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A century of glucagon

In 1923, Kimball and Murlin published work that identified a substance in pancreatic extracts that caused hyperglycaemia, which they named glucagon. A century later, we now know the importance of this hormone in human physiology and disease, and drugs targeting the glucagon receptor family have been developed to treat metabolic diseases.

Following the discovery of insulin by Banting and Best in 1921 (ref. 1), a need arose for low-cost methods to rapidly isolate safe preparations of insulin from the pancreas. Whilst studying different extraction protocols in 1922, Kimball and Murlin isolated a substance from pancreases that could induce hyperglycaemia in dogs and rabbits. They published their findings in 1923, dubbing the mysterious glucogenic factor 'glucagon'[2]. However, the cellular origin of glucagon remained elusive until 1948, when α-cells of the pancreatic islets of Langerhans were discovered to be the source[3].

We now know that glucagon is a 29-amino acid peptide hormone that stimulates glycogenolysis and gluconeogenesis, and thus acts in opposition to the glucose-lowering effects of insulin[4]. Over the years, efforts in glucagon research to measure its blood levels have been complicated by two important factors relating to its physiology. First, glucagon circulates in blood at low picomolar concentrations, making accurate detection difficult. Second, the precursor polypeptide, proglucagon, is cleaved into different peptide fragments depending on the cell of origin (α-cells or intestinal enteroendocrine cells), causing issues with cross-reactivity. Despite these difficulties, Unger and colleagues developed the first sensitive radioimmunoassay for glucagon in 1961 (ref. 5). Nowadays, a high-quality sandwich enzyme-linked immunoabsorbance assay is available[4].

After a century of research, glucagon is known to have a broad range of functions in physiology, including acting to reverse hypoglycaemia. In addition, glucagon has important roles in amino acid turnover and hepatic lipid oxidation in a feedback cycle known as the liver–α-cell axis[4]. The regulation of glucagon secretion is complex, with the most well-known stimulator of secretion being hypoglycaemia. In fact, glucose acts directly on α-cells to inhibit glucagon exocytosis. However, paracrine regulation from factors produced by other islet cells is also important. Furthermore, incretin hormones, amino acids and fatty acids can all modulate glucagon secretion. In pancreatic islets, α-cell–β-cell crosstalk is also being increasingly recognised as crucial for β-cell function[4].

Thus, the importance of glucagon in health is clear. But what about the role of glucagon in disease? In 1970, Unger and colleagues discovered that individuals with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) lack post-prandial suppression of glucagon secretion and have hyperglucagonaemia[6]. Gerich and colleagues then published a study in 1973 showing that some people with long-term T1DM did not secrete glucagon in response to severe insulin-induced hypoglycaemia, which suggested an intrinsic α-cell defect[7]. Nowadays, exogenous glucagon is used to treat severe hypoglycaemia in T1DM. Interestingly, not all individuals with T2DM have fasting hyperglucagonaemia, and some individuals with obesity and normal glucose tolerance have hyperglucagonaemia. This curious observation has led to a theory that hepatic steatosis could be a driver for the development of hyperglucagonaemia[4].

> "Kimball and Murlin isolated a substance from pancreases that could induce hyperglycaemia"

As glucagon drives glucose production, hyperglucagonaemia would seem to be a pathogenic state in metabolic diseases. However, the situation is not so clear cut, as exemplified by the failure of glucagon receptor (GCGR) antagonists as a therapy for diabetes mellitus. When tested in clinical trials in people with T1DM or T2DM, GCGR antagonists were effective in reducing hyperglycaemia; however, patients developed adverse effects, such as hepatic steatosis, increased blood pressure and elevations in blood levels of liver transaminases and/or cholesterol[4]. These effects meant that development of this drug class was halted. Importantly, co-agonist or tri-agonist drugs that include GCGR and incretin receptor agonist activity are now in development for T2DM and obesity, with some encouraging findings reported thus far[4,8].

To mark the centenary of the discovery of glucagon, we have published a Review by Hædersdal and colleagues[5]. We will also be publishing a special collection of articles on glucagon in the Summer. Many questions remain unanswered about the role of glucagon in metabolic diseases, and we hope that research in the coming years will find answers.

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References

1. Banting, F. G. et al. Pancreatic extracts in the treatment of diabetes mellitus: preliminary report. *Can. Med. Assoc. J.* **12**, 141–146 (1922).
2. Kimball, C. & Murlin, J. R. Aqueous extracts of pancreas III. Some precipitation reactions of insulin. *J. Biol. Chem.* **58**, 337–346 (1923).
3. Sutherland, E. W. & de Duve, C. Origin and distribution of the hyperglycemic-glycogenolytic factor of the pancreas. *J. Biol. Chem.* **175**, 663–674 (1948).
4. Hædersdal, S., Andersen, A., Knop, F. K. & Vilsbøll, T. Revisiting the role of glucagon in health, diabetes mellitus and other metabolic diseases. *Nat. Rev. Endocrinol.* https://doi.org/10.1038/s41574-023-00817-4 (2023).
5. Unger, R. H. et al. Glucagon antibodies and an immunoassay for glucagon. *J. Clin. Invest.* **40**, 1280–1289 (1961).
6. Muller, W. et al. Abnormal alpha-cell function in diabetes — response to carbohydrate and protein ingestion. *N. Engl. J. Med.* **283**, 109–115 (1970).
7. Gerich, J. E. et al. Lack of glucagon response to hypoglycemia in diabetes: evidence for an intrinsic pancreatic alpha cell defect. *Science* **182**, 171–173 (1973).
8. Urva, S. et al. LY3437943, a novel triple GIP, GLP-1, and glucagon receptor agonist in people with type 2 diabetes: a phase 1b, multicentre, double-blind, placebo-controlled, randomised, multiple-ascending dose trial. *Lancet* **400**, 1869–1881 (2022).