBC publication, GLP-1R signaling has been shown to reduce cell death in many cell types, from β cells to neurons, to endothelial cells and cardiomyocytes.

As for progress in the field, research into both the basic science and clinical relevance of GLP-1 has expanded tremendously since 2003. GLP-1R agonists are approved for treating patients with diabetes or obesity and are under investigation for managing nonalcoholic steatohepatitis (NASH) and neurological disorders. We continue to explore the mechanisms underlying GLP-1 action in numerous cells and tissues. In 2002, only 196 published studies of GLP-1 were listed in PubMed. In 2018 alone, there were 1461, and the field continues to grow.

What was the impact of your paper on the field of diabetes and clinical research in general?

This is a little difficult to appreciate. The paper has been widely cited [author’s note: at this writing, it has been cited 712 times in Google Scholar], and it was one of the first studies to highlight a cytoprotective role and not just an insulin-secretory role for GLP-1.

It’s also noteworthy that GLP-1 has recently shown some promise in clinical trials investigating its therapeutic role in human neurodegenerative disorders such as Parkinson’s disease, and it continues to be explored for therapeutic intervention in Alzheimer’s disease. So the concept that GLP-1 might generally protect vulnerable cells continues to have high clinical relevance.

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