The pancreas

Garry D Tan

Abstract

Although only the same weight as an apple, the pancreas fulfils endocrine and exocrine functions, and coordinates metabolism throughout the body. For example, insulin, perhaps the best-known pancreatic hormone, not only influences glucose metabolism but also helps to regulate protein and fat metabolism (thus explaining why diabetes is more than just a disease of sugar). The secretion of pancreatic hormones is highly coordinated to exert a concerted effect on the metabolism of a range of organs, from adipose tissue to muscle. This article looks at the physiology of each of the hormones and enzymes released by the pancreas, the factors influencing their secretion, and how their secretion is coordinated.

Keywords Cholecystokinin; endocrinology; glucagon; homeostasis; insulin

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Learning objectives

After reading this article you should be able to describe:

- the main hormones and enzymes produced by the pancreas
- the function of the main pancreatic hormones and enzymes secreted
- how hormonal secretion is coordinated to regulate metabolism

The pancreas weighs 70—100 g, yet secretes 1000 g of pancreatic fluid daily. Most cells in the pancreas have an exocrine function, manufacturing digestive enzymes. A small proportion of pancreatic cells (about 1 million) are aggregated into small clusters (tens of cells to several thousand cells) and are scattered throughout the exocrine cells. These aggregations, the islets of Langerhans, contain at least four different cell types (Table 1) which are densely innervated with autonomic and peptidergic nerves. Despite accounting for only 2% of the mass of the pancreas, the islets receive 10% of the pancreatic blood flow.

Endocrine pancreas

Insulin and C-peptide

Insulin is a polypeptide consisting of two peptide chains, A and B, linked by two disulphide bridges (Figure 1). It is synthesized as preproinsulin, a precursor of insulin. Preproinsulin is cleaved in the endoplasmic reticulum to form proinsulin, which is itself cleaved in the Golgi apparatus to form insulin and C-peptide. These are stored in granules in the β-cell cytoplasm to await secretion.

Glucose is one of a number of stimuli that can cause β-cell degranulation and insulin release. In order for glucose to do this, it must first be metabolized; glucose enters the β-cell via the glucose transporter type 2 (GLUT-2), and it is phosphorylated by the enzyme glucokinase (this is the rate-limiting step of islet glucose use). Glucokinase serves as the 'glucose sensor' for the β-cell and normally triggers insulin secretion as the glucose exceeds about 5 mmol/litre. Mutations in the glucokinase gene lead to a specific type of diabetes: maturity onset diabetes of the young type 2 (MODY2). The β-cells in MODY2 secrete insulin normally, but only do so in response to abnormally high plasma glucose concentrations. So MODY2 is associated with a raised fasting blood glucose from birth, but minimal increases in postprandial glucoses (because insulin secretion is normal once the threshold for glucose secretion is exceeded). It is not associated with usual complications of diabetes and is stable throughout life, although patients may need treatment if they become pregnant.

The glucose-6-phosphate, produced by glucose phosphorylation, undergoes glycolysis to produce adenosine triphosphate (ATP). The ATP-sensitive K^+ channels in the β-cell membrane close, causing membrane depolarization. This causes a calcium influx into the cell as calcium channels open. This leads to granule exocytosis and insulin (and C-peptide) release. Insulin and C-peptide are released into the circulation in equimolar amounts. This is used to differentiate hypoglycaemia caused by insulinoma from that caused by factitious exogenous insulin administration (genetically engineered human insulin contains very little C-peptide). Insulin circulates as unbound monomers, in contrast to its state before release from the secretory granule, when it forms insulin hexamers around a core of two zinc molecules (pharmaceutical preparations of insulin are based on crystalline zinc insulin).

C-peptide has a plasma half-life of 30 minutes and is excreted unchanged by the kidneys. Its physiological action is unclear. In contrast, insulin has a half-life of 4 minutes and is degraded by the kidney and liver as well as by its target cells, where it is internalized with its receptor. Insulin receptors are found in varying concentrations on virtually all mammalian tissues (even largely insulin-unresponsive red blood cells possess about 70 receptors).

In response to a glucose load, insulin secretion is biphasic: there is a sharp peak in plasma insulin levels after 1 minute, as preformed insulin is released. After 5—10 minutes, there is a second, slower rise in plasma insulin levels, which continues for as long as the glucose stimulus continues. Other nutrients such as amino acids also act as insulin secretagogues. Concentrations of ketoacids found in the fasting state can also promote insulin secretion. Factors affecting insulin release are shown in Figure 2.

Interestingly, orally administered glucose induces a greater rise in plasma insulin concentrations than that induced by a similar amount of intravenous glucose. This increased responsiveness of insulin secretion is partly due to the production of incretin hormones such as glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP). These hormones are secreted from the gastrointestinal tract and enhance insulin secretion in response to a glucose load, through direct activation of G-protein-coupled receptors expressed on islet β-cells. This has led to

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Pancreatic islet cell secretion

Cell type	Proportion of islet cells	Peptides secreted	Anatomical distribution
α	25%	Glucagon (GLP-1, GLP-2)	Within islets throughout the pancreas with a preference for pancreatic tail and body
β	60—70%	Insulin, C-peptide (islet amyloid peptide)	Within islets throughout the pancreas
γ	5—15%	Somatostatin 12 and 14	Within islets throughout the pancreas
PP	2%	Pancreatic polypeptide (PP) (and small amounts of gastrin)	Within islets throughout the pancreas with a preference for posterior portion of the head. Also found in acini

GLP, glucagon-like peptide.

