The pancreas

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Abstract

The pancreas plays a vital role in coordinating and regulating digestion and nutrient metabolism, and does so via endocrine and exocrine processes. Insulin and glucagon are produced within the endocrine pancreas to not only achieve glucose homeostasis, but regulate protein and fat metabolism. Enzymes and zymogens are secreted in alkaline pancreatic fluid to aid digestive function. This article looks at how the pancreas achieves such precise synthetic and secretory functions, and reviews the physiology of the secreted hormones and enzymes.

Keywords Cholecystokinin; endocrinology; glucagon; homeostasis; insulin

Royal College of Anaesthetists CPD Matrix: 1A01

Learning objectives

After reading this article you should be able to describe:

- the functional anatomy of the pancreas
- how the endocrine pancreas regulates metabolism and glucose homeostasis
- the role the exocrine pancreas plays in digestion

The pancreas is a complex organ comprised of both exocrine glands (secreting digestive enzymes into the intestinal lumen) and endocrine glands, called the islets of Langerhans, which secrete hormones directly into the blood stream. Although only 10 cm in length and weighing about 100 g, the pancreas is capable of secreting around 1500 ml of pancreatic fluid per day. It receives a rich blood supply from branches of the coeliac and superior mesenteric artery, and venous drainage is via the portal vein. In addition it is densely innervated by both sympathetic fibres (from the splanchnic nerves), parasympathetic fibres (via the vagus nerve), and peptidergic neurones (which stimulate peptide and amine release).

Endocrine pancreas

Functional anatomy

The normal human pancreas contains 1–2 million islets, each of which is an aggregate of tens to thousands of cells. The islets are ovoid in shape and are scattered throughout the pancreas, although are more numerous in the pancreatic tail. There are now known to be at least five major secretory cell types in each islet of Langerhans – α, β, δ, F and ε cells (Table 1).

Pancreatic α cells principally secrete glucagon, and comprise approximately 35% of islet cells. Pancreatic β cells are most numerous and make up around 55% of islet cells. They produce insulin and amylin (or islet amyloid polypeptide (IAPP)). Pancreatic δ cells secrete somatostatin and comprise less than 10% of islet cells. Pancreatic F cells, which secrete pancreatic polypeptide, account for less than 5%. Pancreatic ε cells produce ghrelin, and account for less than 1% of islet cells.

Despite comprising only 2% of the total mass of the pancreas, the islets receive around 10% of the pancreatic blood supply, allowing their secreted hormones ready access to the circulation. Blood from the islets drains into the hepatic portal vein.

Secretions of islet cell hormones are under tight regulatory control via both neurohumoral and paracrine communication. Islet cells receive both sympathetic and parasympathetic innervation, with tight homeostatic control over the smooth muscle cells of islet blood vessels, regulating local blood flow and therefore hormone release. Cholinergic stimulation augments insulin secretion, and adrenergic stimulation has either a stimulatory of inhibitory effect, depending on whether β-adrenergic or α-adrenergic stimulation dominates.

Paracrine, or cell-to-cell regulation, occurs due to the arrangement of both the cells within the islet, and the distribution of the islets alongside the exocrine acinus. The cells within a given islet can influence the secretion of other cells within that islet. Furthermore hormones secreted by the islets of Langerhans are directly transported in the blood to the acinar cells, allowing local regulatory control of both endocrine and exocrine synthesis and secretion.

Within each islet, cells are arranged with an abundance of β cells nearest to the centre of the islet, with α cells and δ cells more abundant at the periphery. This feature enables humoral communication to occur between cells, as blood enters at the centre of the islet and courses outwards towards the periphery, carrying secreted hormonal products with it. This allows the insulin secreted by β cells to exert influence over the secretions of the α cells.

Insulin

Insulin is responsible for maintaining serum glucose between 4 and 8 mmol/litre during periods of feeding and fasting. It regulates lipid and protein metabolism, yet also regulates amino acid and electrolyte transport, and growth. Its net effect is ultimately anabolic, by way of storage of carbohydrate, fat and protein.

Insulin is encoded by a single gene on the short arm of chromosome 11, and is synthesized and secreted in response to β cells being exposed to glucose. It is first synthesized as a *pre-prohormone* protein called preproinsulin in the rough endoplasmic reticulum of the pancreatic β cells. Successive cleaving processes then occur to first produce proinsulin, before being transported to the Golgi apparatus where it is again cleaved by

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Please cite this article in press as: Cade JE, Hanison J, The pancreas, Anaesthesia and intensive care medicine (2017), http://dx.doi.org/10.1016/j.mpaic.2017.06.021

Products of pancreatic islet cells

Cell type	Proportion of islet cells	Hormone secreted	Distribution
α	35%	Glucagon	Throughout pancreas, abundance in body and tail
β	55%	Insulin, amylin, C-peptide	Throughout pancreas, numerous in the centre
δ	<10%	Somatostatin	Throughout pancreas
F	<5%	Pancreatic polypeptide	Uncinate process
ε	<1%	Ghrelin	Sparse

Table 1

proteases to form insulin and C-peptide. The resulting insulin molecule has two polypeptide chains linked by two disulphide bridges (Figure 1). Insulin, along with equimolar concentration of C-peptide and some remaining proinsulin, is then packaged into secretory granules ready for release into the portal blood. Insulin has a half-life of 4 minutes and is rapidly metabolized by the liver and kidneys. In contrast, C-peptide has a half-life of 30 minutes and is excreted unchanged by the kidneys, making it a useful biomarker of endogenous insulin secretion.