Table 1

interest in the use of GLP-1 analogues to treat type 2 diabetes. The first members of this class, exenatide and liraglutide, are given as subcutaneous injections; they induce significant weight loss as well as improving glycaemic control. They also lead to a delay in gastric emptying. Changes in these incretin hormones are being explored as possible explanations for the rapid changes in metabolism seen after gastric bypass surgery. Other drugs that increase GLP-1 concentrations have also recently been licensed; these are oral medications which inhibit dipeptidyl dipeptidase IV (DPP-IV), the enzyme that breaks down GLP-1. They are not associated with weight loss. Whether any of these drugs reduce complications of diabetes is yet to be seen.

After binding to its receptor at the cell surface, insulin causes rapid shifts in the fluxes in various metabolic pathways by the activation or deactivation of enzymes at critical steps. It also leads to alterations in gene expression (e.g. inducing glucokinase gene expression), thus reinforcing metabolic shifts.

Insulin promotes the storage of excess nutrients while inhibiting mobilization of endogenous substrates. It is required for the entry of glucose into most cells, particularly muscle (skeletal and cardiac) cells. The brain and red blood cells are exceptions in which glucose diffuses down a steep concentration gradient into these cells. Insulin also stimulates glycogen formation from glucose in muscle and liver while simultaneously inhibiting glycogen breakdown in the liver. This produces a reduction in the intracellular concentration of glucose in hepatocytes. Glucose diffuses into hepatocytes down this gradient through the GLUT-2 transporter. In contrast, insulin actively enhances glucose uptake into myocytes and adipocytes by inducing GLUT-4 expression (another specialized plasma membrane glucose protein transporter — the only one to be induced by insulin).

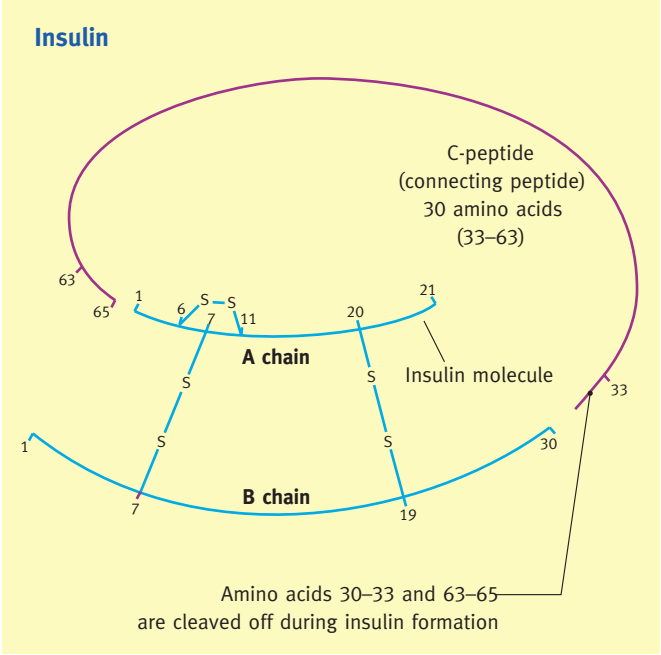

Figure 1

In adipose tissue, insulin inhibits mobilization of intracellular triglycerides by suppressing hormone-sensitive lipase activity. As non-esterified fatty acid (or free fatty acid) release from adipose tissue is suppressed, plasma non-esterified fatty acid concentrations decrease. The resulting fall in their delivery to the liver causes a decrease in their β-oxidation, and hence a decrease in the production of ketone bodies. Only tiny concentrations of insulin are required to suppress the production of non-esterified fatty acids from adipose tissue (much lower concentrations than those required to induce glucose uptake by skeletal muscle). Thus, there needs to be a total absence of insulin (as in untreated type 1 diabetes) for there to be unregulated release of non-esterified fatty acids from adipose tissue; this leads to ketone body production by the liver. If the plasma concentration of ketones overwhelms the body's acid—base buffering system, diabetic ketoacidosis — the hallmark of type 1 diabetes — results.

Other effects of insulin include an anabolic effect on protein metabolism and the promotion of potassium, phosphate and magnesium uptake into muscle cells. The renal tubular reabsorption of potassium, phosphate and sodium is increased. The insulins of different animals differ slightly in their amino acid sequence, but have identical biological actions.

Glucagon

Glucagon is a 29-amino-acid peptide produced from proglucagon in α-cells. Proglucagon is also synthesized in the gut, where it is processed differently to produce GLP-1. The factors affecting glucagon secretion are shown in Figure 2; the stimulating and suppressing factors interact. For example, the suppression of glucagon production by high glucose concentrations is potentiated in the presence of insulin. Despite this, plasma glucagon levels vary less than plasma insulin levels.