Insulin is released from β cells by two mechanisms: stimulated and unstimulated secretion. Unstimulated or basal secretion occurs every 6–8 minutes. Stimulated release occurs in response to several stimuli, the principal stimulus being extracellular glucose. Other stimuli such as galactose, mannose, acetylcholine (Ach) and some amino acids (especially arginine and leucine) can also act as secretagogues.

In response to a rise in serum glucose, glucose is taken up and metabolized by β cells. The main glucose transporter on β cells is GLUT-2, although GLUT-1 and GLUT-3 expression have recently been recognized. Once intracellular, the glucose is phosphorylated by the enzyme glucokinase (the rate-limiting step of islet glucose metabolism) to glucose-6-phosphate, which in turn undergoes glycolysis to produce adenosine triphosphate (ATP). The β cell is rich in ATP-dependent potassium channels, which close in response to a rise in ATP, resulting in membrane depolarization. Depolarization activates voltage-gated calcium channels leading to an influx of calcium into the cell. This causes margination of secretory granules, and exocytosis of insulin and C-peptide into the blood stream (Figure 2).

This process characterizes the 'first phase' of insulin release, where insulin is detected in the circulation within 3–5 minutes of glucose administration. Loss of this first phase is one of the earliest metabolic defects found in the development of type 2 diabetes mellitus (T2DM).

The second, longer lasting phase, reaches a plateau at 2–3 hours. Characterized by dose-dependent mobilization of intracellular granules, it persists as long as the plasma glucose level remains elevated.

The amino acids arginine and leucine also stimulate insulin release. Uptake in this case is via a cationic amino-acid transporter (CAT), leading to membrane depolarization and calcium influx. Other modulators of secretion stimulate different intracellular signalling pathways. Glucagon, which stimulates insulin release, acts via adenylyl cyclase, raising cyclic AMP (cAMP) levels, stimulating protein kinase A and causing degranulation and insulin release. Conversely, somatostatin, which inhibits insulin release, inhibits adenylyl cyclase.

The incretin effect further modulates insulin release from pancreatic β cells. Enteric factors known as incretins are peptides released by gut mucosa in response to the presence of nutrients in the gut lumen, and are potent insulin secretagogues. Gastric inhibitory peptide (GIP) and glucagon-like peptide-1 (GLP-1) are released by duodenal and jejunal K and L cells respectively, and enhance insulin secretion by activation of adenylyl cyclase and cAMP, as above. This explains why orally administered glucose has been shown to stimulate insulin secretion by 25% more than the equivalent intravenously administered dose.

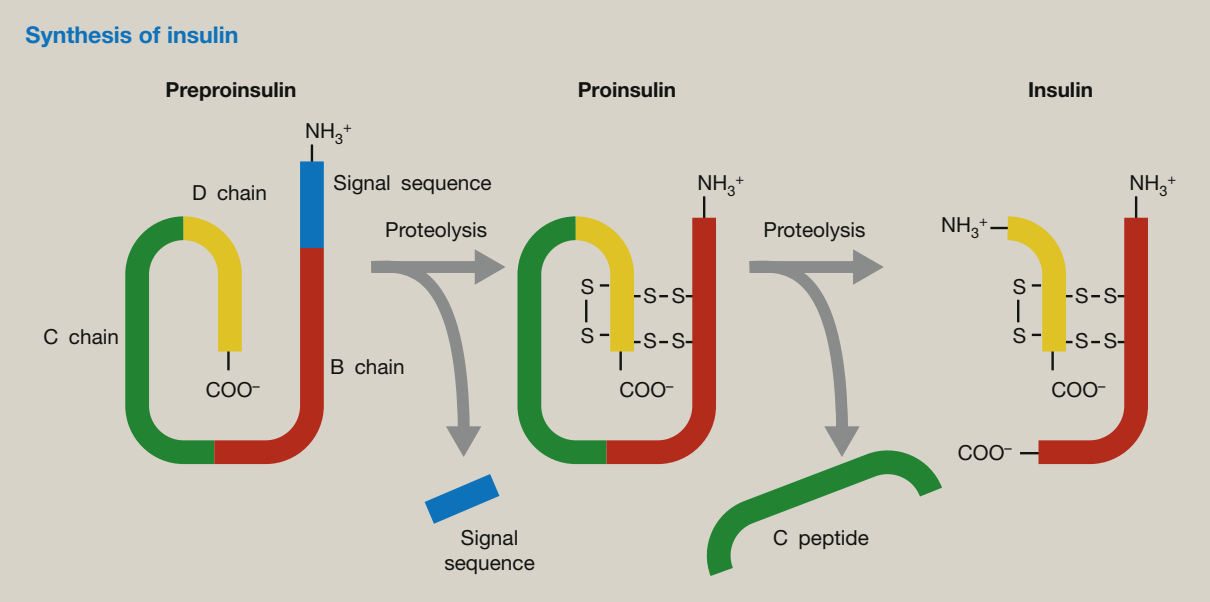

Figure 1

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